

Activate your eBook

LIPPINCOTT MANUAL

The Washington Manual® of Medical Therapeutics

35TH EDITION

Pavan Bhat
Alexandra Dretler
Mark Gdowski
Rajeev Ramgopal
Dominique Williams

Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri



Wolters Kluwer

Washington University in St. Louis
School of Medicine

Dedication

We dedicate this manual to the outstanding medicine house staff at Washington University and Barnes-Jewish Hospital—their wisdom, dedication, and compassion continue to inspire us each and every day.

Chairman's Note

The tremendous advances in medical research place an enormous burden on physicians to keep up with new evidence guiding clinical practice, particularly in novel therapies that will improve patient outcomes. The *Washington Manual® of Medical Therapeutics* provides an easily accessible source of current information that focuses on practical clinical approaches to the diagnosis, investigation, and treatment of common medical conditions that internists encounter on a regular basis. The electronic online version and the pocket-book size of the *Washington Manual®* ensure that it will continue to be of enormous assistance to interns, residents, medical students, and other practitioners in need of readily accessible clinical information. The *Washington Manual®* continues to address an important need in an era of information overload.

I acknowledge the authors, who include the outstanding house officers, fellows, and attendings at Washington University/Barnes-Jewish Hospital. Their efforts and exceptional skills are evident in the quality of the final product. In particular, I am proud of our editors: Drs. Pavan Bhat, Alexandra Dretler, Mark Gdowski, Rajeev Ramgopal, and Dominique Williams, and series editor Dr. Tom De Fer, who have worked tirelessly to produce another outstanding edition of the *Washington Manual® of Medical Therapeutics*. I also recognize Dr. Melvin Blanchard, Chief of the Division of Medical Education in the Department of Medicine at Washington University, for his guidance and advice. I am confident that this edition will meet its desired goal of providing practical knowledge that can be directly applied to improving patient care.

Victoria J. Fraser, MD
Adolphus Busch Professor of Medicine
Chairman, Department of Medicine
Washington University School of Medicine
St. Louis, Missouri

Preface

It is our distinct pleasure to introduce the 35th edition of *The Washington Manual® of Medical Therapeutics.* "The *Manual,*" as it is known here at Washington University, has a proud tradition of being edited by the Internal Medicine Chief Residents. Since its inception as a simple handbook for local medical students and house staff, the *Manual* has grown to be one of the best-selling medical texts in the world. Concurrently, the *Manual* has grown in size and complexity, mirroring the practice of medicine.

From the first edition edited by Wayland MacFarlane in 1943, numerous revisions have occurred, transforming the *Manual* from a short textbook to a portable reference, and now a text with both written and electronic forms with availability on portable electronic devices. Throughout the many revisions, however, the editors have sought to retain the virtues that made the work a success from the start: a concise discussion of pathophysiology, an evidence-based presentation of current therapies, and a sensible format. Additionally, with each new edition, the content is carefully updated to reflect the ever-changing advances in medical technology and therapeutics.

The Washington Manual® of Medical Therapeutics has established a tradition of excellence that we aspire to preserve. No discussion of the *Manual* would be complete without mention of the fantastic Washington University medicine house staff, fellows, medical students, and attendings with whom we work daily. Their brilliance, compassion, and dedication are truly remarkable and inspiring. We are honored that they turn to the *Manual* for guidance. We are deeply indebted for the substantial support and direction that Dr. Tom De Fer, the series editor, provided in the creation of this edition of the *Manual*. We also sincerely thank Katie Sharp and the editorial staff at Wolters Kluwer for their assistance and patience with our busy schedules.

We have had the honor and pleasure of serving as chief residents of Shatz-Strauss, Karl-Flance, Kipnis-Daughaday, and North Campus firms, and the Primary Care Medicine Clinic in the Barnes-Jewish Center for Outpatient Health. Our firm chiefs, Drs. Megan Wren, Emily Fondahn, Geoffrey Cislo, and E.-P. Barrette, have been instrumental over the course of the year, serving as mentors and role models. Our program director, Dr. Melvin Blanchard, provided guidance and support in the production of the *Manual*. Our Chairman of Medicine, Dr. Vicky Fraser, served as an outstanding role model and provided support in the creation of this text. We thank our families for their support, patience, and inspiration. To Muffie, Rob, Charlotte, and Doug; the whole Gdowski family but especially Henry; Carolyn, John, and Stanley; Caroline, Priya, Kolari, and Shashi; and the entire Ramgopal and Martin families—our gratitude is beyond measure.

Pavan Bhat, MD

Alexandra Dretler, MD

Mark Gdowski, MD

Rajeev Ramgopal, MD

Dominique Williams, MD

Editors

Pavat Bhat MD
Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri

Alexandra Dretler MD
Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri

Mark Gdowski MD
Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri

Rajeev Ramgopal MD
Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri

Dominique Williams MD
Department of Medicine
Washington University
School of Medicine
St. Louis, Missouri

Contributors

Patrick Aguilar
Fellow
Division of Pulmonary and Critical Care Medicine

Zarmeena Ali, MD
Instructor in Medicine
Division of Rheumatology

Beau M. Ances, MD, PhD, MS
Associate Professor
Department of Neurology

Jeffrey J. Atkinson, MD

Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Philip M. Barger, MD
Associate Professor of Medicine
Division of Cardiovascular Medicine

Rebecca Bavolek, MD
Instructor in Emergency Medicine
Division of Emergency Medicine

Brad Bemiss, MD
Postdoctorate Research Scholar
Division of Pulmonary and Critical Care Medicine

Morey Blinder, MD
Associate Professor of Medicine
Division of Hematology

Sean Brady, MD
Fellow
Division of Allergy and Immunology

Angela L. Brown, MD
Assistant Professor of Medicine
Division of Cardiology

Robert C. Bucelli, MD, PhD
Assistant Professor
Department of Neurology

Allen Burks, MD
Fellow
Division of Pulmonary and Critical Care Medicine

Abigail L. Carlson, MD
Fellow
Division of Infectious Diseases

Mario Castro, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Murali Chakinala, MD
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Alexander Chen, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Catherine Chen, MD
Fellow
Division of Pulmonary and Critical Care Medicine

Steven Cheng, MD
Assistant Professor of Medicine
Division of Renal Diseases

Praveen Chenna, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine

William E. Clutter, MD
Associate Professor of Medicine
Division of Medical Education

Daniel H. Cooper, MD
Assistant Professor of Medicine
Division of Cardiovascular Medicine

Daniel W. Coyne, MD
Professor of Medicine
Division of Renal Diseases

Matthew P. Crotty, PharmD
Infectious Diseases Pharmacy Resident
BJH Department of Pharmacy

Vladimir Despotovic, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Siddhartha Devarakonda, MD
Fellow
Division of Hematology and Oncology

Mitchell N. Faddis, MD, PhD
Associate Professor of Medicine
Division of Cardiovascular Medicine

Brian F. Gage, MD

Professor of Medicine
Division of General Medical Sciences

Mark Gdowski, MD
Instructor in Medicine
Division of Medical Education

Anne C. Goldberg, MD
Associate Professor of Medicine
Division of Endocrinology and Metabolism

Seth Goldberg, MD
Assistant Professor of Medicine
Division of Nephrology

Jacob S. Goldstein
Fellow
Cardiovascular Division

María González-Mayda, MD
Assistant Professor of Medicine
Division of Rheumatology

Ramaswamy Govindan, MD
Professor of Medicine
Division of Medical Oncology

C. Prakash Gyawali, MD
Professor of Medicine
Division of Gastroenterology

S. Eliza Halcomb, MD
Assistant Professor
Division of Emergency Medicine

Cynthia J. Herrick, MD
Instructor in Medicine
Division of Endocrinology, Metabolism, and
Lipid Research

Ronald Jackups, MD
Assistant Professor of Pathology and Immunology
Laboratory and Genomic Medicine

Judy L. Jang, MD

Assistant Professor of Medicine
Division of Renal Diseases

Junfang Jiao, MD
Fellow
Division of Allergy and Immunology

Eric Johnson, MD
Instructor in Medicine
Division of Hospital Medicine

Andrew L. Kau, MD
Instructor in Medicine
Division of Allergy and Immunology

Daniel S. Kim, MD
Instructor in Medicine
Division of Medical Education

Nigar Kirmani, MD
Professor of Medicine
Division of Infectious Diseases

Marin H. Kollef, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Shane J. LaRue, MD
Instructor in Medicine
Cardiovascular Division

Stephen Y. Liang, MD
Instructor in Medicine
Division of Infectious Diseases

Brian R. Lindman, MD
Assistant Professor of Medicine
Division of Cardiovascular Medicine

Mauricio Lisker-Melman, MD
Professor of Medicine
Division of Gastroenterology

Andrea Loiselle, MD
Instructor in Medicine
Division of Pulmonary and Critical Care Medicine

Caline Mattar, MD
Fellow
Division of Infectious Diseases

Janet B. McGill, MD
Professor of Medicine
Division of Endocrinology

Adam Meyer, MD
Instructor in Medicine
Division of Hospital Medicine

Jennifer M. Monroy, MD
Assistant Professor of Medicine
Division of Allergy and Immunology

Daniel Morgensztern, MD
Associate Professor of Medicine
Division of Medical Oncology

Clare E. Moynihan, MD
Fellow
Division of Endocrinology and Metabolism

Michael E. Mullins, MD
Associate Professor of Emergency Medicine
Department of Medicine

Anubha Mutneja, MD
Fellow
Division of Renal Diseases

Allison L. Nazinitsky, MD
Fellow
Division of Infectious Diseases

Amit Patel, MD
Fellow
Division of Gastroenterology

Rachel Presti, MD
Assistant Professor of Medicine
Division of Infectious Diseases

Rajesh Rajan, MD

Fellow
Division of Renal Diseases

Dominic Reeds, MD
Associate Professor of Medicine
Division of Geriatrics and Nutritional Science

Tom Regenbogen, MD
Fellow
Division of Medical Oncology

Hilary E. L. Reno, MD
Assistant Professor of Medicine
Division of Infectious Diseases

David J. Ritchie, PharmD
Clinical Pharmacist
Division of Infectious Diseases

Daniel B. Rosenbluth, MD
Professor of Medicine and Pediatrics
Division of Pulmonary and Critical Care Medicine

Tonya D. Russell, MD
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Ali Sadoughi, MD
Fellow
Division of Pulmonary and Critical Care Medicine

Maria Samuel, MD
Fellow
Division of Gastroenterology

Kristen M. Sanfilippo, MD
Instructor in Medicine
Division of Hematology

Carlos A. Q. Santos, MD
Assistant Professor of Medicine
Division of Infectious Diseases

Rowena Delos Santos, MD
Assistant Professor of Medicine

Division of Renal Diseases

Evan S. Schwarz, MD
Assistant Professor of Emergency Medicine
Division of Emergency Medicine

Adrian Shifren, MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Kristen Singer, MD
Resident
Department of Internal Medicine

Marc A. Sintek, MD
Fellow
Cardiovascular Division

Rupinder Sodhi, MD
Fellow
Division of Renal Diseases

Mark Thoelke, MD
Associate Professor
Division of Hospital Medicine

Justin M. Vader, MD
Assistant Professor of Medicine
Cardiovascular Division

Tiphanie Vogel, MD
Fellow
Division of Rheumatology

Jason Wagner, MD
Assistant Professor of Emergency Medicine
Division of Emergency Medicine

Tzu-Fei Wang, MD
Assistant Professor of Internal Medicine
Division of Hematology
The Ohio State University

Peter H. Yen, MD
Resident
Department of Medicine

Roger D. Yusen, MD, MPH
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine

Amy Zhou
Fellow
Division of Medical Oncology

1
Inpatient Care in Internal Medicine

Mark Thoelke

Eric Johnson

Adam Meyer

General Care of the Hospitalized Patient

GENERAL PRINCIPLES

- Although a general approach to common problems can be outlined, **therapy must be individualized**. All diagnostic and therapeutic procedures should be explained carefully to the patient, including the potential risks, benefits, and alternatives.
- The period of hospitalization represents a complex interplay of multiple caregivers that subjects the patient to potential harm by **medical errors and iatrogenic complications**. Every effort must be made to minimize these risks. Basic measures include:
  - Use of standardized abbreviations and dose designations
  - Excellent communication between physicians and other caregivers
  - Institution of appropriate prophylactic precautions
  - Prevention of nosocomial infections, including attention to hygiene and discontinuation of unnecessary catheters
  - Medicine reconciliation at all transfers of care
- **Hospital orders**
  - Computer order entry offers admission order sets that should be entered promptly after evaluation of a patient. A contact number should be made available.
  - Daily rounds should include assessment for ongoing need of IV fluids, telemetry, catheters, and supplemental oxygen, all of which can limit mobility.
  - Routine daily labs, such as CBC and BMP, should be discouraged because significant iatrogenic anemia may develop.
- **Discharge**
  - **Discharge planning** begins at the time of admission. Assessment of the patient's social situation and potential discharge needs should be made at this time.
  - **Early coordination** with nursing, social work, and case coordinators/managers facilitates efficient discharge and a complete postdischarge plan.
  - **Patient education** should occur regarding changes in medications and other new therapies.

    Compliance with treatment is influenced by the patient's understanding of that treatment.
  - **Prescriptions** should be written for all new medication, and the patient should be provided with a complete medication list including instructions and indications.

- **Communication** with physicians who will be resuming care of the patient is important for optimal follow-up care and should be a component of the discharge process.

PROPHYLACTIC MEASURES

Venous Thromboembolism Prophylaxis

GENERAL PRINCIPLES

Epidemiology

Venous thromboembolism (VTE) is a preventable cause of death in hospitalized patients. In the largest observational study to date attempting to risk-stratify medical patients, 1.2% of

medical patients developed VTE within 90 days of admission. A total of 10-31% of patients were deemed to be at high risk for VTE, defined as having **2 or more points** by weighted risk factors below (*Chest 2011;140:706*).

Risk Factors

- 3 points: previous VTE, thrombophilia
- 1 point: cancer, age >60

Prevention

- **Ambulation** several times a day should be encouraged.
- **Pharmacologic prophylaxis** results in a 50% decrease in VTE risk, although this includes many asymptomatic calf vein thromboses that do not progress. No overall mortality benefit from prophylaxis has been demonstrated.
- Acutely ill patients at high risk of VTE, without bleeding or high risk of bleeding, should be treated with low-dose unfractionated heparin (UFH), 5000 units SC q12h or q8, or low-molecular-weight heparin (LMWH); enoxaparin, 40 mg SC daily, or dalteparin,

  5000 units SC daily; or fondaparinux, 2.5 mg SC daily.
- Aspirin alone is not sufficient for prophylaxis in hospitalized patients (*Chest 2012;141:e195S*).
- At-risk patients with contraindications to anticoagulation prophylaxis may receive mechanical prophylaxis with intermittent pneumatic compression or graded compression stockings, although evidence of benefit is lacking (*Ann Intern Med 2011;155:625*).

Decubitus Ulcers

GENERAL PRINCIPLES

Epidemiology

Decubitus ulcers typically occur within the first 2 weeks of hospitalization and can develop within 2-6 hours. Once they develop, decubitus ulcers are difficult to heal and have been associated with increased mortality (*J Gerontol A Biol Sci Med Sci 1997;52:M106*). Risk factors for the development of decubitus ulcers include, advanced age, paralysis, and severe illness (*Clin Dermatol 2010;28(5):527*).

Prevention

Prevention is the key to management of decubitus ulcers. It is recognized that not all decubitus ulcers are avoidable (*J Wound Ostomy Continence Nurs 2014;41:313*). Preventative measures include:

- **Risk factor assessment**, including immobility, limited activity, incontinence, impaired nutritional status, impaired circulation, and altered level of consciousness.
- **Advanced static mattresses or** overlays should be used in at-risk patients (*Ann Intern Med 2015;162:359*).
- **Skin care**, including daily inspection with particular attention to bony prominences including heels, minimizing exposure to moisture, and applying moisturizers to dry sacral skin.
- **Nutritional supplements** may be provided to patients at risk.
- **Frequent repositioning** (minimum of every 2 hours, or every 1 hour for wheelchairbound patients) is suggested.

DIAGNOSIS

Clinical Presentation

National Pressure Ulcer Advisory Panel Staging

- **Suspected deep tissue injury:** Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear.

  P.3

  The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue.
- **Stage I:** Intact skin with nonblanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may obscure findings.
- **Stage II:** Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed without slough. May also present as a blister.
- **Stage III:** Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.
- **Stage IV:** Full thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present on some parts of the wound bed. Often includes undermining and tunneling.
- **Unstageable:** Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.

TREATMENT

Optimal treatment of pressure ulcers remains poorly defined. There is evidence to support the following (*Ann Intern Med 2015;162:370*).

- **Hydrocolloid or foam** dressings may reduce wound size.
- **Protein or amino acid supplementation** is recommended, although there are insufficient data to recommend a specific supplement regimen (*Cochrane Database Syst Rev 2014*).
- **Electrical stimulation** may accelerate healing.
- **Other adjunctive therapies** with less supporting evidence include radiant heat, negative pressure, and

platelet-derived growth factor. Topical agents (silver sulfadiazine) may optimizing healing or lead to minor slough debridement (Santyl, Xenaderm).

- There is no role for antibiotics to aid healing of a noninfected ulcer.

Other Precautions

GENERAL PRINCIPLES

- **Fall precautions** should be written for patients who have a history of falls or are at high risk of a fall (e.g., dementia, weakness, orthostasis). Falls are the most common accident in hospitalized patients, frequently leading to injury. **Fall risk should not be equated with bedrest**, which may lead to debilitation and higher risk of future falls.
- **Seizure precautions**, which include padded bed rails and an oral airway at the bedside, should be considered for patients with a history of seizures or those at risk of seizing.
- **Restraint orders** are written for patients who are at risk of injuring themselves or interfering with their treatment due to disruptive or dangerous behaviors. Restraint orders must be renewed every 24 hours. Physical restraints may exacerbate agitation. Bed alarms, sitters, and sedatives are alternatives in appropriate settings.

ACUTE INPATIENT CARE

An approach to selected common complaints is presented in this section. An evaluation should generally include a directed history and physical examination, review of the medical problem list (including chronic conditions), review of medications with attention to recent medication changes, and consideration of recent procedures.

Chest Pain

GENERAL PRINCIPLES

Common causes of chest pain range from life-threatening causes such as myocardial infarction (MI) and pulmonary embolism to other causes including esophageal reflux, peptic ulcer disease, pneumonia, costochondritis, shingles, trauma, and anxiety.

DIAGNOSIS

History and Physical Examination

- History should include previous cardiac or vascular disease history, cardiac risk factors, and factors that would predispose the patient to a pulmonary embolus.
- Physical examination is ideally conducted during an episode of pain and includes vital signs (bilateral blood pressure [BP] measurements if considering aortic dissection), cardiopulmonary and abdominal examination, and inspection and palpation of the chest.

Diagnostic Testing

Assessment of oxygenation status, chest radiography, and ECG is appropriate in most patients. Serial cardiac biomarkers should be obtained if there is suspicion of ischemia. Spiral CT and ventilation/perfusion scans are employed to diagnose pulmonary embolus.

TREATMENT

- If cardiac ischemia is a concern, see Chapter 4, Ischemic Heart Disease, for details.
- If a gastrointestinal (GI) source is suspected, Maalox and diphenhydramine (1:1 mix) can be administered.
- Musculoskeletal pain typically responds to acetaminophen or NSAID therapy.
- Prompt empiric anticoagulation if there is high suspicion for MI or pulmonary embolism.

Dyspnea

GENERAL PRINCIPLES

Dyspnea is most commonly caused by a cardiopulmonary abnormality, such as congestive heart failure (CHF), cardiac ischemia, bronchospasm, pulmonary embolus, infection, mucus plugging, and aspiration. Dyspnea must be promptly and carefully evaluated.

DIAGNOSIS

History and Physical Examination

- Initial evaluation should include a review of the medical history for underlying pulmonary or cardiovascular disease and a directed history.
- A detailed cardiopulmonary examination should take place, including vital signs.

Diagnostic Testing

- Oxygen assessment by pulse oximetry or arterial blood gas and chest radiography are useful in most patients.
- Other diagnostic measures should be directed by the findings in the initial evaluation.

TREATMENT

Oxygen should be administered promptly if needed. Other therapeutic measures should be directed by the findings in the initial evaluation.

Acute Hypertensive Episodes

GENERAL PRINCIPLES

- Acute hypertensive episodes in the hospital are most often caused by inadequately treated essential hypertension. If there is evidence of end-organ damage, IV medications are indicated. Oral agents are more appropriate for hypertensive urgency without end-organ damage.
- Volume overload and pain may exacerbate hypertension and should be recognized appropriately and treated.
- Hypertension associated with withdrawal syndromes (e.g., alcohol, cocaine) and rebound hypertension associated with sudden withdrawal of antihypertensive medications (i.e., clonidine, α-adrenergic antagonists) should be considered. These entities should be treated as discussed in Chapter 3, Preventive Cardiology.

Fever

GENERAL PRINCIPLES

Fever accompanies many illnesses and is a valuable marker of disease activity. Infection is a primary concern. Drug reaction, malignancy, VTE, vasculitis, central fever, and tissue infarction are other possibilities but are diagnoses of exclusion.

DIAGNOSIS

History and Physical Examination

- History should include chronology of the fever and associated symptoms, medications, potential exposures, and a complete social and travel history.
- Physical examination should include oral or rectal temperature. In the hospitalized patient, special attention should be paid to any IV lines, abnormal fluid accumulation, and indwelling devices such as urinary catheters.
- For management of neutropenic fever, see Chapter 22, Cancer.

Diagnostic Testing

- Testing includes blood and urine cultures, complete blood count (CBC) with differential, serum chemistries with liver function tests, urinalysis, and stool cultures if appropriate.
- Diagnostic evaluation generally includes chest radiography.
- Cultures of abnormal fluid collections, sputum, cerebrospinal fluid, and stool should be sent if clinically indicated. Cultures are ideally obtained prior to initiation of antibiotics; however, antibiotics should not be delayed if serious infection is suspected.

TREATMENT

- Antipyretic drugs may be given to decrease associated discomfort. Aspirin, 325 mg, and acetaminophen, 325-650 mg PO or PR q4h, are the drugs of choice.
- Empiric antibiotics should be considered in hemodynamically unstable patients in whom infection is a primary concern, as well as in neutropenic and asplenic patients.

- Heat stroke and malignant hyperthermia are medical emergencies that require prompt recognition and treatment (see Chapter 26, Medical Emergencies).

Pain

GENERAL PRINCIPLES

Pain is subjective, and therapy must be individualized. Chronic pain may not be associated with any objective physical findings. Pain scales should be employed for quantitation.

TREATMENT

- Acute pain usually requires temporary therapy.
- For chronic pain, use a combination of long-acting medication with bolus as needed.

- If pain is refractory to conventional therapy, then nonpharmacologic modalities, such as nerve blocks, sympathectomy, and cognitive behavioral therapy, may be appropriate.

Medications

- Acetaminophen
  - Effects: Antipyretic and analgesic actions; no anti-inflammatory or antiplatelet properties.
  - Dosage: 325-1000 mg q4-6h (maximum dose, 4 g/d), available in oral, IV, and rectal suppository. Dosage in patients with liver disease should not exceed 2 g/d.
  - Adverse effects: The principal *advantage* of acetaminophen is its lack of gastric toxicity. Hepatic toxicity may be serious, and acute overdose with 10-15 g can cause fatal hepatic necrosis (see Chapter 19, Liver Diseases, and Chapter 26, Medical Emergencies).
- Aspirin
  - Effects: Aspirin has analgesic, antipyretic, anti-inflammatory, and antiplatelet effects.

    Aspirin should be used with caution in patients with hepatic or renal disease or bleeding disorders, those who are pregnant, and those who are receiving anticoagulation therapy. Antiplatelet effects may last for up to 1 week after a single dose.
  - Dosage: 325-650 mg q4h PRN (maximum dose, 4 g/d), available in oral and rectal suppository. Enteric coated formulation may minimize GI side effects.
  - Adverse effects: Dose-related side effects include tinnitus, dizziness, and hearing loss. Dyspepsia and GI bleeding can develop and may be severe. Hypersensitivity reactions, including bronchospasm, laryngeal edema, and urticaria, are uncommon, but patients with asthma and nasal polyps are more susceptible. Chronic use can result in interstitial nephritis and papillary necrosis.
- NSAIDs

  Effects: NSAIDs have analgesic, antipyretic, and anti-inflammatory properties mediated by inhibition of cyclooxygenase. All NSAIDs have similar efficacy and toxicities, with a side effect profile similar to that of aspirin. Patients with allergic or bronchospastic reactions to aspirin should not be given NSAIDs. See Chapter 25, Arthritis and Rheumatologic Diseases, for further information on NSAIDs.
- Opioid analgesics
  - Effects: Opioid analgesics are pharmacologically similar to opium or morphine and are the drugs of choice when analgesia without antipyretic action is desired.
  - Dosage: Table 1-1 lists equianalgesic dosages.
    - Constant pain requires continuous (basal) analgesia with supplementary, PRN doses for breakthrough pain at doses of roughly 5-15% of the daily basal dose. If frequent PRN doses are required, the maintenance dose should be increased or the dosing interval should be decreased.

TABLE 1-1 Equipotent Doses of Opioid Analgesics

Drug	Onset (min)	Duration (hr)	IM/IV/SC (mg)	PO (mg)
Fentanyl	7-8	1-2	0.1	NA
Levorphanol	30-90	4-6	2	4

Hydromorphone	15-30	2-4	1.5-2.0	7.5
Methadone	30-60	4-12	10	20
Morphine	15-30	2-4	10	30[a]
Oxycodone	15-30	3-4	NA	20
Codeine	15-30	4-6	120	200

NA, not applicable.

Note: Equivalences are based on single-dose studies.

[a]An IM:PO ratio of 1:2 to 1:3 used for repetitive dosing.

- When changing to a new narcotic due to poor response or patient intolerance, the new medication should be started at 50% the equianalgesic dose to account for incomplete cross-tolerance.
- Parenteral and transdermal administration are useful in the setting of dysphagia, emesis, or decreased GI absorption.
- Agents with short half-lives, such as morphine, should be used. Narcotic-naïve patients should be started on the lowest possible doses, whereas patients with demonstrated tolerance will require higher doses.
- Patient-controlled analgesia often is used to control pain in a postoperative or terminally ill patient. Opioid-naïve patients should not have basal rates prescribed due to risk of overdose.
- Selected opiates

  Codeine is usually given in combination with aspirin or acetaminophen.

  Oxycodone and hydrocodone are both available orally in combination with acetaminophen; oxycodone is available without acetaminophen in immediate-release and sustained-release formulations. Care should be taken to avoid acetaminophen overdose with these formulations.

  Morphine sulfate preparations include both immediate release and sustained release. The liquid form can be useful in patients who have difficulty in swallowing pills. Morphine should be used with caution in renal insufficiency.

  Methadone is very effective when administered orally and suppresses the symptoms of withdrawal from other opioids because of its extended half-life. Despite its long elimination half-life, its analgesic duration of action is much shorter.

  Hydromorphone is a potent morphine derivative, five to seven times the strength of morphine, and caution should be used when ordering this medication.

  Fentanyl is available in a transdermal patch with sustained release over 72 hours. Initial onset of action is delayed. Respiratory depression may occur more frequently with fentanyl.

- Precautions

- Opioids are relatively contraindicated in acute disease states in which the pattern and degree of pain are important diagnostic signs (e.g., head injuries, abdominal pain). They also may increase intracranial pressure.

  - Opioids should be used with caution in patients with hypothyroidism, Addison disease, hypopituitarism, anemia, respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma, kyphoscoliosis, severe obesity), severe malnutrition, debilitation, or chronic cor pulmonale.
  - Opioid dosage should be adjusted for patients with impaired hepatic or renal function.
  - Drugs that potentiate the adverse effects of opioids include phenothiazines, antidepressants, benzodiazepines, and alcohol.
  - Tolerance develops with chronic use and coincides with the development of physical dependence, which is characterized by a withdrawal syndrome (anxiety, irritability, diaphoresis, tachycardia, GI distress, and temperature instability) when the drug is stopped abruptly. It may occur after only 2 weeks of therapy.
  - Administration of an opioid antagonist may precipitate withdrawal after only 3 days of therapy. Tapering the medication slowly over several days can minimize withdrawal.
- Adverse and toxic effects
  - Central nervous system (CNS) effects include sedation, euphoria, and pupillary constriction.
  - Respiratory depression is dose related and pronounced after IV administration.
  - Cardiovascular effects include peripheral vasodilation and hypotension.
  - GI effects include constipation, nausea, and vomiting. Stool softeners and laxatives should be prescribed to prevent constipation. Opioids may precipitate toxic megacolon in patients with inflammatory bowel disease.
  - Genitourinary effects include urinary retention.
  - Pruritus occurs most commonly with spinal administration.
- Opioid overdose

  Naloxone, an opioid antagonist, should be readily available for administration in the case of accidental or intentional overdose. For details of administration, see Chapter 26, Medical Emergencies.
- Alternative medications
  - Tramadol is an opioid agonist and a centrally acting non-opioid analgesic that acts on pain processing pathways.
    - Dosage: 50-100 mg PO q4-6h can be used for acute pain. For elderly patients and those with renal or liver dysfunction, dosage reduction is recommended.
    - Adverse effects: Concomitant use of alcohol, sedatives, or narcotics should be avoided. Nausea, dizziness, constipation, and headache may also occur. Respiratory depression has not been described at prescribed dosages but may occur with overdose. Tramadol should not be used in patients who are taking a monoamine oxidase inhibitor, as it can contribute to serotonin syndrome.
  - Anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, oxcarbazepine), tricyclic antidepressants (e.g., amitriptyline), and duloxetine are PO agents that can be used to treat neuropathic pain.
  - Topical anesthetics (e.g., lidocaine) may provide analgesia to a localized region (e.g., postherpetic neuralgia).

Altered Mental Status

GENERAL PRINCIPLES

Mental status changes have a broad differential diagnosis that includes neurologic (e.g., stroke, seizure, delirium), metabolic (e.g., hypoxemia, hypoglycemia), toxic (e.g., drug effects, alcohol withdrawal), and other etiologies. Infection (e.g., urinary tract infections, pneumonia) is a common cause of mental status changes in the elderly and in patients with underlying

neurologic disease. Sundown syndrome refers to the appearance of worsening confusion in the evening and is associated with dementia, delirium, and unfamiliar environments.

DIAGNOSIS

History and Physical Examination

- Focus particularly on medications, underlying dementia, cognitive impairment, neurologic or psychiatric disorders, and a history of alcohol and/or drug use.
- Family and nursing personnel may be able to provide additional details.
- Physical examination generally includes vital signs, a search for sites of infection, a complete cardiopulmonary examination, and a detailed neurologic examination including mental status evaluation.

Diagnostic Testing

- Testing includes blood glucose, serum electrolytes, creatinine, CBC, urinalysis, and oxygen assessment.
- Other evaluation, including lumbar puncture, toxicology screen, cultures, thyroid function tests, noncontrast head CT, electroencephalogram, chest radiograph, or ECG should be directed by initial findings.

TREATMENT

Management of specific disorders is discussed in Chapter 27, Neurologic Disorders, available in the online version.

Medications

Agitation and psychosis may be features of a change in mental status. The antipsychotic haloperidol and the benzodiazepine lorazepam are commonly used in the acute management of these symptoms. Second-generation antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone, aripiprazole, paliperidone) are alternative agents that may lead to decreased incidence of extrapyramidal symptoms. All of these agents pose risks to elderly patients and those with dementia if given long term.

- Haloperidol is the initial drug of choice for acute management of agitation and psychosis. The initial dose of 0.5-5 mg (0.25 mg in elderly patients) PO and 2-10 mg IM/IV can be repeated every 30-60 minutes. Haloperidol has fewer active metabolites and fewer anticholinergic, sedative, and hypotensive effects than other antipsychotics but may have more extrapyramidal side effects. In low dosages, haloperidol rarely causes hypotension, cardiovascular compromise, or excessive sedation.
- Prolongation of the QT interval. Use should be discontinued with prolongation of QTc >450 msec or 25% above baseline.
- Postural hypotension may occasionally be acute and severe after administration. IV fluids should be

given initially for treatment. If vasopressors are required, dopamine should be avoided because it may exacerbate the psychotic state.

- Neuroleptic malignant syndrome (see Chapter 27, Neurologic Disorders).
- Lorazepam is a benzodiazepine that is useful for agitation and psychosis in the setting of hepatic dysfunction and sedative or alcohol withdrawal. The initial dose is 0.5-1 mg IV. Lorazepam has a short duration of action and few active metabolites. Excessive sedation and respiratory depression can occur.

Nonpharmacologic Therapies

Patients with delirium of any etiology often respond to frequent reorientation, observance of the day-night light cycle, and maintenance of a familiar environment.

Insomnia and Anxiety

GENERAL PRINCIPLES

- Insomnia and anxiety may be attributed to a variety of underlying medical or psychiatric disorders, and symptoms may be exacerbated by hospitalization.
- Causes of insomnia include environmental disruptions, mood and anxiety disorders, substance abuse disorders, common medications (i.e., β-blockers, steroids, bronchodilators), sleep apnea, hyperthyroidism, and nocturnal myoclonus.
- Anxiety may be seen in anxiety disorder, depression, substance abuse disorders, hyperthyroidism, and complex partial seizures.

DIAGNOSIS

The diagnosis of insomnia and anxiety is a clinical one. No laboratory or imaging tests help in establishing the diagnosis; however, they can help to rule out other etiologies.

TREATMENT

- Benzodiazepines are frequently used in management of anxiety and insomnia. Table 1-2 provides a list of selected benzodiazepines and their common uses and dosages.
  - Pharmacology: Most benzodiazepines undergo oxidation to active metabolites in the liver. Lorazepam, oxazepam, and temazepam undergo glucuronidation to inactive metabolites; therefore, these agents may be particularly useful in the elderly and in those with liver disease. Benzodiazepines with long half-lives may accumulate substantially in the elderly, in whom the half-life may be increased manyfold.
  - Dosages: Relief of anxiety and insomnia is achieved at the doses outlined in Table 1-2. Therapy should be started at the lowest recommended dosage with intermittent dosing schedules.
  - Side effects include drowsiness, dizziness, fatigue, psychomotor impairment, and anterograde amnesia. Benzodiazepine toxicity is heightened by malnutrition, advanced age, hepatic disease and concomitant use of alcohol, other CNS depressants, and CYP3A4 inhibitors. The elderly may experience falls, paradoxical agitation, and delirium.
    - IV administration of diazepam and midazolam can be associated with hypotension, bradycardia, and respiratory or cardiac arrest.

- Respiratory depression can occur even with oral administration in patients with respiratory compromise.
- Tolerance to benzodiazepines can develop and dependence may develop after only 2-4 weeks of therapy.
- Seizures and delirium may also occur with sudden discontinuation of benzodiazepines.

  A *withdrawal syndrome* consisting of agitation, irritability, insomnia, tremor, palpitations, headache, GI distress, and perceptual disturbance begins 1-10 days after a rapid decrease in dosage or abrupt cessation of therapy. Short-acting and intermediate-acting drugs should be decreased by 10-20% every 5 days, with a slower taper in the final few weeks. Long-acting preparations can be tapered more quickly.

- Overdose

  Flumazenil, a benzodiazepine antagonist, should be readily available in case of accidental or intentional overdose. For details of administration, see Chapter 26, Medical Emergencies.

- Trazodone
  - Trazodone is a serotonin receptor antagonist antidepressant that may be useful for the treatment of severe anxiety or insomnia. Common dosing is 50-100 mg at bedtime.

TABLE 1-2 Characteristics of Selected Benzodiazepines

Drug	Route	Common Uses	Usual Dosage	Half-life (hr)[a]
Alprazolam	PO	Anxiety disorders	0.75-4.0 mg/24 h (in three doses)	12-15
Chlordiazepoxide	PO	Anxiety disorders, alcohol withdrawal	15-100 mg/24 h (in divided doses)	5-30
Clonazepam	PO	Anxiety disorders, seizure disorders	0.5-4.0 mg/24 h (in two doses)	18-28
Diazepam	PO	Anxiety disorders, seizure disorders, preanesthesia	6-40 mg/24 h (in one to four doses)	20-50
	IV		2.5-20.0 mg (slow IV push)	20-50
Flurazepam	PO	Insomnia	15-30 mg at bedtime	50-100
Lorazepam[b]	PO	Anxiety disorders	1-10 mg/24 h (in two to three doses)	10-20

	IV or IM	Preanesthetic medication	0.05 mg/kg (4 mg max)	10-20
Midazolam	IV	Preanesthetic and intraoperative medication	0.01-0.05 mg/kg	1-12
	IM		0.08 mg/kg	1-12
Oxazepam[b]	PO	Anxiety disorders	10-30 mg/24 h (in three to four doses)	5-10
Temazepam[b]	PO	Insomnia	15-30 mg at bedtime	8-12
Triazolam	PO	Insomnia	0.125-0.250 mg at bedtime	2-5

[a]Half-life of active metabolites may differ.

[b]Metabolites are inactive.

- It is highly sedating and can cause postural hypotension. It is rarely associated with priapism.
- Levels may be substantially increased when used with CYP3A4 inhibitors.

- Nonbenzodiazepine hypnotics

  These agents appear to act on the benzodiazepine receptor and have been shown to be safe and effective for initiating sleep. All should be used with caution in patients with impaired respiratory function.

  - Zolpidem is an imidazopyridine hypnotic agent that is useful for the treatment of insomnia. It has no withdrawal syndrome, rebound insomnia, or tolerance. Side effects

    include headache, daytime somnolence, and GI upset. The starting dose is 5 mg PO every night at bedtime.
  - Zaleplon has a half-life of approximately 1 hour and no active metabolites. Side effects include dizziness and impaired coordination. The starting dose is 10 mg PO at bedtime (5 mg for the elderly or patients with hepatic dysfunction).
  - Eszopiclone offers a longer half-life compared to the previous agents. Side effects include headache and dizziness. Starting dose is 1 mg PO at bedtime.
  - Ramelteon is a melatonin analog. The usual dose is 8 mg PO at bedtime.

- Antihistamines

  Over-the-counter antihistamines can be used for insomnia and anxiety, particularly in patients with a history of drug dependence. Anticholinergic side effects limit the utility, especially in the elderly.

PERIOPERATIVE MEDICINE

The role of the medical consultant is to estimate the level of risk associated with a given procedure, determine the need for further evaluation based upon this risk estimate, and prescribe interventions to mitigate risk. Although preoperative consultations often focus on cardiac risk, it is essential to remember that poor outcomes can result from significant disease in other organ systems. Evaluation of the entire patient is necessary to provide optimal perioperative care.

Preoperative Cardiac Evaluation

GENERAL PRINCIPLES

Perioperative cardiac complications are generally defined as cardiac death, MIs (both ST and non-ST elevation), CHF, and clinically significant rhythm disturbances.

Epidemiology

- Overall, an estimated 50,000 perioperative infarctions and 1 million other cardiovascular complications occur annually (*N Engl J Med 2001;345:1677*). Of those who have a perioperative MI, the risk of in-hospital mortality is estimated at 10-15% (*Chest 2006;130:584*).
- Perioperative MI (PMI) is believed to occur via two distinct mechanisms. Type I PMI results from erosion or rupture of unstable atherosclerotic plaque, leading to coronary thrombosis and subsequent myocardial injury. Type II PMI occurs when myocardial oxygen demand exceeds supply in the absence of overt thrombosis.
- Although angiographic data suggest that existing stenoses may underpin some perioperative events, a significant number of PMIs are "stress" related (Type II) and not due to plaque rupture (*Am J Cardiol 1996;77:1126*; *J Cardiothorac Vasc Anesth 2003;17:90*).
- Autopsy data indicate that fatal PMIs occur predominantly in patients with multivessel and especially left main coronary artery disease, via the same mechanism as non-PMIs (*Int J Cardiol 1996;57:37*).

DIAGNOSIS

Clinical Presentation

History

The aim is to identify patient factors and comorbid conditions that will affect perioperative risk. Current guidelines focus on identification of active cardiac disease and known risk factors for perioperative events, which include:

- Unstable coronary syndromes including severe angina
- Recent MI (defined as >7 but <30 days)

- Decompensated CHF (New York Heart Association class IV, worsening or new-onset heart failure [HF])
- Significant arrhythmia including non-sinus rhythm (rate controlled and stable)
- Severe valvular disease
- Clinical risk factors for coronary artery disease (CAD)
- Preexisting, stable CAD
- Compensated or prior CHF
- Diabetes mellitus
- Prior cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Chronic kidney disease

- Poorly controlled hypertension
- Abnormal ECG (e.g., left ventricular hypertrophy, left bundle branch block, ST-T wave abnormalities)
- Age >70 years identified in several studies as a significant risk factor (*JAMA 2001; 285:1865*; *Eur Heart J 2008;29:394*) but not uniformly accepted as independent

Physical Examination

Specific attention should be paid to the following:

- Vital signs, with particular evidence of hypertension. Systolic blood pressure (SBP) <180 and diastolic blood pressure (DBP) <110 are generally considered acceptable. The management of stage III hypertension (SBP >180 or DBP >110) is controversial. However, postponing elective surgery to allow adequate BP control in this setting seems reasonable; how long to wait after treatment is implemented remains unclear.
- Evidence of decompensated CHF (elevated jugular venous pressure, rales, S3, edema).
- Murmurs suggestive of significant valvular lesions. According to the 2014 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Management of Patients with Valvular Heart Disease, the risk of noncardiac surgery is increased in all patients with significant valvular heart disease, although symptomatic aortic stenosis (AS) is thought to carry the greatest risk. The estimated rate of cardiac complications in patients with undiagnosed severe AS undergoing noncardiac surgery is 10-30%. However, aortic valve replacement is also associated with considerable risk. Risk-benefit analysis appears to favor proceeding to intermediate-risk elective noncardiac surgery (see below) with appropriate intra- and postoperative hemodynamic monitoring (including intraoperative right heart catheter or transesophageal echocardiogram) as opposed to prophylactic aortic valve replacement in the context of asymptomatic severe disease. The same recommendations (albeit with less supporting evidence) apply to asymptomatic severe mitral regurgitation, asymptomatic severe AR with normal ejection fraction, and asymptomatic severe mitral stenosis (assuming valve morphology is not amenable to percutaneous balloon mitral commissurotomy, which should otherwise be considered to optimize cardiac status prior to proceeding to surgery). Symptomatic severe valvular disease of any type should prompt preoperative cardiology consultation. See the section on Valvular Heart Disease in Chapter 6.

Diagnostic Criteria

The 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery offers a stepwise approach to preoperative evaluation and risk stratification (Figure 1-1).

- Step 1: Establish the urgency of surgery. Many surgeries are unlikely to allow for a timeconsuming evaluation.
- Step 2: Assess for active cardiac conditions (see History, above).
- Step 3: Determine the surgery-specific risk as follows:
  - Low-risk surgeries (<1% expected risk of adverse cardiac events) include superficial procedures, cataract/breast surgery, endoscopic procedures, and most procedures that can be performed in an ambulatory setting.

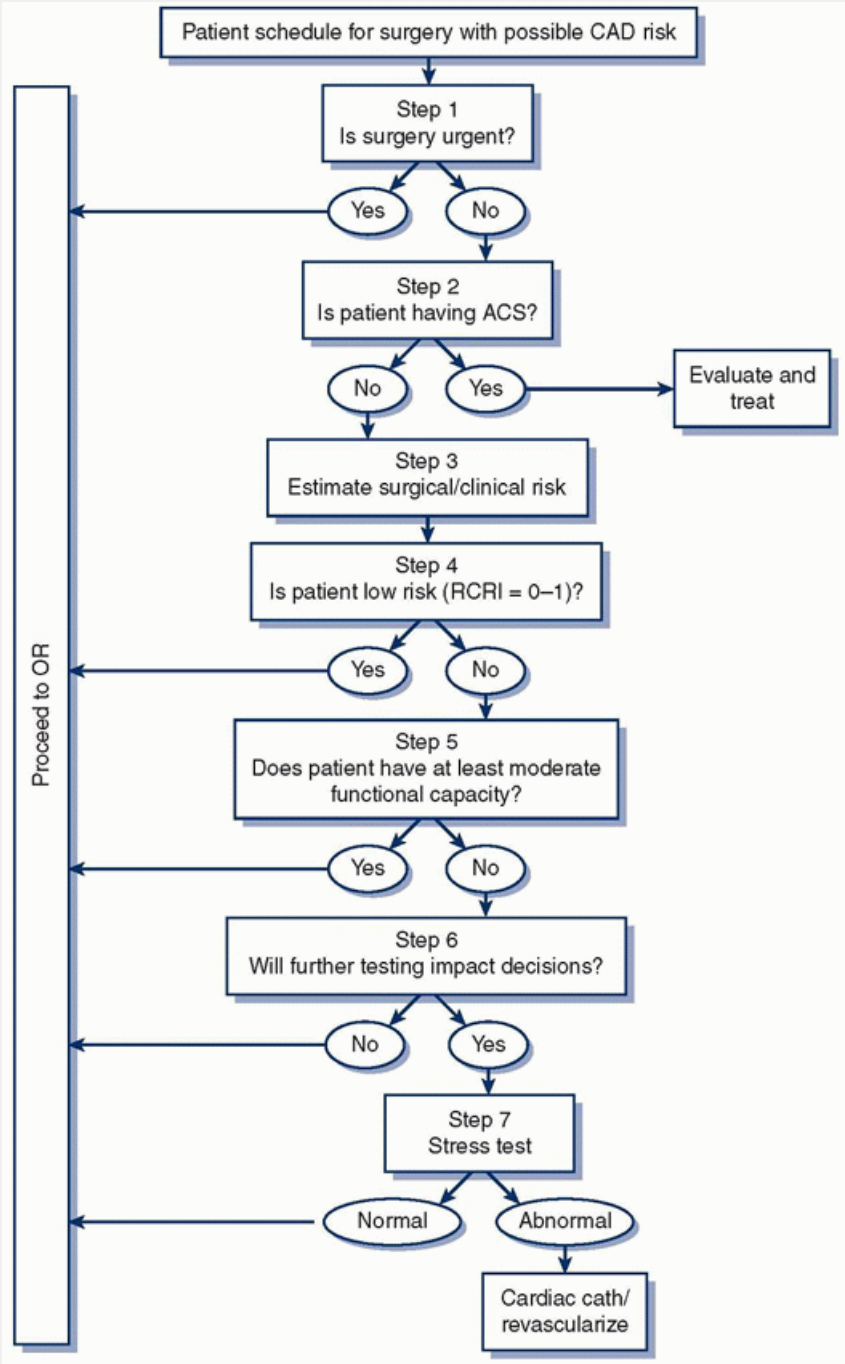


Figure 1-1. Cardiac evaluation algorithm for noncardiac surgery. (Modified from *Circulation 2014;130:e278-e333.*)

- Intermediate risk surgeries (1-5% risk of adverse cardiac events) include carotid endarterectomy, intraperitoneal/intrathoracic surgery, orthopedic surgery, head and neck surgery, and prostate surgery.
- Vascular surgery involving extremity revascularization or aortic repair generally carries the highest risk (>5% risk of adverse cardiac events).

- Step 4: Assess the patient's functional capacity.

  Poor functional capacity (<4 metabolic equivalents [METs]) is associated with an increased risk of perioperative cardiac events (*Arch Intern Med 1999;159:2185*; *Chest 1999;116:355*). Although exercise testing is the gold standard, functional capacity can be reliably estimated by patient self-report (*Am J Cardiol 1989;64:651*). Examples of activities that suggest at least moderate functional capacity (>4 METs) include climbing one to two flights of stairs or walking a block at a brisk pace. Patients with a functional capacity of >4 METs without symptoms can proceed to surgery with relatively low risk.

- Step 5: Assess the patient's clinical risk factors.
  - The number of risk factors combined with the surgery-specific risk (intermediate vs. vascular) determines further management. The following risk factors are adapted from the Revised Cardiac Risk Index (RCRI) (*Circulation 1999;100:1043*):
    - Ischemic heart disease
    - History of TIA or CVA
    - History of CHF
    - Preoperative serum creatinine ≥2 mg/dL
    - Diabetes mellitus requiring insulin
  - Patients with no clinical risk factors are at inherently low risk (<1% risk of cardiac events) and may proceed to surgery without further testing. Patients with one or two clinical risk factors are generally at intermediate risk and may proceed to surgery, although stress testing might help refine risk assessment in selected cases. Patients with three or more clinical risk factors are at high risk of adverse cardiac events, particularly when undergoing vascular surgery. In this population especially, stress testing may provide a better estimate of cardiovascular risk and may be considered if knowledge of this increased risk would change management (*J Am Coll Cardiol 2006;48:964*). A positive stress test in a high-risk patient portends a substantially increased risk of a perioperative cardiac event, whereas a negative study suggests a lower risk than that predicted by clinical factors alone (*JAMA 2001;285:1865*).

Revascularization

- The best available data on preoperative revascularization come from the Coronary Artery Revascularization Prophylaxis (CARP) trial, a prospective study of patients scheduled to undergo vascular surgery (*N Engl J Med 2004;351:2795*). Patients with angiographically proven significant CAD were randomized to revascularization versus no revascularization. There was no difference between the groups in the occurrence of MI or death at 30 days or in mortality with long-term follow-up. Patients with three or more clinical risk factors and extensive ischemia on stress testing were evaluated in a separate small study (*J Am Coll Cardiol 2007;49:1763*). High event rates were seen in both study arms, and no benefit was seen with revascularization. Taken together, these studies suggest that the risk of adverse cardiac events is not altered by attempts at preoperative revascularization, even in high-risk populations. A notable possible exception are patients with left main disease, who appeared to have benefited from preoperative revascularization in a subset analysis of the CARP trial data (*Am J Cardiol 2008;102:809*).
- Based on these cumulative results, a strategy of routinely pursuing coronary revascularization as a method of decreasing perioperative cardiac risk cannot be recommended. However, careful screening of patients is still essential to identify those high-risk subsets who may obtain a survival benefit from revascularization independent of their need for noncardiac surgery.

Special Considerations

- Patients with drug-eluting coronary stents: see Perioperative Anticoagulation and Antithrombotic Management.
- Multiple studies have reported a correlation between delayed repair of hip fracture and increased morbidity and mortality (*Br Med J (Clin Res Ed) 1986;293(6556):1203*; *Clin Orthop 1984;(186):45*). For urgent surgical procedures (i.e., those that should be done within

48 hours of diagnosis), the value of additional testing is typically outweighed by the risk of worsened short- and long-term outcomes incurred with surgical delay. Unnecessary preoperative cardiac testing may be an independent risk factor for postoperative complications in hip fracture patients (*Am J Orthop 2008;37(1):32*). In such cases, it is advisable to optimize the patient's medical status and modifiable risk factors and then proceed to the operating room.

Diagnostic Testing

- **12-Lead ECG.** The value of a routine ECG is controversial. Per the 2014 ACC/AHA guidelines (level of evidence: B):
  - ECG is “reasonable” in patients with known CAD, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, or other significant structural heart disease prior to intermediate-risk surgery and above (Class IIa);
  - “May be considered” for asymptomatic patients without known coronary heart disease prior to intermediate- and high-risk surgery (Class IIb);
  - Is “not useful” for asymptomatic patients undergoing low-risk surgical procedures (Class III).
- **Resting echocardiogram**. In general, the indications for preoperative echocardiographic evaluation are no different from those in the nonoperative setting. Murmurs found on physical exam suggestive of significant underlying valvular disease (see above) should be evaluated by echocardiogram. Assessment of left ventricular function should be considered when there is clinical concern for underlying undiagnosed CHF or if there is concern for deterioration since the last exam.
- **Noninvasive stress testing.** The decision to pursue a stress evaluation should be guided by an assessment of preoperative risk as detailed above. For further details on stress testing see Chapter 4, Ischemic Heart Disease.

TREATMENT

Medications

- β-Blockers
  - Multiple studies have provided support for perioperative β-blockade in patients with or at risk for CAD undergoing noncardiac surgeries. The most pronounced benefit has been observed in high-risk patients undergoing vascular surgery where β-blocker dose was titrated to heart rate control (*J Am Coll Cardiol 2006;48:964*; *Circulation 2006;114(suppl):I344*). However, a subsequent analysis has called into question the role of dose titration (*J Am Coll Cardiol 2014 Aug 1, E-pub ahead of print*). Although reduction in perioperative cardiac events has been observed consistently, it warrants mentioning that few data support the effectiveness of perioperative β-blockade in reducing mortality.
  - According to the 2014 ACC/AHA guidelines:
    - In patients with three or more RCRI risk factors (see above) or evidence of myocardial ischemia on preoperative stress testing, starting preoperative β-blockade is reasonable (level of evidence: B).
    - β-blockade should not be started on the day of surgery, as it is at minimum ineffective and may actually be harmful (level of evidence: B).
    - Patients already taking β-blockers should be continued on their medication (level of evidence: B).

- Statins
  - Statins are believed to improve cardiovascular outcomes by enhancing endothelial function, reducing vascular inflammation, and stabilizing atherosclerotic plaque in addition to their lipid-lowering effects. Multiple trials have shown a decrease in perioperative cardiac events and/or mortality with statin use in patients undergoing vascular surgery. Moreover, a recent cohort study of statin therapy in patients undergoing intermediate-risk noncardiac, nonvascular surgery revealed a fivefold reduced risk of 30-day all-cause mortality along with a statistically significant reduction in the composite end point of 30-day allcause mortality, atrial fibrillation (AF), and nonfatal MI (*Clin Cardiol 2013;36(8):456*).
  - Per the 2014 ACC/AHA guidelines:
    - Patients currently taking statins should be maintained on therapy (level of evidence: B).
    - Patients undergoing vascular surgery, and those with risk factors undergoing intermediate risk surgery, may benefit from initiation of statin therapy perioperatively (level of evidence: B and C, respectively). Optimal dose, duration of therapy, and target low-density lipoprotein (LDL) levels for perioperative risk reduction are unclear.
- Aspirin

  For discussion, see Perioperative Anticoagulation and Antithrombotic Management.

MONITORING/FOLLOW-UP

Postoperative Infarction and Surveillance

- Most events will occur within 48-72 hours of surgery, with the majority in the first 24 hours (*CMAJ 2005;173:779*).
- Most are not heralded by chest pain and may be **clinically asymptomatic** (*Anesthesiology 1990;72:153*). Although overall 30-day mortality has been linked to postoperative troponin elevation (*JAMA 2012;307:2295*), the cause of death is not predictable, and no specific course of therapy may be offered.
- The 2014 ACC/AHA (*Circulation 2014;130;e278*) guidelines offer the following:
  - Routine postoperative ECGs and troponins are not recommended.
  - The benefit of troponin measurements and ECGs in high cardiac risk patients is uncertain.
  - Symptomatic infarctions should be addressed according to standard therapy of acute coronary syndromes (see Chapter 4, Ischemic Heart Disease). The major caveat is that bleeding risk with anticoagulants must be carefully considered.

Perioperative Anticoagulation and Antithrombotic Management

GENERAL PRINCIPLES

- Patients on chronic anticoagulation for AF, VTE, or mechanical heart valves often need to undergo procedures that pose risk of bleeding.
- The indication for anticoagulation and risk of interruption must be weighed against the risk of bleeding of the procedure (including possible neuraxial anesthesia).
- Until better research is available, decisions regarding perioperative anticoagulation will have to be made with the help of guidelines with relatively weak strength of evidence (*Chest 2012;141:326S*).

TREATMENT

- Recommended management varies according to the indication for anticoagulation, medication used, and surgical bleeding risk.

- **For patients being treated with oral anticoagulants/vitamin K antagonists (VKA):**
  - **Low bleeding risk** procedures permit continuation of **oral anticoagulation** through the perioperative period (e.g., minor dental and dermatologic procedures, cataract extraction, endoscopy without biopsy, arthrocentesis). Pacemaker and implantable cardioverter defibrillator (ICD) placement lead to less hematoma if anticoagulation is not interrupted (*N Engl J Med 2013;368:2084*).
  - **Significant bleeding risk procedures** require the anticoagulation to be discontinued.
    - Although the international normalized ratio (INR) at which surgery can be safely performed is subjective, an INR of <1.5 is typically a reasonable goal.
    - The VKA (e.g., warfarin) will typically need to be stopped 5 days preoperatively.
    - The INR should be checked the day before surgery. If a level <1.5 is not obtained, 1-2.5 mg oral vitamin K effectively achieves an INR <1.5 on the day of surgery.
    - The VKA can generally be resumed 12-24 hours postoperatively if postoperative bleeding has been controlled (*Chest 2012;141:326S*).
  - **High bleeding risk procedures** (e.g., intracranial or spinal) with potential catastrophic outcomes due to bleeding will preclude any anticoagulation in the perioperative period. Other procedures with high bleeding risk (e.g., sessile polypectomy; bowel resection; kidney, liver, or spleen biopsy; extensive orthopedic or plastic surgery) should lead to a delay of at least 48 hours prior to resumption of anticoagulation.
- **Bridging therapy** refers to the administration of an alternative anticoagulation during the time the INR is anticipated to be below the therapeutic range. The potential decrease in thrombosis must be weighed against the increased risk of bleeding (*Circulation 2012;126:1630*).
- **High thrombotic risk patients** below should typically be treated with bridging therapy.
  - Mechanical mitral valve
  - Older-generation mechanical valve (e.g., Starr-Edwards ball-in-cage valve)
  - Any mechanical valve with a history of cardioembolism within the preceding 6 months
  - Nonvalvular AF with either a history of embolism in the last 3 months or CHADS2 score ≥5 (see Chapter 7, Cardiac Arrhythmias)
  - Valvular AF
  - Recent VTE (<3 months)
  - Known thrombophilic state (e.g., protein C deficiency)
- For **moderate thrombotic risk patients** as below, bridging may be considered in patients with low bleeding risk. Deep venous thrombosis (DVT) prophylaxis dosing is acceptable.
  - Mechanical aortic valve (bileaflet) with one or more associated risk factors: AF, CHF, hypertension, age ≥75, DM, and prior CVA or TIA
  - AF with a $CHADS_2$ score of 3 or 4, or history of prior embolism
  - History of VTE within preceding 3-12 months
  - Non-high-risk thrombophilia (e.g., heterozygous factor V Leiden mutation)

- History of recurrent VTE
- Active malignancy

- **Low thrombotic risk** patients are **not** believed to require bridging therapy. Treatment with DVT prophylaxis doses of LMWH or UFH is an alternative. This group includes patients with:
  - Mechanical aortic valve (bileaflet) without associated risk factors, as above
  - Nonvalvular AF with a $CHADS_2$ score ≤2 and no history of embolism
  - Prior VTE >12 months prior (without history of recurrent VTE or known hypercoagulable state)
- **Choices for bridging therapy** are generally the LMWHs and UFH, including patients with mechanical heart valves (*Chest 2012;141:326S*). There is less experience in this setting with other agents (e.g., fondaparinux), and their use cannot be considered routine.
  - **LMWHs** have the advantages of relatively predictable pharmacokinetics and ability to be administered SC. Monitoring of anticoagulant effect is typically not required.

    Renal dosing is available for patients not on dialysis. Subcutaneous administration allows for outpatient therapy in appropriate patients. This decreases the length and cost of hospitalization. The last dose should be given 24 hours prior to surgery.
  - **UFH** is the agent of choice for patients with end-stage renal disease (ESRD). It is typically administered IV and requires frequent monitoring of the activated partial thromboplastin time. UFH should be stopped at least 4 hours prior to the planned surgical procedure to allow the anticoagulant effect to wane. Fixed-dose subcutaneous UFH has been proven efficacious for treatment of VTE and may be considered as an option (*JAMA 2006;295:1152*).
  - **Novel oral anticoagulants** have relatively short half-lives (dabigatran = 14 hours, rivaroxaban = 9 hours, apixaban = 12 hours), obviating the need for bridging anticoagulation. Agents should be held for two or three half-lives for low bleed risk procedures and three or four half-lives for high bleed risk procedures, keeping in mind the effects of renal function on clearance. Reversal agents are currently being developed.
- **Patients being treated with antiplatelet agents**
  - Continuing antiplatelet agents perioperatively also carries a risk of bleeding, whereas discontinuation may increase cardiovascular events. Irreversible agents must be withheld for 5-7 days before effects fully abate. Clinicians are again left with little evidence and sometimes conflicting guidelines.
  - **Low bleeding risk procedures** (e.g., minor dermatologic or dental procedures) allow continuation of aspirin (acetylsalicylic acid [ASA]) being given for secondary prevention of cardiovascular disease.
  - **Noncardiac surgery patients** should generally have clopidogrel (or other thienopyridines) held 5 days preoperatively. Prompt reinitiation with a loading dose of

    300 mg should take place postoperatively. Further stratification drives decisions regarding ASA:
    - **Moderate to high cardiac risk**, in which case ASA should be continued perioperatively
    - **Low cardiac risk**, in which case ASA should be held 7 days preoperatively
  - **Coronary artery bypass graft** candidates should generally continue ASA perioperatively and have clopidogrel held 5 days preoperatively.
  - **Coronary stents** pose a particular risk of in-stent thrombosis and infarction if dual antiplatelet therapy is prematurely withheld. Whenever possible, surgery should be deferred until the minimum period of dual antiplatelet therapy is completed (balloon angioplasty without stent, 14 days; drug-eluting stents,

12 months; bare metal stents, 6 weeks).

- **Urgent surgeries** within the previous time frames should proceed with continued dual antiplatelet treatment, if possible. If the bleeding risk is felt to be high, ASA alone should be continued. Heparin bridging has not been shown to be of benefit. Bridging with IV glycoprotein IIb/IIIa antagonists or reversible oral agents (e.g., ticagrelor) is not routinely recommended (*Chest 2012;141:326S*).

PERIOPERATIVE MANAGEMENT OF SPECIFIC CONDITIONS

Hypertension

GENERAL PRINCIPLES

- **Severe hypertension** (BP >180/110) preoperatively often results in wider fluctuations in intraoperative BP and has been associated with an increased rate of perioperative cardiac events (see the previous section, Preoperative Cardiac Evaluation).

- Antihypertensive agents that the patient has taken prior to admission for surgery may have an impact on the perioperative period.
  - When the patient is receiving β-blockers or clonidine chronically, withdrawal of these medications may result in tachycardia and rebound hypertension, respectively.
  - Evidence suggests that holding angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on the day of surgery may reduce perioperative hypotension. This is believed to be due to the effect of this class of medication in blunting the compensatory activation of the renin-angiotensin system perioperatively.

DIAGNOSIS

BP monitoring should be done as part of a patient's routine vital signs. A portable or wall blood pressure cuff should be used. In the setting of severe hypertension, BP should be checked in both arms and with two different types of BP cuffs in order to ensure accuracy.

TREATMENT

- Hypertension in the postoperative period is a common problem with multiple possible causes.
  - All **remediable causes of hypertension**, such as pain, agitation, hypercarbia, hypoxia, hypervolemia, and bladder distention, should be excluded or treated.
  - Poor control of essential hypertension secondary to discontinuation of medications the patient was previously taking in the immediate postoperative period is not uncommon; thus, reviewing the patient's home medication list is recommended.
  - A rare cause of perioperative hypertension is **pheochromocytoma**, particularly if its presence was unrecognized. Patients can develop an acute hypertensive crisis perioperatively which should be treated, with **phentolamine** or **nitroprusside** recommended in this situation. When the diagnosis of pheochromocytoma is suspected, preoperative treatment to minimize risk is recommended and can be classically accomplished by titration of **phenoxybenzamine** preoperatively.
- Many parenteral antihypertensive medications are available for patients who are unable to take

medications orally. Transdermal clonidine also is an option, but the onset of action is delayed.

Pacemakers and ICDs

GENERAL PRINCIPLES

- The use of electrocautery intraoperatively can have adverse effects on the function of implanted cardiac devices.
- A variety of errors can occur, from resetting the device to inadvertent discharge of an ICD.
- Complications are rare but are more likely with abdominal and thoracic surgeries.
- The type of device (i.e., pacemaker or ICD) and manufacturer should be determined.
- The initial indication for placement and the patient's underlying rhythm should be determined. Ideally, this can be determined from the history and an ECG.
- The device should be interrogated within 3-6 months of a significant surgical procedure.

TREATMENT

If the patient is pacemaker dependent, the device should be reprogrammed to an asynchronous mode (e.g., VOO, DOO) for the surgery.

- The application of a magnet will cause most pacemakers to revert to an asynchronous pacing mode; however, if this is the planned management, it should be tested preoperatively, especially in the pacemaker-dependent patient.

- It should be noted that the effect of a magnet on ICDs is typically different from the effect on pacemakers in that it affects the anti-tachycardia function but does not alter the pacing function of most models. If the pacing function of an ICD needs to be altered perioperatively, the device will need to be reprogrammed.
- The anti-tachycardia function of an ICD will typically need to be programmed off for surgical procedures in which electrocautery may cause interference with device function, leading to the potential for unintentional discharge. The effect of a magnet on this function is variable, so programming is the preferred management. Continuous monitoring for arrhythmia is essential during the period when this function is suspended.
- Continuous ECG and pulse monitoring is recommended during surgery. Pulse monitoring should not be affected by electrocautery interference.
- Postoperative interrogation may be necessary, particularly if the device settings were changed perioperatively or if the patient is pacemaker dependent.
- **Consultation with an electrophysiologist** is strongly recommended if there is any uncertainty regarding the perioperative management of a device.

Pulmonary Disease and Preoperative Pulmonary Evaluation

GENERAL PRINCIPLES

Postoperative pulmonary complications are probably more common than cardiac complications, and the occurrence of one may predispose to the other (*Am J Med 2003;115:515*; *Am J Respir Crit Care Med 2005;171:514*). Clinically significant pulmonary complications include pneumonia, bronchospasm, atelectasis,

exacerbation of underlying chronic lung disease, and respiratory failure. Postoperative respiratory failure can be a life-threatening complication, with a 30-day mortality rate as high as 26.5% (*J Am Coll Surg 2007;204:1188*).

Risk Factors

- Both patient-dependent and surgery-specific risk factors determine overall risk (*Ann Intern Med 2006;144:575*).
- Procedure-related risk factors
  - Surgical site is generally considered the greatest determinant of risk of pulmonary complications, with upper abdominal and thoracic surgeries associated with highest risk (*N Engl J Med 1999;340:937*). Neurosurgery and surgeries involving the mouth and palate also impart increased risk (*Ann Surg 2000;232:242*; *J Am Coll Surg 2007;204:1188*).
  - Duration of surgery correlates positively with risk in multiple studies (*Chest 1997;111:564*; *Acta Anaesthesiol Scand 2001;45:345*; *Am J Respir Crit Care Med 2003;167:741*).
  - Type of anesthesia may influence pulmonary risk as well. Although somewhat controversial due to conflicting data and study heterogeneity, it seems that neuraxial anesthesia affords reduced risk of pneumonia, respiratory failure, and possibly shortterm mortality in comparison to general anesthesia (*Br Med J 2000;321:1493*; *Lancet 2008;372(9638):562*).
- Patient-dependent risk factors
  - COPD has reliably been found to be a risk factor for postoperative pulmonary complications. Disease severity correlates with risk of serious complications (*Chest 1993;104:1445*). However, even patients with advanced lung disease can safely undergo surgery if deemed medically necessary (*Br Med J 1975;3:670*; *Arch Intern Med 1992;152:967*). In contradistinction to hepatic disease, there is no identified threshold that precludes surgery.
  - Interstitial lung disease likely places patients at elevated risk but is not well studied in patients undergoing general surgery (*Chest 2007;132:1637*). Well-controlled asthma

and restrictive physiology associated with obesity do not appear to be significant risk factors (*Ann Intern Med 2006;144:575*; *Br J Anaesth 2009;103(1):i57*).
  - Pulmonary hypertension is associated with significant morbidity in patients undergoing surgery (*J Am Coll Cardiol 2005;45:1691*; *Br J Anaesth 2007;99:184*).
  - Data from the systematic review that formed the basis for the American College of Physicians guideline regarding pulmonary risk stratification for noncardiothoracic surgery suggest that heart failure may increase the risk of pulmonary complications to a greater degree than that seen with COPD (pooled adjusted odds ratios 2.93 and 2.36, respectively) (*Ann Intern Med 2006;144:581*).
  - Poor general health status is associated with increased perioperative pulmonary risk. Multiple indices of general health status including degree of functional dependence and American Society of Anesthesiologists class have been linked to poor pulmonary outcomes (*Ann Intern Med 2006;144:581*). Odds ratios for postoperative respiratory failure of 2.53 and 2.29 were observed for hypoalbuminemia (<3 g/dL) and azotemia (BUN >30 mg/dL), respectively, in a large cohort (*Ann Surg 2000;232:242*).
  - The above-mentioned systematic review for the American College of Physicians identified age >50 years as an independent predictor of postoperative pulmonary complications after adjustment for age-related comorbidities; risk was noted to increase linearly with increasing age. Large observational studies informing

risk prediction models currently in use (see below) have further validated this observation, in contrast to postsurgical cardiac risk.

- Smoking is a well-established risk factor for both postoperative pulmonary and nonpulmonary complications (*Ann Surg 2014;259:52*). As with malignancy, risk appears to be dose-dependent and associated with active use (*Chest 1998;113(4):883*; *Am J Respir Crit Care Med 2003;167:741*).
- Obstructive sleep apnea (OSA) is increasingly being recognized as a risk factor for perioperative complications, both pulmonary and cardiac (*Chest 2008;133:1128*). A meta-analysis showed that OSA increased the odds of various postoperative complications by a factor of 2-4 (*Br J Anaesth 2012;109:897*); the most frequent pulmonary complication appears to be hypoxemia (*Anesthesiology 2008;108:822*). Unrecognized sleep apnea may pose an even greater risk (*Mayo Clin Proc 2001;76:897*). It is estimated that over half of patients with OSA presenting for surgery are undiagnosed (*Br J Anaesth 2013;110:629*; *Sleep Med 2013;14:407*).

DIAGNOSIS

Clinical Presentation

History

Preoperative pulmonary evaluation should focus on the above-mentioned patient-dependent risk factors.

- Any history of lung disease should be elucidated. If chronic lung disease is present, an effort should be made to determine the patient's baseline and whether there has been any recent deterioration, such as increased cough, wheezing, or sputum production.
- Symptoms of current upper respiratory tract infection should be ascertained. Although not an absolute contraindication to surgery, it seems prudent to postpone purely elective procedures until such infections have resolved.
- A full smoking history should be obtained.
- Patients should be questioned regarding symptoms potentially consistent with OSA (snoring, daytime somnolence, observed apneas). See the section on Obstructive Sleep Apnea-Hypopnea Syndrome in Chapter 10.
- As myriad nonpulmonary comorbidities impact the likelihood of pulmonary complications (as delineated previously), a complete medical history is vital.

Physical Examination

- Body mass index (BMI) should be calculated. Although obesity itself is not associated with postoperative pulmonary complications, prevalence of OSA increases with increasing BMI. Uncontrolled hypertension may also suggest undiagnosed sleep apnea. Measurement of oxygen saturation by pulse oximetry assists in risk stratification (*Anesthesiology 2010;113:1338*).
- A Mallampati score should be determined. A study of 137 adults being evaluated for OSA found that every 1-point increase in the Mallampati score increased the odds of OSA by 2.5 (95% confidence interval 1.2-5.0) (*Sleep 2006;29:903*).
- Attention should be paid to evidence of chronic lung disease such as increased anteroposterior dimension of the chest, digital clubbing, and the presence of adventitious lung sounds (see Chapter 9, Obstructive Lung Disease, and Chapter 10, Pulmonary Diseases). Persistent coughing after a voluntary cough is also a marker of increased risk (*Am J Respir Crit Care Med 2003;167:741*).
- Again, signs of decompensated heart failure (see the section on Preoperative Cardiac Evaluation in this

chapter, and Chapter 5, Heart Failure and Cardiomyopathy) should be actively sought.

Risk Stratification

Several risk indices have been developed for quantitating risk of postoperative respiratory failure (defined here as failure to wean from mechanical ventilation within 48 hours of surgery) or pneumonia (*Ann Surg 2000;232:242*; *Chest 2011;140:1207*; *Mayo Clin Proc 2013;88:1241*). The Arozullah respiratory failure index was based on multivariate analysis of a cohort of 81,719 patients and validated on another 99,390 patients. It offers the advantage of manual calculation at the bedside. The Gupta calculators for postoperative pneumonia and respiratory failure are derived from a data set of 211,410 patients and validated on another 257,385. Although considerably more complicated than the Arozullah index, these calculators are accessible online and may be downloaded for free.

Diagnostic Testing

- **Pulmonary function tests (PFTs)**

  The value of preoperative PFTs is debatable outside of lung resection surgery, where its role is relatively well defined (see the section on Chronic Obstructive Pulmonary Disease in Chapter 9, and the section on Lung Cancer in Chapter 22). In other surgical contexts, measurements gleaned from PFTs either fail to predict pulmonary complications or add little beyond what can be gathered clinically (*Chest 1997;111:1536*). Although routine PFTs do not appear warranted per the current guidelines (*Ann Intern Med 2006;144:575*), they should be considered for patients with unexplained dyspnea or exercise intolerance or for patients with known lung disease and an unclear baseline.

- **Arterial blood gas (ABG) analysis**

  No data exist that suggest that ABG results contribute to preoperative pulmonary risk estimation beyond other clinically derived variables as discussed earlier. Nevertheless, an ABG should be obtained when otherwise indicated; for example, to determine if a patient's lung disease is compensated (see the section on Respiratory Failure in Chapter 8).

- **Chest radiography**

  In general, a chest radiograph is recommended only if otherwise indicated (e.g., for evaluation of unexplained dyspnea). Many findings deemed abnormal are chronic and do not alter management (*Can J Anesth 2005;52:568*).

TREATMENT

Treatment should be focused on modifiable patient-related and procedure-related risk factors.

- The effect of preoperative smoking cessation on pulmonary complications has been largely described in cardiothoracic surgeries, where a benefit to quitting smoking at least

  2 months prior to surgery has been shown (*Mayo Clin Proc 1989;64:609*). The effect on a general surgical population is less clear, because most of the observed benefit in this latter group relates to improvements in nonpulmonary outcomes, such as fewer wound complications (*Ann Surg 2008;248:739*). Nevertheless, given the long-term benefits of smoking cessation, all patients should be counseled to stop smoking even if <8 weeks from surgery. Previous concerns about a paradoxical increase in complications appear unfounded (*Arch Intern Med 2011;171(11):983*).

- COPD and asthma therapy should be optimized (see Chapter 9, Obstructive Lung Disease). Nonemergent surgery may need to be postponed to allow recovery of pulmonary function to baseline.

- OSA should be treated prior to elective high-risk surgery when possible. Data in the preoperative setting are limited, but in a recent open-label trial, patients with moderate OSA who were randomized to auto-titrated continuous positive airway pressure treatment had improved postoperative oxygen saturation and markedly decreased apnea-hypopnea indices compared with control patients, even despite observed low compliance (*Anesthesiology 2013;119:837*).
- Alternative procedures with reduced pulmonary risk should be considered for high-risk patients if feasible. Laparoscopic procedures may yield fewer pulmonary complications (*Br J Anaesth 1996;77:448*; *Ann Intern Med 2006;144:581*); regional nerve block also appears to be associated with decreased risk (*Am Rev Respir Dis 1979;119:293*). If general anesthesia is absolutely necessary, duration should be minimized to the degree possible.

Anemia and Transfusion Issues in Surgery

GENERAL PRINCIPLES

- Transfusion-associated risks include transmission of blood-borne infections, transfusionrelated acute lung injury, transfusion reactions, and immunosuppressive effects.
- Preoperative anemia is present in 5-35% of patients depending on the definition of anemia and type of surgery studied (*Lancet 2011 Oct 15;378(9800):1396-407*).

DIAGNOSIS

- A history of anemia, hematologic disease, or bleeding diathesis should be noted on history or review of medical records.
- Any clinical signs of anemia (e.g., pallor) or coagulopathy (e.g., petechiae) should prompt further evaluation.
- There is no standardized preoperative evaluation for anemia.
  - For low-risk procedures, there is no evidence that routine testing of asymptomatic individuals before low-risk procedures increases safety (*Ann Surg 2012;256(3):518-28*).
  - For higher risk procedures, particularly those with higher bleeding risk, a baseline CBC and coagulation profile are typically obtained. Further testing should be performed as indicated.

TREATMENT

Volume resuscitation and control of active bleeding are the initial therapy of anemia, particularly in the perioperative period when acute blood loss is a common occurrence.

- Guidelines for perioperative blood transfusions are variable.
- Preoperative anemia, hematocrit <39% in men and <36% in women, is independently associated with an increase in 30-day morbidity/mortality risk. (*Lancet 2011 Oct 15;378(9800)*).

- Postoperatively, in a cohort of patients who refused transfusion, no mortality was observed for hemoglobin >7 g/dL. A marked increase in risk was seen at hemoglobin <5 g/dL threshold (*Transfusion 2002;42:812*).
- The benefit of transfusion at physiologically tolerable levels of anemia is unclear.

- The TRICC trial, a study of intensive care unit patients, showed no mortality difference between transfusion thresholds of hemoglobin <7 g/dL or <10 g/dL. Subgroup analysis showed improved mortality in younger, less critically ill patients when using transfusion threshold of hemoglobin <7 g/dL. (*N Engl J Med 1999;336:933*). The applicability of this study to the perioperative setting is uncertain.
- The FOCUS trial showed no mortality difference between a restrictive (hemoglobin <8 g/dL) and liberal (hemoglobin <10 g/dL) transfusion threshold in high-risk (known or have risk factors for cardiovascular disease) patients after hip surgery (*N Engl J Med 2011;365(26):2453-2462*).
- In general, no transfusion is indicated for hemoglobin >10 g/dL in a stable patient.
- In stable patients, transfusion may be considered at hemoglobin of 7-8 g/dL.
- In stable patients with cardiovascular disease, a transfusion threshold of 8 g/dL should be utilized.
- In patients with concern for active cardiac ischemia, transfusions may be indicated to achieve a hemoglobin of 8-10 g/dL, but there is no consistent recommendation.

Other Nonpharmacologic Therapies

Measures to reduce the need for allergenic blood should be utilized where feasible.

- Preoperative autologous blood donation should be considered for elective procedures where the anticipated need for transfusion is high.
- Preoperative erythropoietin is generally not indicated, but can be considered in patients who may refuse blood products due to personal or religious reasons (*Transfusion 1994; 34(1):66*).
- Avoidance of perioperative hypothermia may also limit blood loss, and thereby decrease transfusion requirements (*Anesthesiology 2008;108:71*).

SPECIAL CONSIDERATIONS

Patients with sickle cell anemia should generally be transfused to a hemoglobin of 10 g/dL preoperatively to decrease the incidence of complications (*Lancet 2013;381:930*).

Liver Disease

GENERAL PRINCIPLES

- Patients with hepatic dysfunction face an increased risk of morbid outcomes when undergoing surgery and may develop acute hepatic decompensation postoperatively.
- The myriad systemic effects of hepatic dysfunction result in an increased frequency of other complications as well, such as bleeding and infection.

Classification

- Both Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores (see Chapter 19, Liver Diseases) are well-validated statistical models for predicting surgical risk.
- A large review of patients undergoing a variety of surgical procedures clearly identified a demarcation between CTP class A (score <7) and those with class B and C disease (*Anesthesiology 1999;90:42*). The 30-day mortality was 9.4% in the CTP class A group versus 16.7% in classes B and C group combined. Other complications were also significantly more common.

- Patients with CTP class C disease have particularly elevated operative risk; perioperative mortality exceeds 80% with abdominal surgery in this group (*Surgery 1997;122:730*).
- The 30-day mortality correlated linearly with the MELD score in a study of 772 cirrhotic patients who underwent major digestive, orthopedic, or cardiovascular surgery (*Gastroenterology 2007;132:1261*). MELD score >20 predicted >50% mortality.
- The superiority of either model as a nontransplant surgical risk predictor is a subject of continuing debate. It has been suggested that patients with CTP class A or MELD <10 cirrhosis can safely undergo elective surgery, those with class B or MELD of 10-15 may undergo elective surgery with caution, and those with class C or MELD >15 should not undergo elective surgery (*Natl Clin Pract Gastroenterol Hepatol 2007;4:266*).

DIAGNOSIS

Clinical Presentation

History

Historical details suggesting risk for hepatic disease (e.g., alcohol/drug use, prior blood transfusion, family history of cirrhosis) should be elicited.

Physical Examination

Findings potentially consistent with liver dysfunction should be noted. Some should be obvious, such as icterus and abdominal distention with ascites, but other abnormalities such as spider nevi, palmar erythema, and testicular atrophy may be more subtle.

Diagnostic Testing

- Because significant disease is usually clinically manifest, routine laboratory screening for hepatic dysfunction in patients presenting for surgery is not recommended (*Med Clin North Am 2003;87:211*).
- Patients with known or suspected liver disease should undergo a thorough evaluation of liver function including hepatic enzyme levels, albumin and bilirubin measurements, and evaluation for coagulopathy.
- Renal function, including electrolytes, blood urea nitrogen (BUN), and creatinine measurements, should also be evaluated.

TREATMENT

- Patients with acute viral or alcoholic hepatitis tolerate surgery poorly, and delaying surgery until recovery is recommended if possible.
- Patients with chronic hepatitis without evidence of hepatic decompensation generally tolerate surgery well.
- Based on the aforementioned high perioperative mortality rates in patients with advanced cirrhosis, nonoperative alternatives should be strongly considered.
- For patients who do require surgery, steps should be taken to optimize preoperative status:
  - Coagulopathy should be corrected to the degree possible.
    - Vitamin K should be administered if the INR is elevated. However, as the coagulopathy may prove refractory to this measure in the setting of impaired hepatic synthetic function, fresh frozen plasma and/or cryoprecipitate may ultimately be required.
    - Thrombocytopenia also is a common finding and should be corrected if severe. The general recommendation for most surgical procedures is a minimum platelet count of 50,000. However,

coexisting platelet dysfunction due to liver disease should be considered, particularly if there is clinical evidence of bleeding.

- Renal and electrolyte abnormalities should be addressed and careful attention should be paid to volume status.
  - Nephrotoxic agents, such as NSAIDs and aminoglycosides, should be avoided.
  - Patients with cirrhosis often have hypokalemia and alkalosis. These conditions should be corrected preoperatively to minimize the risk of cardiac arrhythmias and to limit encephalopathy.
  - If hyponatremia develops, free water restriction may be required.
  - Ascites should be treated. Ascites has been found to be an independent risk factor for postoperative pulmonary complications (*J Am Coll Surg 2007;204:1188*). If time permits, diuretic therapy should be instituted. Paracentesis should be considered preoperatively if diuretics are ineffective or if circumstances prevent their use.
- Encephalopathy should be treated aggressively.
  - Lactulose titrated to two to three soft bowel movements per day should be started in patients with encephalopathy.
  - Protein restriction has been recommended for individuals who respond poorly to lactulose, but this should be done cautiously because excessive restriction may actually contribute to malnutrition.
  - Sedatives and opioids can precipitate or worsen encephalopathy. They should be used sparingly, and dose reductions should be considered.
- Adequate nutrition should be provided. Malnutrition often accompanies advanced cirrhosis, and deficiencies of fat-soluble vitamins and electrolytes are not uncommon in the context of chronic cholestasis and alcohol abuse, respectively.

Diabetes Mellitus

GENERAL PRINCIPLES

- Medical and surgical patients with hyperglycemia are at increased risk for poor outcomes (*J Clin Endocrinol Metab 2002;87:978*).
- Poor preoperative glucose control, as indicated by elevated hemoglobin A1C levels, is associated with an increased risk of surgical infections (*Arch Surg 2006;141:375*). Hyperglycemia postoperatively also appears to be associated with an increased risk of postoperative infection (*JPEN J Parenter Enteral Nutr 1998;22:77*).
- There is some suggestion, particularly in patients undergoing cardiothoracic surgery, that more aggressive medical management of hyperglycemia mitigates the risk of infection and possibly mortality (*Ann Thorac Surg 1997;63:356*; *J Thorac Cardiovasc Surg 2003;125:1007*).
- The fact that hyperglycemia is a marker for poor outcomes appears to be relatively clear. However, whether aggressive management truly improves outcomes is uncertain. Trial results have been mixed.
  - In a population of mostly surgical patients requiring critical care, impressive reductions in mortality were demonstrated in a single institution study (*N Engl J Med 2001;345:1359*). The results of this trial prompted widespread adoption of aggressive insulin protocols in surgical intensive care units.
  - However, a recent larger multicenter trial of both surgical and medical critical care patients was unable to

show improvements in outcome and actually found a slight increase in risk with aggressive treatment of hyperglycemia (*N Engl J Med 2009;360:1283*).

- Diabetics are at **increased risk for cardiovascular disease**. Appropriate risk stratification for cardiac complications of surgery is vital to the perioperative evaluation of these patients.

Classification

- Establishing the etiology of hyperglycemia has important implications for subsequent patient care.
  - **Stress hyperglycemia** can occur in the perioperative setting because of the body's response to surgery with the release of counterregulatory hormones and cytokines that impede glucose metabolism. These patients need adequate glucose control during the perioperative period but are unlikely to require such treatment later.
  - Type 2 diabetes is notoriously underdiagnosed, and the notation of perioperative hyperglycemia may be the first indication of its presence.
- It is essential to distinguish between type 1 and type 2 diabetes mellitus.
  - **Type 1 diabetics** will require a continuous supply of insulin regardless of glucose level and oral intake.
  - The insulin requirement, if any, of **type 2 diabetics** during the perioperative period will vary.

DIAGNOSIS

- A **hemoglobin A1C** level should be obtained.
  - This can assist in differentiating perioperative stress hyperglycemia from undiagnosed diabetes.
  - Knowledge of recent glycemic control in known diabetics also is helpful in determining what therapy is required.
- Evaluating **renal function** also is recommended given the increased prevalence of renal disease in diabetics.
- Cardiovascular risk stratification may require other evaluations (see the previous section, Preoperative Cardiac Evaluation).

TREATMENT

- Elective surgery in patients with uncontrolled diabetes mellitus should preferably be scheduled after acceptable glycemic control has been achieved.
- If possible, the operation should be scheduled for early morning to minimize prolonged fasting.
- Frequent monitoring of blood glucose levels is required in all situations.
- **Type 1 diabetes**
  - Some form of basal insulin is required at all times.
  - On the evening prior to surgery, the regularly scheduled basal insulin should be continued. If taken in the morning, it is still recommended to give the regularly scheduled basal insulin without dose adjustment (*Diabetes Care 2004;27:553*). However, patients who are very tightly controlled may be at increased risk for hypoglycemia and will need to be monitored closely. A decrease in the last

preoperative basal insulin dose may be considered in this circumstance.

- Glucose infusions (e.g., D5-containing fluids) can be administered to avoid hypoglycemia while the patient is NPO and until tolerance of oral intake postoperatively is established.
- For complex procedures and procedures requiring a prolonged NPO status, a continuous insulin infusion will likely be necessary.
- **Caution should be exercised with the use of subcutaneous insulin** in the intraoperative and critical care settings, as alterations in tissue perfusion may result in variable absorption.

- **Type 2 diabetes**
  - Treatment of type 2 diabetics varies according to their preoperative requirements and the complexity of the planned procedure (*Med Clin North Am 2003;87:175*).

  - Consideration should be given to the efficacy of the patient's current regimen. If the patient is not well controlled at baseline, then an escalation in therapy may be required.
    - **Diet-controlled type 2 diabetes** can generally be managed without insulin therapy. Glucose values should be checked regularly and elevated levels (>180 mg/dL) can be treated with intermittent doses of short-acting insulin.
    - **Type 2 diabetes managed with oral therapy**

      Short-acting sulfonylureas and **other oral agents** should be withheld on the operative day.

      Metformin and **long-acting sulfonylureas** (e.g., chlorpropamide) should be with-held 1 day before planned surgical procedures. Metformin is generally held for 48 hours postoperatively provided there is no acute renal injury. Other oral agents can be resumed when patients are tolerating their pre-procedure diet.

      Most patients can be managed without an insulin infusion.

      Glucose values should be checked regularly and elevated levels (>180 mg/dL) can be treated with intermittent doses of short-acting insulin.

    - **Type 2 diabetes managed with insulin**

      If it is anticipated that the patient will be able to eat postoperatively, basal insulin is still given on the morning of surgery.

      If given as long-acting insulin (e.g., glargine insulin) and the patient usually takes the dose in the morning, 50-100% of the usual dose can be given.

      If the patient utilizes intermediate-acting insulin (e.g., NPH), one-half to two-thirds of the usual morning dose is given to avoid periprocedural hyperglycemia.

      Dextrose-containing IV fluids may be required to avoid hypoglycemia.

      Patients undergoing major procedures will typically require an insulin drip perioperatively.

      The usual insulin treatment can be reintroduced once oral intake is established postoperatively.

- **Target glucose levels**
  - There are no generally agreed-upon target glucose levels applicable to the entire postsurgical population.
    - Earlier literature recommends aggressive glucose control in the critical care setting (*Diabetes Care 2008;31S:S12*; *N Engl J Med 2009;360:1283-1297*).
    - In a general medical-surgical population, recurring glucose values >200 mg/dL were associated with

a poor outcome (*J Clin Endocrinol Metab 2002;87:978*).

- Pending further research, a goal of maintaining glucose levels <180 mg/dL in the postoperative setting seems reasonable. It should be noted that this may still require intensive treatments such as insulin infusion.
- In patients treated with sliding scale insulin, it is essential to monitor the response to therapy. Patients who are hyperglycemic consistently are unlikely to have adequate glucose control with intermittent treatment alone, and a basal/bolus regimen should be introduced if hyperglycemia is persistent (*Diabetes Care 2007;30:2181*).

Adrenal Insufficiency and Corticosteroid Management

GENERAL PRINCIPLES

- Surgery is a potent activator of the hypothalamic-pituitary axis, and patients with adrenal insufficiency may lack the ability to respond appropriately to surgical stress.
- Patients receiving corticosteroids as anti-inflammatory therapy may rarely develop postoperative adrenal insufficiency. Case reports of presumed adrenal insufficiency from the 1950s led to the widespread use of perioperative "stress-dose" steroids in this population (*JAMA 1952;149:1542*; *Ann Intern Med 1953;39:116*).

- The dose and duration of exogenous corticosteroids required to produce clinically significant tertiary adrenal insufficiency is highly variable, but general principles can be outlined (*Med Clin North Am 2003;87:175*).
  - Daily therapy with 5 mg or less of prednisone (or its equivalent), alternate-day corticosteroid therapy, and any dose given for <3 weeks should not result in clinically significant adrenal suppression.
  - Patients receiving >20 mg/d prednisone (or equivalent) for >3 weeks and patients who are clinically "cushingoid" in appearance can be expected to have significant suppression of adrenal responsiveness.
  - The function of the hypothalamic-pituitary axis cannot be readily predicted in patients receiving doses of prednisone 5-20 mg for >3 weeks.

DIAGNOSTIC TESTING

Cosyntropin stimulation test may also be performed to determine adrenal responsiveness, measuring cortisol levels at 30 minutes after 250 µg of cosyntropin. This can be done any time of day and there is no need for baseline cortisol. Levels >18 µg/dL at 30 minutes generally suggest an intact hypothalamic-pituitary axis.

TREATMENT

- If there is concern for secondary adrenal insufficiency, it is reasonable **to simply continue to provide baseline steroid supplementation** perioperatively (*Arch Surg 2008; 143:1222*). It may be prudent to switch to an IV formulation to ensure it is not withheld while the patient is NPO.
- For patients with primary adrenal insufficiency, a stress stratification scheme has been developed, based on expert opinion. Please refer to Chapter 24, Endocrine Diseases, for details of treatment.

Chronic Renal Insufficiency and ESRD

GENERAL PRINCIPLES

- **Chronic renal insufficiency (CRI)** is an independent risk factor for **perioperative cardiac complications**, so all patients with renal disease need appropriate cardiac risk stratification (*JAMA 2001;285:1865*).
- **Patients with ESRD** have a substantial mortality risk when undergoing surgery (*Arch Intern Med 1994;154:1674*).
- Most general anesthetic agents have no appreciable nephrotoxicity or effect on renal function other than that mediated through hemodynamic changes (*Anesthesiol Clin 2006;24:523*).

TREATMENT

- **Volume status**
  - Every effort should be made to **achieve euvolemia** preoperatively to reduce the incidence of volume-related complications intraoperatively and postoperatively (*Med Clin North Am 2003;87:193*).
  - Although this typically entails removing volume, some patients may be hypovolemic and require hydration.

  - Patients with CRI not receiving hemodialysis may require treatment with loop diuretics.
  - Patients being treated with **hemodialysis** should undergo dialysis preoperatively, which is commonly performed on the day prior to surgery. Hemodialysis can be performed on the day of surgery as well, but the possibility should be considered that transient electrolyte abnormalities and hemodynamic changes post dialysis can occur.
- **Electrolyte abnormalities**
  - **Hyperkalemia** in the preoperative setting should be treated, particularly because tissue breakdown associated with surgery may elevate the potassium level further postoperatively.
    - For patients on dialysis, preoperative dialysis should be utilized.
    - For patients with CRI not undergoing dialysis, alternative methods of potassium excretion will be necessary.

      Loop diuretics can be utilized, particularly if the patient is also hypervolemic.

      Sodium polystyrene sulfonate (SPS) resins can also be utilized. The possibility that **intestinal necrosis** with SPS resins occurs more frequently in the perioperative setting has been suggested (*Am J Kidney Dis 1992;20:159*).
  - Although chronic **metabolic acidosis** has not been associated with elevated perioperative risk, some local anesthetics have reduced efficacy in acidotic patients. Preoperative metabolic acidosis should be corrected with sodium bicarbonate infusions or dialysis.
- **Bleeding diathesis**
  - **Platelet dysfunction** has long been associated with uremia.
    - The value of a preoperative bleeding time in predicting postoperative bleeding has been questioned (*Blood 1991;77:2547*). A preoperative bleeding time is, therefore, not recommended.
    - Patients with evidence of perioperative bleeding should, however, be treated.

      Dialysis for patients with ESRD will improve platelet function.

      Desmopressin (0.3 μg/kg IV or intranasally) can be utilized.

      Cryoprecipitate, 10 units over 30 minutes IV, is an additional option.

In patients with coexisting anemia, **red blood cell transfusions** can improve uremic bleeding.

For patients **with a history of prior uremic bleeding**, preoperative desmopressin or **conjugated estrogens** (0.5 mg/kg/d IV for 5 days) should be considered.

- **Heparin** given with dialysis can increase bleeding risk. Heparin-free dialysis should be discussed with the patient's nephrologist when surgery is planned.

Acute Renal Failure

GENERAL PRINCIPLES

Surgery has been associated with an increased risk of **acute renal failure (ARF)** (*Med Clin North Am 2003;87:193*).

- Patients with **CRI** are at increased risk of ARF.
- ARF among patients with normal preoperative renal function is a relatively rare event but is associated with increased mortality when it occurs (*Anesthesiology 2007; 107:892*).

DIAGNOSIS

- The approach to ARF in the perioperative setting is not substantially different from that in the nonoperative setting (see Chapter 13, Renal Diseases).

- However, certain additional factors have to be considered when evaluating the cause in the perioperative setting:
  - **Intraoperative hemodynamic changes**, particularly hypotension, should be considered.
    - Intraoperative factors associated with ARF postoperatively include vasopressor use and diuretic use (*Anesthesiology 2007;107:892*).
    - A careful review of the operative record is advised.
  - Certain procedures can have an adverse effect on the renal function (e.g., aortic clamping procedures). Therefore, careful attention to the details of the procedure is necessary.
  - The possibility that bleeding is responsible for a prerenal state deserves special attention.

TREATMENT

For a detailed discussion regarding the management of acute renal failure, please refer to Chapter 13, Renal Diseases.

2
Nutrition Support

Dominic Reeds

Peter H. Yen

Nutrient Requirements

GENERAL PRINCIPLES

- **Energy**
  - **Total daily energy expenditure** (TEE) is composed of resting energy expenditure (normally ˜70% of TEE), the thermic effect of food (normally ˜10% of TEE), and energy expenditure of physical activity (normally ˜20% of TEE).
  - It is impossible to determine **daily energy requirements** precisely with predictive equations because of the complexity of factors that affect metabolic rate. Judicious use of predictive equations can provide a reasonable estimate that should be modified as needed based on the patient's clinical course.
  - **Malnutrition** and **hypocaloric feeding** may decrease resting energy expenditure to values 15-20% below those expected for actual body size, whereas metabolic stressors, such as inflammatory diseases or trauma, often increase energy requirements (usually by ˜50% of pre-illness values).
  - The **Harris-Benedict equation** provides a reasonable estimate of resting energy expenditure (in kilocalories [kcal] per day) in healthy adults. The equation takes into account the effect of body size and lean tissue mass (which is influenced by gender and age) on energy requirements and can be used to estimate total daily energy needs in hospitalized patients:
    - Men = 66 + (13.7 × *W*) + (5 × *H*) - (6.8 × *A*)
    - Women = 665 + (9.6 × *W*) + (1.8 × *H*) - (4.7 × *A*) where *W* is the weight in kilograms, *H* the height in centimeters, and *A* is the age in years (*Publication No. 279. Carnegie Institute of Washington. Philadelphia: JB Lippincott, 1919:223*).
  - Energy requirements per kilogram of body weight are inversely related to body mass index (BMI) (Table 2-1). The lower range within each category should be considered in insulin-resistant, critically ill patients unless they are depleted in body fat.
  - **Ideal body weight** can be estimated based on height:
    - For men: 106 lb + 6 lb for each inch over 5 ft
    - For women, 100 lb + 5 lb for each inch over 5 ft
- **Protein**
  - Protein intake of 0.8 g/kg/d meets the requirements of 97% of the adult population.
  - Protein requirements are affected by several factors, such as the amount of nonprotein calories provided, overall energy requirements, protein quality, the patient's baseline nutritional status, and the presence of metabolic stressors (Table 2-2).
  - Inadequate amounts of any of the essential amino acids result in inefficient utilization.
  - Illness increases the efflux of amino acids from skeletal muscle; however, increasing protein intake to >1.2 g/kg/d of prehospitalization body weight in critically ill patients may not reduce the loss of lean body mass (*Crit Care Med 1998;26(9):1529*).
- **Essential fatty acids**
  - The liver can synthesize most fatty acids, but humans lack the desaturase enzyme needed to produce the ω-3 and ω-6 fatty acid series. Therefore, linoleic acid should constitute at least 2% and linolenic acid at least 0.5% of the daily caloric intake to prevent essential fatty acid deficiency.

TABLE 2-1 Estimated Energy Requirements for Hospitalized Patients Based on Body Mass Index

Body Mass Index (kg/m^2)	Energy Requirements (kcal/kg/d)
15	35-40
15-19	30-35
20-24	20-25

25-29	15-20
≥30	<15

Note: These values are recommended for critically ill patients and all obese patients; add 20% of total calories in estimating energy requirements in non-critically ill patients.

- The plasma pattern of increased triene-to-tetraene ratio (>0.4) can be used to detect essential fatty acid deficiency.
- Patients who are unable to receive IV or oral lipid solutions may receive a daily topical application of 1 tbsp of safflower oil to provide essential fatty acids.

- **Carbohydrates**

  Certain tissues, such as bone marrow, erythrocytes, leukocytes, renal medulla, eye tissues, and peripheral nerves, cannot metabolize fatty acids and require glucose (˜40 g/d) as a fuel. Endogenous protein and glycerol from lipid stores can undergo gluconeogenesis to supply glucose-requiring organs.

- **Major minerals**

  Major minerals are important for ionic equilibrium, water balance, and normal cell function.

- **Micronutrients (trace elements and vitamins)**

  Trace elements and vitamins are essential constituents of enzyme complexes. The recommended dietary intake for trace elements, fat-soluble vitamins, and water-soluble vitamins is set at 2 standard deviations above the estimated mean so that it will cover the needs of 97% of the healthy population. See Table 2-3 for specifics regarding the assessment of micronutrient nutritional states as well as signs and symptoms of micronutrient deficiency and toxicity.

TABLE 2-2 Recommended Daily Protein Intake

Clinical Condition	Protein Requirements (g/kg IBW/d)[a]
Normal	0.8
Metabolic stress (illness/injury)	1.0-1.5
Acute renal failure (undialyzed)	0.8-1.0
Hemodialysis	1.2-1.4
Peritoneal dialysis	1.3-1.5

IBW, ideal body weight.

[a]Additional protein intake may be needed to compensate for excess protein loss in specific patient populations such as those with burn injury, open wounds, and protein-losing enteropathy or nephropathy. Lower protein intake may be necessary in patients with chronic renal insufficiency who are not treated by dialysis and certain patients with hepatic encephalopathy.

P.35
P.36
P.37
P.38
P.39
P.40
P.41
P.42
P.43

TABLE 2-3 Trace Minerals, Fat-Soluble Vitamins, and Water-Soluble Vitamins: Recommended Daily Intake, Deficiency, At-Risk Populations, Toxicity, and Status Evaluation

	Recommended Daily Enteral

Nutrient	Intake[1] *Parenteral Intake*[2]	Signs and Symptoms of Deficiency[4]	Populations At Risk for Deficiency[1,4]	Signs and Symptoms of Toxicity[4]	Status Evaluation[4,5]
Chromium (Cr^{3+})	30-35 µg/***10-15 µg***	Glucose intolerance, peripheral neuropathy[a]	None[a,4]	PO: gastritis IV: skin irritation Cr^{6+}: (steel, welding) lung carcinogen if inhaled	$Chromium_s$
Copper (Cu^{2+})	900 µg/***300-500 µg***	Hypochromic normocytic or macrocytic anemia (rarely microcytic), neutropenia, thrombocytopenia, diarrhea, osteoporosis/pathologic fractures[a] Intrinsic: Menkes disease[18]	Chronic diarrhea, high-zinc/low-protein diets[7,8]	PO: gastritis, nausea, vomiting, coma, movement/neurologic abnormalities, hepatic necrosis Intrinsic: Wilson disease	$Copper_{s,u}$ $Ceruloplasmin_p$
Iodine (I^-)	150 µg/***70-140 µg (not routinely added)***	Thyroid hyperplasia (goiter) + functional hypothyroidism Intrinsic in utero: cretinism, poor CNS development, hypothyroidism	Those without access to fortified salt, grain, milk, or cooking oil[11]	Deficiency: causes hypothyroidism Excess: acutely causes hypothyroidism; chronic excess: hyperthyroidism	TSH_s, $iodine_u$ (24-hour intake and iodine: Cr ratio are more representative than a single sample) $Thyroglobulin_s$[13]
Iron ($Fe^{2+,3+}$)	8 mg/***1.0-1.5 mg (not routinely added)***	Fatigue, hypochromic microcytic anemia, glossitis, koilonychia	Reproductive age females, pregnant females, chronic anemias, hemoglobinopathies, post-gastric bypass/duodenectomy, alcoholics	PO or IV: hemosiderosis, followed by deposition in liver, pancreas, heart, and glands Intrinsic: Hereditary hemochromatosis	$Ferritin_s$, $TIBC_s$, % $transferrin\ saturation_c$, $iron_s$
Manganese (Mn^{2+})	2.3 mg/***60-100 µg***	Hypercholesterolemia, dermatitis, dementia, weight loss[b]	Chronic liver disease, iron-deficient populations	PO: None[b] Inhalation: hallucination, Parkinsonian-type symptoms[9]	No reliable markers $Manganese_s$ does not reflect bodily stores, especially in the CNS
Selenium (SeO_4^{2-})	55 µg/***20-60 µg***	Myalgias, cardiomyopathy[a] Intrinsic: Keshan disease (Chinese children), Kashin-Beck disease, myxedematous endemic cretinism	Endemic areas of low soil content include certain parts of China and New Zealand[13]	PO: Nausea, diarrhea, AMS, irritability, fatigue, peripheral neuropathy, hair loss, white splotchy nails, halitosis (garlic-like odor)	$Selenium_s$, $glutathione\ peroxidase\ activity_b$
Zinc (Zn^{2+})	11 mg/***2.5-5.0 mg***	Poor wound healing, diarrhea (high fistula risk), dysgeusia, teratogenicity, hypogonadism, infertility, acro-oroficial skin lesions (glossitis, alopecia), behavioral changes	Chronic diarrhea, cereal-based diets, alcoholics, chronic liver disease, sickle cell, HIV, pancreatic insufficiency/any intestinal malabsorptive states, fistulas/ostomies,	PO: Nausea, vomiting, gastritis, diarrhea, low HDL, gastric erosions Competition with GI absorption can precipitate Cu^{2+} *deficiency* Inhaled: Hyperpnea,	$Zinc_{s,p}$, $alkaline\ phosphatase_s$ (good for those on TPN, but in general $Zinc_{s,p}$ hair, RBC, WBC levels can be misleading) Zinc radioisotope studies (most

		Intrinsic: Acrodermatitis enteropathica	nephrotic syndrome, diabetes, post-gastric bypass/duodenectomy, anorexia, pregnancy[12] Intrinsic: Acrodermatitis enteropathica	weakness, diaphoresis	accurate tests at present; limited by cost and availability)[12]
Molybdenum	45 µg/***45 µg***	CNS toxicity, hyperoxypurinemia, hypouricemia, low urinary sulfate excretion[a],[10] (also reported with parenteral sulfite infusion) Intrinsic: Molybdenum cofactor deficiency, isolated sulfite oxidase deficiency	None[a]	PO or any exposure: Hyperuricemia + gout Inhaled: Pneumoconiosis (industrial exposure)	$Molybdenum_b$
Vitamin A *Retinol*	900 µ/***3300 IU***	Conjunctival xerosis, keratomalacia, follicular hyperkeratosis, night blindness, *Bitot's spots*, corneal + retinal dysfunction	Any malabsorptive state involving proximal small bowel, vegetarians, chronic liver disease	Acute: Teratogenic, skin exfoliation, intracranial hypertension, hepatocellular necrosis Chronic: Alopecia, ataxia, cheilitis, dermatitis, conjunctivitis, pseudotumor cerebri, hyperlipidemia, hyperostosis	$Retinol_s$, retinol $esters_p$, electroretinogram, liver biopsy (diagnostic for toxicity), retinol binding protein (useful in ESRD; accurately assesses blood levels)[14]
Vitamin D *Ergocalciferol*	5-15 µg/***200 IU***	Rickets/osteomalacia	Any malabsorptive state involving proximal small bowel, chronic liver disease Of note: Those with higher skin melanin content (i.e., darker skin) have low baseline 25-OH vitamin D levels; it is unclear whether this merits their inclusion as an "atrisk" population[15]	Hypercalcemia, hyperphosphatemia, which can lead to $CaPO_4$ precipitation, systemic calcification +/− AMS +/− AKI	25-OH vitamin D_s Of note: lively debate between IOM and Endocrine Society regarding definitions of deficiency, goal serum 25-OH levels, and at-risk populations[15],[16]
Vitamin E (α, γ)-*Tocopherol*	15 mg/***10 IU***	Hemolytic anemia, posterior column degeneration, ophthalmoplegia, peripheral neuropathy Seen in severe malabsorption, abetalipoproteinemia	Any malabsorptive state involving proximal small bowel, chronic liver disease	Possible increased risk in hemorrhagic CVA, functional inhibition of vitamin K-mediated procoagulants	Tocopherol Must account for cholesterol/triglyceride ratio: otherwise, higher cholesterol/triglyceride ratio overestimates vitamin E, lower cholesterol/triglyceride ratio underestimates vitamin E[2],[c]
Vitamin K *Phylloquinone*	120 µg/***150 IU***	Hemorrhagic disease of newborn, coagulopathy	Any malabsorptive state involving proximal small bowel, chronic liver disease	In utero: Hemolytic anemia, hyperbilirubinemia, kernicterus	$Prothrombin\ time_p$

				IV: flushing, dyspnea, hypotension (possibly related to dispersal agent)	
Vitamin B_1 *Thiamine*	1.2 mg/***6 mg***	Irritability, fatigue, headache *Wernicke encephalopathy, Korsakoff psychosis, "wet" beriberi, "dry" beriberi*	Alcoholics, severely malnourished	IV: Lethargy and ataxia	RBC transketolase activity$_b$, thiamine$_{b\&u}$
Vitamin B_2 *Riboflavin*	1.3 mg/***3.6 mg***	Cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, normocytic normochromic anemia	Alcoholics, severely malnourished	None[b]	RBC glutathione reductase activity$_p$
Vitamin B_3 *Niacin*	16 mg/***40 mg***	*Pellagra* dysesthesias, glossitis, stomatitis, vaginitis, vertigo Intrinsic: Hartnup disease	Alcoholics, malignant carcinoid syndrome, severely malnourished	Flushing, hyperglycemia, hyperuricemia, hepatocellular injury[b]	N-methylnicotinamide$_u$
Vitamin B_5 *Pantothenic acid*	5 mg/***15 mg***	Fatigue, abdominal pain, vomiting, insomnia, paresthesias[b]	Alcoholics[6]	PO: Diarrhea	Pantothenic acid$_u$
Vitamin B_6 *Pyridoxine*	1.3-1.7 mg/***6 mg***	Cheilosis, stomatitis, glossitis, irritability, depression, confusion, normochromic normocytic anemia	Alcoholics, diabetics, celiac sprue, chronic isoniazid or penicillamine use[6]	Peripheral neuropathy, photosensitivity	Pyridoxal phosphate$_p$
Vitamin B_7 *Biotin*	30 µg/***60 µg***	Mental status changes, myalgias, hyperesthesias, anorexia[c],[5] (excessive egg white consumption results in avidin-mediated biotin inactivation)	Alcoholics[6]	None[b],[5]	Biotin$_p$, methylcitrate$_u$, 3-methyl-crotonyglycine$_u$, 3-hydroxyisovalerate$_u$
Vitamin B_9 *Folic acid*	400 µg/***600 µg***	Bone marrow suppression, macrocytic megaloblastic anemia, glossitis, diarrhea Can be precipitated by sulfasalazine + phenytoin	Alcoholics, celiac or tropical sprue, chronic sulfasalazine use[6]	PO: May lower seizure threshold in those taking anticonvulsants	Folic acid$_s$, RBC folic acid$_p$
Vitamin B_{12} *Cobalamin*	2.4 µg/***5 µg***	Bone marrow suppression, macrocytic megaloblastic anemia, glossitis, diarrhea, posterolateral column demyelination, AMS, depression, psychosis	Vegetarians, atrophic gastritis, pernicious anemia, celiac sprue, Crohn disease, patients post gastrectomy or ileal resection	None[b]	Cobalamin (B_{12})$_s$, methylmalonic acid$_{s\&p}$
Vitamin C	90 mg/***200 mg***	*Scurvy*, ossification abnormalities Tobacco	Fruit-deficient diet,	Nausea, diarrhea, increased oxalate	Ascorbic acid$_p$,

Ascorbic acid	lowers plasma and WBC vitamin C[2] Sudden cessation of high-dose vitamin C can precipitate scurvy	smokers,[1] ESRD[3]	synthesis (theoretical nephrolithiasis risk)	leukocyte ascorbic acid

AKI, acute kidney injury; AMS, altered mental status; CNS, central nervous system; CVA, cerebrovascular accident; ESRD, end-stage renal disease; IOM, Institute of Medicine; GI, gastrointestinal; HDL, high-density lipoprotein (cholesterol); RBC, red blood cell; TIBC, total iron bonding capacity; TPN, total parenteral nutrition; TSH, thyroid-stimulating hormone; WBC, white blood cell. *Subscript:* b, blood; c, calculated; p, plasma; s, serum; u, urine.

[a]Only reported in patients on long-term TPN.

[b]Never demonstrated in humans.

[c]Only able to induce under experimental conditions and/or only been able to induce in animals.

[1]Trumbo P, Yates AA, Schlicker S, et al. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc.* 2001;101(3):294-301.

[2]Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28:S39-S74.

[3]Deicher R, Hörl WH. Vitamin C in chronic kidney disease and hemodialysis patients. *Kidney Blood Press Res.* 2003;26:100-6.

[4]Office of Dietary Supplements: National Institutes of Health. Dietary supplement fact sheet: chromium. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/pdf/factsheets/Chromium-HealthProfessional.pdf. August 5, 2005. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: iodine. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/pdf/factsheets/Iodine-HealthProfessional.pdf. June 24, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: iron. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/Iron-HealthProfessional/. August 22, 2014. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: selenium. Office of Dietary Supplement: National Institutes of Health. http://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/. November 22, 2013. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: vitamin A. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. April 23, 2006. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: vitamin B12. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/. June 24, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: vitamin C. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/. June 24, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: vitamin D. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/. June 24, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary supplement fact sheet: vitamin B6. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/. September 15, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary Supplement fact sheet: vitamin E. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/. October 11, 2011. Accessed 1/6/15-1/11/15. Ibid. Dietary Supplement fact sheet: zinc. Office of Dietary Supplements: National Institutes of Health. http://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/. September 20, 2011. Accessed 1/6/15-1/11/15.

[5]Feldman M, Friedman LS, Brandt LJ. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th ed. Philadelphia: Saunders Elsevier, 2010.

[6]Said HM. Intestinal absorption of water-soluble vitamins in health and disease. *Biochem J.* 2011;437:357-72.

[7]Stern BR. Essentiality and toxicity in copper health risk assessment: overview, update and regulatory considerations. *J Toxicol Environ Health A.* 2010;73:114-27.

[8]Abumrad NN, Schneider AJ, Steel D, et al. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. *Am J Clin Nutr.* 1981;34(11):2551-9.

[9]Santamaria AB, Sulsky, SI. Risk assessment of an essential element: manganese. *J Toxicol Environ Health A.* 2010;73:128-55.

[10]Linus Pauling Institute. http://lpi.oregonstate.edu/. Higdon J, Drake VL, Turnlund JR. Micronutrient information center: molybdenum. Linus Pauling Institute, Micronutrient Research and Optimum Health. http://lpi.oregonstate.edu/infocenter/minerals/molybdenum/. Accessed 1/6/15-1/11/15. Higdon J, Drake VL, Mock D. Micronutrient information center: biotin. Linus Pauling Institute, Micronutrient Research and Optimum Health. http://lpi.oregonstate.edu/infocenter/vitamins/biotin/. Accessed 1/6/15-1/11/15.

[11]Zimmermann MB. Iodine deficiency. *Endocr Rev.* 2009 Jun;30(4):376-408.

[12]Semrad C. Zinc and intestinal function. *Curr Gastroenterol Rep.* 1999;1:398-403.

[13]Fairweather-Tait SJ, Collings R, Hurst R. Selenium bioavailability: current knowledge and future research requirements. *Am J Clin Nutr.* 2010;91(suppl):1484S-91S.

[14]Mahmood K, Samo AH, Lairamani KL, et al. Serum retinol binding protein as an indicator of vitamin A status in cirrhotic patients with night blindness. *Saudi J Gastroenterol.* 2008;14(1):7-11.

[15]Rosen CJ, Abrams SA, Aloia JF, et al. IOM committee members respond to Endocrine Society vitamin D guideline. *J Clin Endocrinol Metab.* 2012;97:1146-52.

[16]Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2001;96:1911-30.

[17]Ford L, Farr J, Morris P, et al. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. *Ann Clin Biochem.* 2006;43:130-4.

[18]Uauy R, Olivares O, Gonzales M. Essentiality of copper in humans. *Am J Clin Nutr.* 1998;67(suppl):952S-59S.

SPECIAL CONSIDERATIONS

- Both the amount and location of prior gut resection influence nutrient needs. Patients with a reduced length of functional small bowel may require additional vitamins and minerals if they are not receiving parenteral nutrition. Table 2-4 provides guidelines for supplementation in these patients.
- Distal ileum inflammation, resection, inflammatory bowel disease (IBD), and bypass (ileojejunal bypass) can cause B_{12} deficiency and bile salt loss. Diarrhea in this setting may be improved with oral cholestyramine given with the first meal of the day.
- Proximal gut resection (stomach or duodenum) via partial gastrectomy, Billroth I and II, duodenal switch/biliopancreatic diversion, Roux-en-Y gastric bypass, pancreaticoduodenectomy (Whipple), and sleeve gastrectomy may impair absorption of divalent cations such as iron, calcium, and copper. Copper deficiency is extremely common in post-gastric bypass patients who do not receive routine supplementation (*Int J Obes (Lond) 2012;36(3):328*).
- Patients with excessive gastrointestinal (GI) tract losses require additional fluids and electrolytes.

  An assessment of fluid losses due to diarrhea, ostomy output, and fistula volume should be made to help determine fluid requirements. Intestinal mineral losses may be calculated by multiplying the volume of fluid loss by the fluid electrolyte concentration (Table 2-5).

TABLE 2-4 Guidelines for Vitamin and Mineral Supplementation in Patients with Severe Malabsorption

Supplement	Dose	Route
Prenatal multivitamin with minerals[a]	1 tablet daily	PO
Vitamin D[a]	50,000 units 2-3 times per wk	PO
Calcium[a]	500 mg elemental calcium tid-qid	PO
Vitamin B_{12}[b]	1 mg daily	PO
	100-500 µg q1-2 mo	SC
Vitamin A[b]	10,000-50,000 units daily	PO
Vitamin K[b]	5 mg/d	PO
	5-10 mg/wk	SC
Vitamin E[b]	30 units/d	PO

Magnesium gluconate[b]	108-169 mg elemental magnesium qid	PO
Magnesium sulfate[b]	290 mg elemental magnesium 1-3 times per week	IM/IV
Zinc gluconate or zinc sulfate[b]	25 mg elemental zinc daily plus 100 mg elemental zinc per liter intestinal output	PO
Ferrous sulfate[b]	60 mg elemental iron tid	PO
Iron dextran[b]	Daily dose based on formula or table	IV

[a]Recommended routinely for all patients.

[b]Recommended for patients with documented nutrient deficiency or malabsorption.

TABLE 2-5 Electrolyte Concentrations in Gastrointestinal Fluids

Location	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	HCO_3 (mEq/L)
Stomach	65	10	100	-
Bile	150	4	100	35
Pancreas	150	7	80	75
Duodenum	90	15	90	15
Mid-small bowel	140	6	100	20
Terminal ileum	140	8	60	70
Rectum	40	90	15	30

Assessment of Nutritional Status

GENERAL PRINCIPLES

- Patients should be assessed for protein-energy malnutrition as well as specific nutrient deficiencies.
- A thorough history and physical exam combined with appropriate laboratory studies is the best approach to evaluate nutritional status.

DIAGNOSIS

Clinical Presentation

History

- Assess for changes in diet pattern (size, number, and content of meals). If present, the reason for altered food intake should be investigated.
- Unintentional weight loss of >10% body weight in the last 6 months is associated with a poor clinical outcome (*Am J Med 1980;69:491*).
- Look for evidence of **malabsorption** (diarrhea, weight loss).
- For symptoms of specific **nutrient deficiencies**, see Table 2-3.
- Consider factors that may increase metabolic stress (e.g., infection, inflammatory disease, malignancy).
- Assess patient's functional status (e.g., bedridden, suboptimally active, very active).

Physical Examination

- By World Health Organization (WHO) criteria, patients can be classified by BMI as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class I obesity (30.0-34.9 kg/m^2), class II obesity (35.0-39.9 kg/m^2), or class III obesity (≥40.0 kg/m^2) (*Obes Res 1998;6(suppl 2):S53*).

- Patients who are **extremely underweight** (BMI <14 kg/m^2) or those **with rapid, severe weight loss** (even with supranormal BMI) have a high risk of death and should be considered for admission to the hospital for nutritional support.
- Look for **tissue depletion** (loss of body fat and skeletal muscle wasting).
- Assess **muscle function** (strength testing of individual muscle groups).
- **Fluid status:** Evaluate patients for dehydration (e.g., hypotension, tachycardia, mucosal xerosis) or excess body fluid (edema or ascites).

- Evaluate patients for sources of protein or nutrient losses: large wounds, burns, nephrotic syndrome, surgical drains, etc. Quantify the volume of drainage and the concentration of fat and protein content.

Diagnostic Testing

- Perform laboratory studies to determine specific nutrient deficiencies only when clinically indicated because the plasma concentration of many nutrients may not reflect true body stores (Table 2-3).
- Plasma albumin and prealbumin concentrations should not be used to assess patients for protein-calorie malnutrition or to monitor the adequacy of nutrition support. Although levels of these plasma proteins correlate with clinical outcome, inflammation and injury can alter their synthesis and degradation, limiting their usefulness for nutritional assessment (*Crit Care Med 1982;10:305*; *Gastroenterology 1990;99:1845*).
- Most hospitalized patients are vitamin D deficient, and caregivers should have a low threshold for checking plasma 25-OH vitamin D levels (*N Engl J Med 1998;338:777*).

Enteral Nutrition

GENERAL PRINCIPLES

Whenever possible, **oral/enteral** feeding is preferred to **parenteral** feeding because it limits mucosal atrophy, maintains IgA secretion, and prevents cholelithiasis. Additionally, oral/enteral feeds are less expensive than parenteral nutrition.

- **Types of feedings**

  Hospital diets include a regular diet and those modified in either nutrient content (amount of fiber, fat, protein, or sodium) or consistency (liquid, puréed, soft). There are ways that food intake can often be increased:

  - Encourage patients to eat.
  - Provide assistance at mealtime.
  - Allow some food to be supplied by relatives and friends.
  - Limit missed meals for medical tests and procedures.
  - Avoid unpalatable diets. Milk-based formulas (e.g., Carnation Instant Breakfast) contain milk as a source of protein and fat and tend to be more palatable than other defined formula diets.
  - Use calorically dense supplements (e.g., Ensure, Boost).

- **Defined liquid formulas**

  - **Polymeric formulas** (e.g., Osmolite, Jevity) are appropriate for most patients. They contain nitrogen in the form of whole proteins and include blenderized food, milkbased, and lactose-free formulas. Other formulas are available with modified nutritional content including high-nitrogen, high-calorie, fiber-enriched, and low-potassium/phosphorus/magnesium formulas.
  - **Semielemental *oligomeric* formulas** (e.g., Peptamen) contain hydrolyzed protein in the form of small peptides and free amino acids. Although these formulas may have benefit in those with exocrine pancreatic insufficiency or short gut, pancreatic enzyme replacement is a less expensive, equally effective intervention in most of these patients.
  - **Elemental monomeric formulas** (e.g., Vivonex, Glutasorb) contain nitrogen in the form of free amino acids and small amounts of fat (<5% of total calories) and are hyperosmolar (550-650 mOsm/kg). These formulas are not palatable and therefore require either tube feeding or mixing with other foods or flavorings for oral ingestion. Free amino acids are poorly absorbed, and these formulas have not been shown to be clinically superior to oligomeric or polymeric formulas in patients with adequate

    pancreatic digestive function. These formulas may exacerbate osmotic diarrhea in patients with short gut.
  - **Oral rehydration solutions** stimulate sodium and water absorption by taking advantage of the sodium-glucose cotransporter present in the brush border of intestinal epithelium.

    Oral rehydration therapy (using 90-120 mEq/L solutions to avoid intestinal sodium secretion and negative sodium and water balance) can be especially useful in patients with short bowel syndrome (*Clin Ther 1990;12(suppl A):129*). The characteristics of several oral rehydration solutions are listed in Table 2-6.

- **Tube feeding**

  - Tube feeding is useful in patients who have a **functional GI tract** but who cannot or will not ingest adequate nutrients.
  - The type of tube feeding approach selected (nasogastric, nasoduodenal, nasojejunal, gastrostomy, jejunostomy, pharyngostomy, and

esophagostomy tubes) depends on physician experience, clinical prognosis, gut patency and motility, risk of aspirating gastric contents, patient preference, and anticipated duration of feeding.

- Short-term (<6 weeks) tube feeding can be achieved by placement of a soft, smallbore nasogastric or nasoenteric feeding tube. Although nasogastric feeding is usually the most appropriate route, orogastric feeding may be needed in those who are intubated or in patients with nasal injury or deformity. Nasoduodenal and nasojejunal feeding tubes can be placed at the bedside with a success rate approaching 90% when inserted by experienced personnel (*Nutr Clin Pract 2001;16:258*).
- Long-term (>6 weeks) tube feeding usually requires a gastrostomy or jejunostomy tube that can be placed percutaneously by endoscopic or radiographic assistance. Alternatively, they can be placed surgically, depending on the clinical situation and local expertise.

- **Feeding schedules:** Patients who have feeding tubes in the stomach can often tolerate intermittent bolus or gravity feedings, in which the total amount of daily formula is divided into four to six equal portions.
  - **Bolus feedings** are given by syringe as rapidly as tolerated.
  - **Gravity feedings** are infused over 30-60 minutes.
  - The patient's upper body should be elevated by 30-45 degrees during feeding and for at least 2 hours afterward. Tubes should be flushed with water after each feeding. Intermittent feedings are useful for patients who cannot be positioned with continuous head-of-the-bed elevation or who require greater freedom from feeding. Patients who experience nausea and early satiety with bolus gravity feedings may require continuous infusion at a slower rate.
  - **Continuous feeding** can often be started at 20-30 mL/h and advanced by 10 mL/h every 6 hours until the feeding goal is reached. Patients who have gastroparesis often tolerate gastric tube feedings when they are started at a slow rate (e.g., 10 mL/h) and advanced by small increments (e.g., 10 mL/h every 8-12 hours). Patients with severe gastroparesis may require passage of the feeding tube tip past the ligament of Treitz. **Continuous feeding should always be used when feeding directly into the duodenum or jejunum to avoid distention, abdominal pain, and dumping syndrome.**
  - **Jejunal feeding** may be possible in closely monitored patients with mild to moderate **acute pancreatitis** (*J Am Coll Nutr 1995;14(6):662*).
- **Contraindications:** The intestinal tract cannot be used effectively in some patients due to:
  - Persistent nausea or vomiting
  - Intolerable postprandial abdominal pain or diarrhea
  - Mechanical obstruction or severe hypomotility
  - Severe malabsorption
  - Presence of high-output fistula

TABLE 2-6 Enteral Feeding Formulas: Comparing Composition

Formula	kcal/mL	% Protein	% Lipid	% Carbohydrate	K^+ (mEq/L)	PO_4^{3-} (mg/L)	Purpose/Niche
Osmolite	1.0	16.7	29	54.3	40.2	760	Standard polymeric
Jevity	1.5	17	29	53.6	40.2	1200	Standard polymeric
TwoCal HN	2	16.7	40.1	43.2	62.6	1050	Volume restricted
Nepro with Carb Steady	1.8	18	48	34	27.2	700	ESRD
Glucerna	1.2	20	45	35	51.8	800	Glucose intolerance/diabetes
Promote	1.0	25	23	52	50.8	1200	High protein
Peptamen AF	1.2	25	39	36	41	800	Short gut, exocrine pancreatic insufficiency
Vivonex RTF	1.0	20	10	70	31	670	Fat malabsorption
Oxepa	1.5	16.7	55.2	28.1	50.1	1060	SIRS, ARDS, sepsis

ARDS, acute respiratory distress syndrome; ESRD, end-stage renal disease; SIRS, systemic inflammatory response syndrome. Table adapted from Barnes-Jewish Hospital Enteral Nutrition Formulary (8/2009).

COMPLICATIONS

- **Mechanical complications**
  - **Nasogastric feeding tube misplacement** occurs more commonly in unconscious patients. Intubation of the tracheobronchial tree has been reported in up to 15% of patients. Intracranial placement can occur in patients with skull fractures.
  - **Erosive tissue damage** can lead to nasopharyngeal erosions, pharyngitis, sinusitis, otitis media, pneumothorax, and GI tract perforation.
  - **Tube occlusion** is often caused by inspissated feedings or pulverized medications given through small-diameter (<#10 French) tubes. Frequent flushing of the tube with 30-60 mL of water and avoiding administration of pill fragments or "thick" medications help to prevent occlusion. Techniques used to unclog tubes include the use of a small-volume syringe (10 mL) to flush warm water or pancreatic enzymes (Viokase dissolved in water) through the tube.
- **Hyperglycemia**
  - The precise level at which glucose should be maintained in hospitalized patients remains controversial.
  - Subcutaneously administered insulin can usually maintain good glycemic control. IV insulin drip protocols should be used to control blood glucose in critically ill patients with anasarca or hemodynamic instability to ensure adequate insulin absorption.
  - Intermediate-duration insulin (e.g., NPH) can often be used safely once tube feedings reach 1000 kcal/d. Long-duration insulin (e.g., detemir, glargine) should be used with caution in critically ill patients because changes in clinical status may affect pharmacokinetics and increase the risk of sustained hypoglycemia.
  - Patients who are receiving bolus feeds should receive short-acting insulin at the time of the feed.
  - Patients who are being given continuous (24 hours per day) feeding should receive intermediate-duration insulin every 8 hours when clinically stable. If tube feeds are interrupted and insulin has been given, an infusion of dextrose-containing fluid should be given at a rate to match the infusion rate of the scheduled tube feeds until the insulin has worn off.
- **Pulmonary aspiration**
  - The etiology of **pulmonary aspiration** can be difficult to determine in tube-fed patients because aspiration can occur from refluxed tube feedings or oropharyngeal secretions that are unrelated to feedings. Recent evidence suggests that oral secretions play a far greater role in the development of ventilator-associated pneumonia than aspiration of tube feedings (*JAMA 2013;309(3):249-56*).
  - Addition of food coloring to tube feeds **should not be used** for the diagnosis of aspiration. This method is insensitive for diagnosis, and several case reports suggest that food coloring can be absorbed by the GI tract in critically ill patients and can lead to serious complications and death (*N Engl J Med 2000;343:1047*).
  - Gastric residuals are poorly predictive of aspiration risk.
  - Prevention of reflux: Decrease gastric acid secretion with pharmacologic therapy (H2 blocker, proton pump inhibitor), elevate head of bed during feeds, and avoid gastric feeding in high-risk patients (e.g., those with gastroparesis, frequent vomiting, gastric outlet obstruction).
- **GI complications**
  - Nausea, vomiting, and abdominal pain are common.
  - **Diarrhea** is often associated with antibiotic therapy (*JPEN J Parenter Enteral Nutr 1991;15:27*) and the use of liquid medications that contain nonabsorbable carbohydrates, such as sorbitol (*Am J Med 1990;88:91*). If diarrhea from tube feeding persists after proper evaluation of possible causes, a trial of antidiarrheal agents or fiber is

    justified. Diarrhea is common in patients who receive tube feeding and occurs in up to 50% of critically ill patients.
  - Diarrhea in patients with short gut, who do not have other causes such as *Clostridium difficile* infection, may be minimized by use of small, frequent meals that do not contain concentrated sweets (e.g., soda). Intestinal transit time should be maximized to allow nutrient absorption using tincture of opium, loperamide, or diphenoxylate. Lowdose clonidine (0.025-0.05 mg orally bid) may be used to reduce diarrhea in hemodynamically stable patients with short bowel syndrome (*JPEN J Parenter Enteral Nutr 2004;28(4):265*).
  - **Intestinal ischemia/necrosis** has been reported in patients receiving tube feeding. These cases have occurred predominantly in critically ill patients receiving vasopressors for blood pressure support in conjunction with enteral feeding. There are no reliable clinical signs for diagnosis, and the mortality rate is high. **Caution should be used when enterally feeding critically ill patients requiring vasopressors.**

Parenteral Nutrition

GENERAL PRINCIPLES

- Parenteral nutrition should be considered if energy intake cannot, or it is anticipated that it cannot, be met by enteral nutrition (<50% of daily requirements) for more than 7-10 days. This guideline originates from two intensive care unit (ICU)-focused meta-analyses citing increased complications (*Am J Clin Nutr 2001;74:534*) and increased overall mortality (*JAMA 1998;280:2013*) in ICU patients receiving early parenteral

nutrition (i.e., within 7 days of admission), compared to those receiving no nutrition support (*JPEN J Parenter Enteral Nutr 2009;33(3):285*). Recent studies have found that critically ill patients who are unable to meet caloric goals by enteral nutrition alone for the first 8 days of hospitalization have longer durations of stay and greater mortality rates than those in whom total parenteral nutrition (TPN) is withheld for the first 8 days after admission (*N Engl J Med 2011;365:506*).

- **Recommendations**
  - **Central parenteral nutrition (CPN)**
    - The infusion of hyperosmolar (usually >1500 mOsm/L) nutrient solutions requires a large-bore, high-flow vessel to minimize vessel irritation and damage.
    - Percutaneous subclavian vein **catheterization** and peripherally inserted central venous catheterization (PICC) are the most commonly used techniques for CPN access. The internal jugular, saphenous, and femoral veins are also used, although they are less desirable due to decreased patient comfort and difficulty in maintaining sterility. Tunneled catheters are preferred in patients who are likely to receive >8 weeks of TPN to reduce the risk of mechanical failure.
    - PICCs (which reduce the risk of pneumothorax) are increasingly used to provide CPN in patients with adequate antecubital vein access. These catheters are not suitable for patients in whom CPN is anticipated to be necessary for an extended duration (>6 months).
  - **CPN macronutrient solutions**
    - Crystalline **amino acid solutions** containing 40-50% essential and 50-60% nonessential amino acids (usually with little or no glutamine, glutamate, aspartate, asparagine, tyrosine, and cysteine) are used to provide protein needs (Table 2-2). Infused amino acids are oxidized and should be included in the estimate of energy provided as part of the parenteral formulation.
    - Some amino acid solutions have been modified for specific disease states such as those enriched in branched-chain amino acids for use in patients who have hepatic

      encephalopathy and solutions that contain mostly essential amino acids for use in patients with renal insufficiency.
    - **Glucose** (dextrose) in IV solutions is hydrated; each gram of dextrose monohydrate provides 3.4 kcal. Although there is no absolute requirement for glucose in most patients, providing >150 g of glucose per day maximizes protein balance.
    - **Lipid emulsions** are available as a 10% (1.1 kcal/mL) or 20% (2.0 kcal/mL) solution and provide energy as well as a source of essential fatty acids. Emulsion particles are similar in size and structure to chylomicrons and are metabolized like nascent chylomicrons after acquiring apoproteins from contact with circulating endogenous high-density lipoprotein cholesterol particles. Lipid emulsions are as effective as glucose in conserving body nitrogen economy once absolute tissue requirements for glucose are met. The optimal percentage of calories that should be infused as fat is not known, but 20-30% of total calories is reasonable for most patients. The rate of infusion should not exceed 1.0 kcal/kg/h (0.11 g/kg/h) because most complications associated with lipid infusions have been reported when providing more than this amount (*Curr Opin Gastroenterol 1991;7:306*). A rate of 0.03-0.05 g/kg/h is adequate for most patients who are receiving continuous CPN. Lipid emulsions should not be given to patients who have triglyceride concentrations of >400 mg/dL. Moreover, patients at risk for hypertriglyceridemia should have serum triglyceride concentrations checked at least once during lipid emulsion infusion to ensure adequate clearance. Underfeeding obese patients by the amount of lipid calories that would normally be given (e.g., 20-30% of calories) facilitates mobilization of endogenous fat stores for fuel and may improve insulin sensitivity. IV lipids should still be administered twice per week to these patients to provide essential fatty acids.
- **Peripheral parenteral nutrition**
  - Peripheral parenteral nutrition is often considered to have limited usefulness because of the high risk of thrombophlebitis.
  - Appropriate adjustments in the management of peripheral parenteral nutrition can increase the life of a single infusion site to >10 days. The following guidelines are recommended:
    - Provide at least 50% of total energy as a lipid emulsion piggybacked with the dextrose-amino acid solution.
    - Add 500-1000 units of heparin and 5 mg of hydrocortisone per liter (to decrease phlebitis).
    - Place a fine-bore 22- or 23-gauge polyvinylpyrrolidone-coated polyurethane catheter in as large a vein as possible in the proximal forearm using sterile technique.
    - Place a 5-mg glycerol trinitrate ointment patch (or 0.25 inch of 2% nitroglycerin ointment) over the infusion site.
    - Infuse the solution with a volumetric pump.
    - Keep the total infused volume <3500 mL/d.
    - Filter the solution with an inline 1.2-m filter (*Nutrition 1994;10:49*).
- **Long-term home parenteral nutrition**
  - Long-term home parenteral nutrition is usually given through a **tunneled catheter** or an implantable subcutaneous port inserted in the subclavian vein.
  - **Nutrient formulations** can be infused overnight to permit daytime activities in patients who are able to tolerate the fluid load. IV lipids may not be necessary in patients who are able to ingest and absorb adequate amounts of fat.

- Patient selection for appropriate patients for home TPN is crucial due to the high rates of complications (˜50% at 6 months). Risk factors for complications include use of a nontunneled or multilumen catheter, blood draws from the catheter, infusion of nonparenteral medications, use of lipid infusions, anticoagulation, older age, and open wounds (*JPEN J Parenter Enteral Nutr 2014;38:6*; *JPEN J Parenter Enteral Nutr;in press*).

COMPLICATIONS

- **Mechanical complications**
  - Complications at time of line placement include pneumothorax, air embolism, arterial puncture, hemothorax, and brachial plexus injury.
  - Thrombosis and pulmonary embolus: Radiologically evident subclavian vein thrombosis occurs commonly; however, clinical manifestations (upper extremity edema, superior vena cava syndrome) are rare. Fatal microvascular pulmonary emboli can be caused by nonvisible precipitate in parenteral nutrition solutions. Inline filters should be used with all solutions to minimize the risk of these emboli.
- **Metabolic complications:** Usually caused by overzealous or inadequate nutrient administration.
  - Fluid overload.
  - Hypertriglyceridemia.
  - Hypercalcemia.
  - Specific nutrient deficiencies. Consider providing supplemental **thiamine** (100 mg for 3-5 days) during initiation of CPN in patients at risk for thiamine deficiency (e.g., alcoholism).
  - Hypoglycemia.
  - **Hyperglycemia.** Tight blood glucose control (between 90-120 mg/dL) historically was the standard dogma in ICU populations (*N Engl J Med 2001;345:1359*); however, this practice has been called into question in light of a 2009 randomized controlled trial illustrating significantly higher overall mortality and incidence of critical hypoglycemia in patients whose blood glucose was being tightly controlled (*N Engl J Med 2009;360(13):1283*). Management of patients with hyperglycemia or type 2 diabetes (*Mayo Clin Proc 1996;71:587*) can be performed in the following way:
    - If blood glucose is >200 mg/dL, consider obtaining better control of blood glucose before starting CPN.
    - If CPN is started, (a) limit dextrose to <200 g/d, (b) add 0.1 unit of regular insulin for each gram of dextrose in CPN solution (e.g., 15 units for 150 g), (c) discontinue other sources of IV dextrose, and (d) order routine, regular insulin with blood glucose monitoring by fingerstick every 4-6 hours or IV regular insulin infusion with blood glucose monitoring by fingerstick every 1-2 hours.
    - In outpatients who use insulin, an estimate of the reduction in blood sugar that will be caused by the administration of 1 unit of insulin may be calculated by dividing 1500 by the total daily insulin dose (e.g., for a patient receiving 50 units of insulin as an outpatient, 1 unit of insulin may be predicted to reduce plasma glucose concentration by 1500/50 = 30 mg/dL).
    - If blood glucose remains >200 mg/dL and the patient has been requiring SC insulin, add 50% of the supplemental short-acting insulin given in the last 24 hours to the next day's CPN solution and double the amount of SC insulin sliding-scale dose for blood glucose values >200 mg/dL.
    - The insulin-to-dextrose ratio in the CPN formulation should be maintained while the CPN dextrose content is changed.
- **Infectious complications**
  - Catheter-related sepsis is the most common life-threatening complication in patients who receive CPN and is most commonly caused by skin flora: *Staphylococcus epidermidis* and *Staphylococcus aureus.*
  - In **immunocompromised patients** and those with long-term (>2 weeks) CPN, *Enterococcus*, *Candida* species, *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, *Proteus*, and *Xanthomonas* should be considered.
  - The principles of **evaluation and management** of suspected catheter-related infection are outlined in Chapter 14, Treatment of Infectious Diseases.

  - Although antibiotics are often infused through the central line, the **antibiotic lock technique** has been used successfully to treat and prevent central catheter-related infections (*Nutrition 1998;14:466*; *Antimicrob Agents Chemother 1999;43:2200*). This technique involves local delivery of antibiotics in the catheter without systemic administration.
- **Hepatobiliary complications.** Although these abnormalities are usually benign and transient, more serious and progressive disease may develop in a small subset of patients, usually after 16 weeks of CPN therapy or in those with short bowel (*Diseases of the Liver. 7th ed. Philadelphia: JB Lippincott; 1993:1505*).
  - Biochemical: Elevated aminotransferases and alkaline phosphatase are commonly seen.
  - Histologic alterations: Steatosis, steatohepatitis, lipidosis, phospholipidosis, cholestasis, fibrosis, and cirrhosis have all been seen.
  - Biliary complications usually occur in patients who receive CPN for >3 weeks.
    - Acalculous cholecystitis
    - Gallbladder sludge
    - Cholelithiasis
  - Routine efforts to prevent hepatobiliary complications in all patients receiving longterm CPN include providing a portion (20-40%) of calories

as fat, cycling CPN so that the glucose infusion is stopped for at least 8-10 hours per day, encouraging enteral intake to stimulate gallbladder contraction and maintain mucosal integrity, avoiding excessive calories, and preventing hyperglycemia.
    - If abnormal liver biochemistries or other evidence of liver damage occurs, evaluation for other possible causes of liver disease should be performed.
    - If mild hepatobiliary complications are noted, parenteral nutrition does not need to be discontinued, but the same principles used in preventing hepatic complications can be applied therapeutically.
    - When cholestasis is present, copper and manganese should be deleted from the CPN formula to prevent accumulation in the liver and basal ganglia. A 4-week trial of metronidazole or ursodeoxycholic acid has been reported to be helpful in some patients.
- **Metabolic bone disease**
    - Metabolic bone disease has been observed in patients receiving long-term (>3 months) CPN.
    - Patients may be asymptomatic. Clinical manifestations include bone fractures and pain (*Annu Rev Nutr 1991;11:93*). Demineralization may be seen in radiologic studies. Osteopenia, osteomalacia, or both may be present.
    - The precise causes of metabolic bone disease are not known, but several mechanisms have been proposed, including aluminum toxicity, vitamin D toxicity, and negative calcium balance.
    - Several therapeutic options should be considered in patients who have evidence of bone abnormalities.
    - Remove vitamin D from the CPN formulation if the parathyroid hormone and 1,25-hydroxy vitamin D levels are low.
    - Reduce protein to <1.5 g/kg/d because amino acids cause hypercalciuria.
    - Maintain normal magnesium status because magnesium is necessary for normal parathormone action and renal conservation of calcium.
    - Provide oral calcium supplements of 1-2 g/d.
    - Consider bisphosphonate therapy to decrease bone resorption.

SPECIAL CONSIDERATIONS

Monitoring nutrition support

- Adjustment of the nutrient formulation is often needed as medical therapy or clinical status changes.

- When nutrition support is initiated, other sources of **glucose** (e.g., peripheral IV dextrose infusions) should be stopped and the volume of other IV fluids adjusted to account for CPN.
- Vital signs should be checked every 8 hours.
- In certain patients, body weight, fluid intake, and fluid output should be followed daily.
- Serum electrolytes (including phosphorus) should be measured every 1-2 days after CPN is started until values are stable and then rechecked weekly.
- Serum glucose should be checked up to every 4-6 hours by fingerstick until blood glucose concentrations are stable and then rechecked weekly.
- If lipid emulsions are being given, **serum triglycerides** should be measured during lipid infusion in patients at risk for hypertriglyceridemia to demonstrate adequate clearance (triglyceride concentrations should be <400 mg/dL).
- Careful attention to the catheter and catheter site can help to prevent **catheter-related infections**.
    - Gauze dressings should be changed every 48-72 hours or when contaminated or wet, but transparent dressings can be changed weekly.
    - Tubing that connects the parenteral solutions with the catheter should be changed every 24 hours.
    - A 0.22-µm filter should be inserted between the IV tubing and the catheter when **lipidfree CPN** is infused and should be changed with the tubing.
    - A 1.2-µm filter should be used when a total nutrient admixture containing a **lipid emulsion** is infused.
    - When a **single-lumen** catheter is used to deliver CPN, the catheter should not be used to infuse other solutions or medications (with the exception of compatible antibiotics) and should not be used to monitor central venous pressure.
    - When a **triple-lumen** catheter is used, the distal port should be reserved solely for the administration of CPN.

Refeeding the Severely Malnourished Patient

COMPLICATIONS

Initiating nutritional therapy in patients who are severely malnourished and have had minimal nutrient intake can have adverse clinical consequences and precipitate the refeeding syndrome.

- **Hypophosphatemia, hypokalemia, and hypomagnesemia:** Rapid and marked decreases in these electrolytes occur during initial refeeding because of insulin-stimulated increases in cellular mineral uptake from extracellular fluid. For example, plasma phosphorus concentration can fall below 1 mg/dL and cause death within hours of initiating nutritional therapy if adequate phosphate is not given (*Am J Clin Nutr 1981;34:393*).

- **Fluid overload** and **congestive heart failure** are associated with decreased cardiac function and insulin-induced increased sodium and water reabsorption in conjunction with nutritional therapy containing water, glucose, and sodium. Renal mass may be reduced, limiting the ability to excrete salt or water loads.
- **Cardiac arrhythmias:** Patients who are severely malnourished often have bradycardia. Sudden death from ventricular tachyarrhythmias can occur during the first week of refeeding in severely malnourished patients and may be associated with a prolonged QT interval (*Ann Intern Med 1985;102:49*) or plasma electrolyte abnormalities. Patients with ECG changes should be monitored on telemetry, possibly in an ICU.
- **Glucose intolerance:** Starvation causes insulin resistance such that refeeding with highcarbohydrate meals or large amounts of parenteral glucose can cause marked elevations in blood glucose concentration, glycosuria, dehydration, and hyperosmolar coma.

P.55

P.56

P.57

In addition, carbohydrate refeeding in patients who are depleted in thiamine can precipitate Wernicke encephalopathy.

TABLE 2-7 Major Mineral Daily Requirements, Deficiency, Toxicity, and Diagnostic Evaluation

Mineral	Recommended Daily Enteral[1] Intake/Parenteral[2] Intake	Signs and Symptoms of Deficiency	Signs and Symptoms of Toxicity	Diagnostic Evaluation
Sodium	1.2-1.5 g[3,5]/1-2 mEq/kg	Encephalopathy, seizure, weakness, dehydration, cerebral edema	Encephalopathy, seizure	$Sodium_p$ (correct for hyperglycemia) $Sodium_u$ (will often only provide a rough estimate [i.e., too low, too high])
Potassium	4700 mg[4,5]/1-2 mEq/kg	Abdominal cramping, diarrhea, paresthesias, QT prolongation, weakness	QRS widening, QT shortening (sine wave morphology in extreme cases), peaked T waves	$Potassium_{w,b}$
Calcium	1000-1200 mg/10-15 mEq	QRS widening, paresthesias (Trousseau sign), tetany (Chvostek sign), osteomalacia	Encephalopathy, headache, abdominal pain, nephrolithiasis, metastatic calcification	$Calcium_{w,b}$, 24-hour $calcium_u$ (correct for $albumin_s$)
Magnesium	420 mg/8-20 mEq	Tachyarrhythmia, weakness, muscle cramping, peripheral and central nervous system overstimulation (seizure, tetany)	Hyporeflexia, nausea, vomiting, weakness, encephalopathy, decreased respiratory drive, hypocalcemia, hyperkalemia, heart block	$Magnesium_s$, $magnesium_u$
Phosphorus	700 mg/20-40 mmol	Weakness, fatigue, increased cell membrane fragility (hemolytic anemias, leukocyte + platelet dysfunction), encephalopathy	Metastatic calcification, theoretic higher risk of nephrolithiasis, secondary hyperparathyroidism	$Phosphorus_p$

Subscript: b, blood; p, plasma; s, serum; u, urine; w, whole blood.

[1]Trumbo P, Yates AA, Schlicker S, et al. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc.* 2001;101(3):294-301.

[2]Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28:S39-S74.

[3]Higdon J, Drake V, Obarzanek E. Micronutrient Information Center: sodium (chloride). Linus Pauling Institute: Micronutrient Research for Optimum Health. http://lpi.oregonstate.edu/infocenter/minerals/sodium/. Accessed 1/6/15-1/11/15.

[4]Higdon J, Drake V, Pao-Hwa L. Micronutrient Information Center: potassium. Linus Pauling Institute: Micronutrient Research for Optimum Health. http://lpi.oregonstate.edu/infocenter/minerals/potassium/. Accessed 1/6/15-1/11/15.

[5] *Note:* Adequate daily intake.

- **Recommendations**
  - Careful **evaluation** of cardiovascular function and plasma electrolytes (history, physical examination, ECG, and blood tests) and correction of abnormal plasma electrolytes are **important before initiation of feeding**.
  - Refeeding by the oral or enteral route involves the frequent or continuous administration of small amounts of food or an isotonic liquid formula.
  - Parenteral supplementation or complete parenteral nutrition may be necessary if the intestine cannot tolerate feeding.
  - During initial refeeding, fluid intake should be limited to approximately 800 mL/d plus insensible losses. Adjustments in fluid and sodium intake are needed in patients who have evidence of fluid overload or dehydration.
  - Changes in body weight provide a useful guide for evaluating the efficacy of fluid administration. Weight gain >0.25 kg/d or 1.5 kg/wk probably represents fluid accumulation in excess of tissue repletion. Initially, approximately 15 kcal/kg, containing approximately 100 g carbohydrate and 1.5 g protein per kilogram of actual body weight, should be given daily.
  - The rate at which the caloric intake can be increased depends on the severity of the malnutrition and the tolerance to feeding. In general, increases of 2-4 kcal/kg every 24-48 hours are appropriate.
  - Sodium should be restricted to approximately 60 mEq or 1.5 g/d, but liberal amounts of phosphorus, potassium, and magnesium should be given to patients who have normal renal function.
  - All other nutrients should be given in amounts needed to meet the recommended dietary intake (Table 2-7).
  - Body weight, fluid intake, urine output, plasma glucose, and electrolyte values should be **monitored daily** during early refeeding (first 3-7 days) so that nutritional therapy can be appropriately modified when necessary.

3
Preventive Cardiology

Angela L. Brown
Daniel S. Kim
Clare E. Moynihan
Anne C. Goldberg

Hypertension

GENERAL PRINCIPLES

Definition

Hypertension is defined as the presence of a blood pressure (BP) elevation to a level that places patients at increased risk for target organ damage in several vascular beds including the retina, brain, heart, kidneys, and large conduit arteries (Table 3-1, Table 3-2).

Classification

- **Normal BP** is defined as systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; pharmacologic intervention is not indicated.
- **Prehypertension** is defined as SBP of 120-139 mm Hg or DBP of 80-89 mm Hg. These patients should engage in comprehensive lifestyle modifications to delay progression or prevent the development of hypertension. Pharmacologic therapy should be initiated in prehypertensive patients with evidence of target organ damage or diabetes.
- **In stage 1** (SBP 140-159 mm Hg or DBP 90-99 mm Hg) **and stage 2** (SBP >160 mm Hg or DBP >100 mm Hg) **hypertension**, pharmacologic therapy should be initiated in addition to lifestyle modification to lower BP to <140/90 mm Hg in patients without diabetes or chronic kidney disease and age <60 years. For those age ≥60 years without diabetes or chronic kidney disease, pharmacologic therapy should be initiated in addition to lifestyle modification to lower BP to >150/90 mm Hg. In patients with diabetes or chronic kidney disease and age ≥18 years, BP should be lowered to <140/90 mm Hg.
- Patients with BP levels >20/10 mm Hg above their treatment target will often require more than one medication to achieve adequate control, and a two-drug regimen may be initiated as initial therapy. Patients with an average BP of 200/120 mm Hg or greater require immediate therapy and, if symptomatic end-organ damage is present, hospitalization.
- **Hypertensive crisis** includes hypertensive emergencies and urgencies. It usually develops in patients with a previous history of elevated BP but may arise in those who were previously normotensive. The severity of a hypertensive crisis correlates not only with the absolute level of BP elevation but also with the rapidity of development because autoregulatory mechanisms have not had sufficient time to adapt.
  - **Hypertensive urgencies** are defined as a substantial increase in BP, usually with a DBP >120 mm Hg, and occur in approximately 1% of hypertensive patients. Hypertensive urgencies (i.e., upper levels of stage 2 hypertension, hypertension with optic disk edema, progressive end-organ complications rather than damage, and severe perioperative hypertension) warrant BP reduction within several hours (*JAMA 2003;289:2560*).
  - **Hypertensive emergencies** include **accelerated hypertension**, typically defined as an SBP >210 mm Hg and DBP >130 mm Hg presenting with headaches, blurred vision, or focal neurologic symptoms and **malignant hypertension** (which requires the presence of papilledema). Hypertensive emergencies require immediate BP reduction by 20-25% to prevent or minimize end-organ damage (i.e., hypertensive encephalopathy, intracranial hemorrhage, unstable angina [UA] pectoris, acute myocardial infarction [MI], acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, progressive renal failure, or eclampsia).
- **Isolated systolic hypertension**, defined as an SBP >140 mm Hg and normal DBP, occurs frequently in the elderly (beginning after the fifth decade and increasing with age).

Nonpharmacologic therapy should be initiated with medications added as needed to lower SBP to the appropriate level based on age and comorbidities.

TABLE 3-1 Manifestations of Target Organ Disease

Organ System	Manifestation

Large vessel	Aneurysmal dilation Accelerated atherosclerosis Aortic dissection
Cardiac	*Acute:* Pulmonary edema, myocardial infarction *Chronic:* Clinical or ECG evidence of CAD; LVH by ECG or echocardiogram
Cerebrovascular	*Acute:* Intracerebral bleeding, coma, seizures, mental status changes, TIA, stroke *Chronic:* TIA, stroke
Renal	*Acute:* Hematuria, azotemia *Chronic:* Serum creatinine >1.5 mg/dL, proteinuria >1 + on dipstick
Retinopathy	*Acute:* Papilledema, hemorrhages *Chronic:* Hemorrhages, exudates, arterial nicking

CAD, coronary artery disease; LVH, left ventricular hypertrophy; TIA, transient ischemic attack.

Epidemiology

- The **public health burden** of hypertension is enormous, affecting an estimated 67 million American adults (*Circulation 2014;130:1692*). Indeed, for nonhypertensive individuals aged 55-65 years, the lifetime risk of developing hypertension is 90% (*JAMA 2002;287:1003*).
- Data derived from the Framingham Study have shown that hypertensive patients have a *fourfold* increase in cerebrovascular accidents as well as a *sixfold* increase in congestive heart failure (CHF) when compared to normotensive control subjects.

TABLE 3-2 Classification of Blood Pressure for Adults Age 18 Years and Older[a]

Category	Systolic Pressure (mm Hg)	Diastolic Pressure (mm Hg)
Normal	<120 and	<80
Prehypertension	120-139 or	<80-89
Hypertension, stage 1	140-159 or	90-99
Hypertension, stage 2	>160 or	>100

[a]Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status.

From National High Blood Pressure Education Program. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* Bethesda, MD: National Heart, Lung, and Blood Institute (US); 2004.

- Disease-associated morbidity and mortality, including atherosclerotic cardiovascular disease, stroke, heart failure (HF), and renal insufficiency, increase with higher levels of SBP and DBP.
- Over the last three decades, aggressive treatment of hypertension has resulted in a substantial decrease in death rates from stroke and coronary heart disease (CHD). Unfortunately, rates of end-stage renal disease (ESRD) and hospitalization for CHF have continued to increase. BP control rates have improved but remain poor, with only 50.1% of treated hypertensive patients below their goal BP level (*JAMA 2010;303:2043*).

Etiology

- BP rises with age. Other contributing factors include overweight/obesity, increased dietary sodium intake, decreased physical activity, increased alcohol consumption, and lower dietary intake of fruits, vegetables, and potassium.
- Of all hypertensive patients, more than 90% have primary or essential hypertension; the remainder have secondary hypertension due to causes such as renal parenchymal disease, renovascular disease, pheochromocytoma, Cushing syndrome, primary hyperaldosteronism, coarctation of the aorta, obstructive sleep apnea, and uncommon autosomal dominant or autosomal recessive diseases of the adrenal-renal axis that result in salt retention.

DIAGNOSIS

Clinical Presentation

- BP elevation is usually discovered in asymptomatic individuals during routine health visits.
- Optimal detection and evaluation of hypertension require accurate noninvasive BP measurement, which should be obtained in a seated patient with the arm resting level with the heart. A calibrated, appropriately fitting BP cuff (inflatable bladder encircling at least 80% of the arm) should be used because falsely high readings can be obtained if the cuff is too small.
- Two readings should be taken, separated by 2 minutes. SBP should be noted with the appearance of Korotkoff sounds (phase I) and DBP with the disappearance of sounds (phase V).
- In certain patients, the Korotkoff sounds do not disappear but are present at 0 mm Hg. In this case, the initial muffling of Korotkoff sounds (phase IV) should be taken as the DBP. One should be careful to avoid reporting spuriously low BP readings due to an auscultatory gap, which is caused by the disappearance and reappearance of Korotkoff sounds in hypertensive patients and may account for up to a 25-mm Hg gap between true and measured SBP. Hypertension should be confirmed in both arms, and the higher reading should be used.

History

- History should seek to discover secondary causes of hypertension and note the presence of medications and supplements that can affect BP (e.g., decongestants, oral contraceptives, appetite suppressants, sympathomimetics, venlafaxine, tricyclic antidepressants, monoamine oxidase inhibitors [MAOIs], chlorpromazine, some herbal supplements [ma huang], steroids, NSAIDs, cyclosporine, caffeine, thyroid hormones, cocaine, alcohol use, erythropoietin).
  - A diagnosis of secondary hypertension should be considered in the following situations:
  - Age at onset younger than 30 or older than 60 years
  - Hypertension that is difficult to control after therapy has been initiated
  - Stable hypertension that becomes difficult to control
  - Clinical occurrence of a hypertensive crisis
  - The presence of signs or symptoms of a secondary cause such as hypokalemia or metabolic alkalosis that is not explained by diuretic therapy

- In patients who present with significant hypertension at a young age, a careful family history may give clues to forms of hypertension that follow simple Mendelian inheritance.

Physical Examination

Physical examination should include investigation for target organ damage or a secondary cause of hypertension by noting the presence of carotid bruits, an S3 or S4, cardiac murmurs, neurologic deficits, elevated jugular venous pressure, rales, retinopathy, unequal pulses, enlarged or small kidneys, cushingoid features, and abdominal bruits. Overweight/obesity should be assessed by measurement of height and weight and/or abdominal waist circumference.

Differential Diagnosis

- Hypertension may be part of several important syndromes of withdrawal from drugs, including alcohol, cocaine, and opioid analgesics. Rebound increases in BP also may be seen in patients who abruptly discontinue antihypertensive therapy, particularly β-adrenergic antagonists and central α_2-agonists (see Complications).
- Cocaine and other sympathomimetic drugs (e.g., amphetamines, phencyclidine hydrochloride) can produce hypertension in the setting of acute intoxication and when the agents are discontinued abruptly after chronic use. Hypertension is often complicated by other end-organ insults, such as ischemic heart disease, stroke, and seizures. Phentolamine is effective in acute management, and sodium nitroprusside or nitroglycerin can be used as an alternative. β-Adrenergic antagonists should be avoided due to the risk of unopposed α-adrenergic activity, which can exacerbate hypertension.

Diagnostic Testing

- Tests are needed to help identify patients with possible target organ damage, to help assess cardiovascular risk, and to provide a baseline for monitoring the adverse effects of therapy.
- Basic laboratory data should include urinalysis, hematocrit, plasma glucose, serum potassium, serum creatinine, calcium, and uric acid and fasting lipid levels.
- Other testing includes ECG and chest radiography. Echocardiography may be of value for certain patients to assess cardiac function or detection of left ventricular hypertrophy (LVH).

TREATMENT

- The goal of treatment is to prevent long-term sequelae (i.e., target organ damage) while controlling other modifiable cardiovascular risk factors.
  - In isolated systolic hypertension, the therapeutic goal should be to lower SBP to <140 mm Hg. SBP >140 mm Hg is associated with increased cerebrovascular and cardiac events.
  - In patients with chronic kidney disease or diabetes, BP should be reduced to a goal of <140/90 mm Hg.
  - In patients age ≥60 without chronic kidney disease or diabetes, BP should be reduced to a goal of <150/90 mm Hg. Discretion is warranted in prescribing medication to lower BP that may affect cardiovascular risk adversely in other ways (e.g., glucose control, lipid metabolism, uric acid levels).
- In the absence of hypertensive crisis, BP should be reduced gradually to avoid end-organ (e.g., cerebral) ischemia.
- Lifestyle modifications should be encouraged in all hypertensive patients regardless of whether they require medication (Table 3-3). These changes may have beneficial effects on other cardiovascular risk factors. Some of these lifestyle modifications include cessation of smoking, reduction in body weight if the patient is overweight, judicious consumption of alcohol, adequate nutritional intake of minerals and vitamins, reduction in sodium intake, and increased physical activity.

TABLE 3-3 Lifestyle Modifications and Effects

Modification	Approximate SBP Reduction
Weight reduction (for every 10-kg weight loss)	5-20 mm Hg
Adoption of DASH eating plan	8-14 mm Hg
Dietary sodium reduction (intake <2 g/d)	2-8 mm Hg
Physical activity (150 min/wk)	4-9 mm Hg
Moderation of alcohol consumption (intake <2 drinks/d)	2-4 mm Hg

DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure.

- Barring an overt need for immediate pharmacologic therapy, most patients should be given the opportunity to achieve a reduction in BP over an interval of 3-6 months by applying nonpharmacologic modifications and pharmacologic therapies if needed.

Medications

- **Initial drug therapy**
  - Initial drug choice may be affected by coexistent factors such as age, race, angina, HF, renal insufficiency, LVH, obesity, hyperlipidemia, gout, and bronchospasm. Cost and drug interactions should also be considered. The BP response is usually consistent within a given class of agents; therefore, if a drug fails to control BP, another agent from the same class is unlikely to be effective. At times, however, a change within drug class may be useful in reducing adverse effects. The lowest possible effective dosage should be used to control BP, adjusted every 1-2 months as needed (Table 3-4).
    - Diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) should be considered first-line therapy for the general nonblack population, including those with diabetes (those with chronic kidney disease are discussed below). Multiple large randomized controlled trials have shown comparable effects on decreasing overall cardiovascular and cerebrovascular mortality for all four drug classes (*JAMA 2014;311(5):507*).
    - In the general black population, including those with diabetes, a diuretic or CCB can be considered for first-line therapy. Data from the ALLHAT trial have shown decreased cardiovascular and cerebrovascular morbidity and mortality with the use of thiazide diuretics or CCB over an ACE inhibitor (*JAMA 2002;288:2981*).
  - In patients with chronic kidney disease, initial or combination therapy with an ACE inhibitor or ARB should be considered.
- **Additional therapy.** When a second drug is needed, it should generally be chosen from among the other first-line agents.
- **Adjustments of a therapeutic regimen.** Before considering a modification of therapy because of inadequate response to the current regimen, other possible contributing factors should be investigated. Poor patient compliance, use of antagonistic drugs (i.e.,

sympathomimetics, venlafaxine, tricyclic antidepressants, MAOIs, chlorpromazine, some herbal supplements [ma huang], steroids, NSAIDs, cyclosporine, caffeine, thyroid hormones, cocaine, erythropoietin), inappropriately high sodium intake, or increased alcohol consumption should be considered and may be the cause of inadequate BP response. Secondary causes of hypertension should be considered when a previously effective regimen becomes inadequate and other confounding factors are absent.

TABLE 3-4 Commonly Used Antihypertensive Agents by Functional Class

Drugs by Class	Properties	Initial Dose	Dosage Range (mg)
β-Adrenergic Antagonists			
Atenolol[a]	Selective	50 mg PO daily	25-100
Betaxolol[a]	Selective	10 mg PO daily	5-40
Bisoprolol[a]	Selective	5 mg PO daily	2.5-20
Metoprolol	Selective	50 mg PO bid	50-450
Metoprolol XL	Selective	50-100 mg PO daily	50-400
Nebivolol[a,b]	Selective with vasodilatory properties	5 mg PO daily	5-40
Nadolola	Nonselective	40 mg PO daily	20-240
Propranolol	Nonselective	40 mg PO bid	40-240
Propranolol LA	Nonselective	80 mg PO daily	60-240
Timolol	Nonselective	10 mg PO bid	20-40
Pindolol	ISA	5 mg PO daily	10-60
Labetalol	α- and β-antagonist properties	100 mg PO bid	200-1200
Carvedilol	α- and β-antagonist properties	6.25 mg PO bid	12.5-50
Carvedilol CR[b]	α- and β-antagonist properties	10 mg PO daily	10-80
Acebutolol[a]	ISA, selective	200 mg PO bid, 400 mg PO daily	200-1200
Calcium Channel Antagonists			
Amlodipine	DHP	5 mg PO daily	2.5-10
Diltiazem		30 mg PO qid	90-360
Diltiazem LA		180 mg PO daily	120-540
Diltiazem CD		180 mg PO daily	120-480
Diltiazem XR		180 mg PO daily	120-540

Diltiazem XT		180 mg PO daily	120-480
Isradipine	DHP	2.5 mg PO bid	2.5-10
Nicardipine[b]	DHP	20 mg PO tid	60-120
Nifedipine	DHP	10 mg PO tid	30-120
Nifedipine XL (or CC)	DHP	30 mg PO daily	30-90
Nisoldipine	DHP	20 mg PO daily	20-40
Verapamil		80 mg PO tid	80-480
Verapamil SR		120 mg PO daily	120-480
Angiotensin-Converting Enzyme Inhibitors[c]			
Benazepril		10 mg PO bid	10-40
Captopril		25 mg PO bid-tid	50-450
Enalapril		5 mg PO daily	2.5-40
Fosinopril		10 mg PO daily	10-40
Lisinopril		10 mg PO daily	5-40
Moexipril		7.5 mg PO daily	7.5-30
Quinapril		10 mg PO daily	5-80
Ramipril		2.5 mg PO daily	1.25-20
Trandolapril		1-2 mg PO daily	1-4
Perindopril		4 mg PO daily	2-16
Angiotensin II Receptor Blockers[c]			
Azilsartan[b]		40 mg PO daily	40-80
Candesartan		8 mg PO daily	8-32
Eprosartan		600 mg PO daily	600-800
Irbesartan		150 mg PO daily	150-300
Olmesartanb		20 mg PO daily	20-40
Losartan		50 mg PO daily	25-100
Telmisartan		40 mg PO daily	20-80
Valsartan		80 mg PO daily	80-320

Direct Renin Inhibitors[c]			
Aliskiren[b]		150 mg PO daily	150-300
Diuretics[c]			
Chlorthalidone	Thiazide diuretic	25 mg PO daily	12.5-50
Hydrochlorothiazide	Thiazide diuretic	12.5 mg PO daily	12.5-50
Hydroflumethiazide[b]	Thiazide diuretic	50 mg PO daily	50-100
Indapamide	Thiazide diuretic	1.25 mg PO daily	2.5-5
Methyclothiazide	Thiazide diuretic	2.5 mg PO daily	2.5-5
Metolazone	Thiazide diuretic	2.5 mg PO daily	1.25-5
Bumetanide	Loop diuretic	0.5 mg PO daily (or IV)	0.5-5
Ethacrynic acid[b]	Loop diuretic	50 mg PO daily (or IV)	25-100
Furosemide	Loop diuretic	20 mg PO daily (or IV)	20-320
Torsemide	Loop diuretic	5 mg PO daily (or IV)	5-10
Amiloride	Potassium-sparing diuretic	5 mg PO daily	5-10
Triamterene[b]	Potassium-sparing diuretic	50 mg PO bid	50-200
Eplerenone	Aldosterone antagonist	25 mg PO daily	25-100
Spironolactone	Aldosterone antagonist	25 mg PO daily	25-100
α-Adrenergic Antagonists			
Doxazosin		1 mg PO daily	1-16
Prazosin		1 mg PO bid-tid	1-20
Terazosin		1 mg PO at bedtime	1-20
Centrally Acting Adrenergic Agents			
Clonidine		0.1 mg PO bid	0.1-1.2
Clonidine patch		TTS 1/wk (equivalent to 0.1 mg/d release)	0.1-0.3
Guanfacine		1 mg PO daily	1-3
Guanabenz		4 mg PO bid	4-64
Methyldopa[a]		250 mg PO bid-tid	250-2000

Direct-Acting Vasodilators		
Hydralazine[a]	10 mg PO qid	50-300
Minoxidil	5 mg PO daily	2.5-100
Miscellaneous		
Reserpine	0.5 mg PO daily	0.01-0.25

DHP, dihydropyridine; ISA, intrinsic sympathomimetic activity; TTS, transdermal therapeutic system.

[a]Adjusted in renal failure.

[b]Available only in brand name. Assume all drugs are available in generic form unless otherwise denoted by superscript "*b*."

[c]Renal function should be considered for all angiotensin-converting enzyme inhibitors before initiation.

P.63

P.64

P.65

P.66

- **Diuretics** (see Table 3-4) are effective agents in the therapy of hypertension and have been shown to reduce the incidence of stroke and cardiovascular events. Several classes of diuretics are available, generally categorized by their site of action in the kidney.
- **Thiazide** and thiazide-like diuretics (e.g., hydrochlorothiazide, chlorthalidone) block sodium reabsorption predominantly in the distal convoluted tubule by inhibition of the thiazide-sensitive Na/Cl cotransporter. Thiazide diuretics can produce weakness, muscle cramps, and impotence. Metabolic side effects include hypokalemia, hypomagnesemia, hyperlipidemia (with increases in low-density lipoproteins [LDLs] and triglyceride levels), hypercalcemia, hyperglycemia, hyperuricemia, hyponatremia, and rarely, azotemia. Thiazide-induced pancreatitis has also been reported. Metabolic side effects may be limited when thiazides are used in low doses (e.g., hydrochlorothiazide, 12.5-25.0 mg/d).
- **Loop diuretics** (e.g., furosemide, bumetanide, ethacrynic acid, torsemide) block sodium reabsorption in the thick ascending loop of Henle through inhibition of the Na/K/2Cl cotransporter and are the most effective agents in patients with renal insufficiency (estimated glomerular filtration rate <35 mL/min/1.73 m^2). Loop diuretics can cause electrolyte abnormalities such as hypomagnesemia, hypocalcemia, and hypokalemia, and can also produce irreversible ototoxicity (usually dose related and more common with parenteral therapy).
- **Spironolactone and eplerenone, potassium-sparing agents**, act by competitively inhibiting the actions of aldosterone on the kidney. Triamterene and amiloride are potassium-sparing drugs that inhibit the epithelial Na^+ channel in the distal nephron to inhibit reabsorption of Na^+ and secretion of potassium ions. Potassium-sparing diuretics are weak agents when used alone; thus, they are often combined with a thiazide for added potency. Aldosterone antagonists may have an additional benefit in improving myocardial function in HF; this effect may be independent of its effect on renal transport mechanisms. Spironolactone and eplerenone can produce hyperkalemia; however, the gynecomastia that may occur in men and breast tenderness in women are not seen with eplerenone. Triamterene (usually in combination with hydrochlorothiazide) can cause renal tubular damage and renal calculi. Unlike thiazides, potassium-sparing and loop diuretics do not cause adverse lipid effects.
- **Calcium channel antagonists** (see Table 3-4) generally have no significant central nervous system (CNS) side effects and can be used to treat diseases, such as angina pectoris, that can coexist with hypertension. **Due to the concern that the use of short-acting dihydropyridine calcium channel antagonists may increase the number of ischemic cardiac events, they are not indicated for hypertension management** (*JAMA 1995;274:620*); long-acting agents are considered safe in the management of hypertension (*Am J Cardiol 1996;77:81*).
  - **Classes of calcium channel antagonists** include diphenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and dihydropyridines (e.g., nifedipine). The dihydropyridines include many newer second-generation drugs (e.g., amlodipine, felodipine, isradipine, and nicardipine), which are more vasoselective and have longer plasma half-lives than nifedipine. Verapamil and diltiazem have negative cardiac inotropic and chronotropic effects. Nifedipine also has a negative inotropic effect, but in clinical use, this effect is much less pronounced than that of verapamil or diltiazem because of peripheral vasodilation and reflex tachycardia. Less negative inotropic effects have been observed with the second-generation dihydropyridines. All calcium channel

antagonists are metabolized in the liver; thus in patients with cirrhosis, the dosing interval should be adjusted accordingly. Some of these drugs also inhibit the metabolism of other hepatically cleared medications (e.g., cyclosporine). Verapamil and diltiazem should be used with caution in patients with cardiac conduction abnormalities, and they can worsen HF in patients with decreased left ventricular function.

- **Side effects** of verapamil include constipation, nausea, headache, and orthostatic hypotension. Diltiazem can cause nausea, headache, and rash. Dihydropyridines can cause lower extremity edema, flushing, headache, and rash. Calcium channel antagonists have no significant effects on glucose tolerance, electrolytes, or lipid profiles.

- **Inhibitors of the renin-angiotensin system** (see Table 3-4) include ACE inhibitors, ARBs, and a direct renin inhibitor.
  - **ACE inhibitors** may have beneficial effects in patients with concomitant HF or kidney disease. One study has also suggested that ACE inhibitors (ramipril) may significantly reduce the rate of death, MI, and stroke in patients without HF or low ejection fraction (*N Engl J Med 2000;342:145*). Additionally, they can reduce hypokalemia, hypercholesterolemia, hyperglycemia, and hyperuricemia caused by diuretic therapy and are particularly effective in states of hypertension associated with a high renin state (e.g., scleroderma renal crisis). **Side effects** associated with the use of ACE inhibitors are infrequent. They can cause a dry cough (up to 20% of patients), angioneurotic edema, and hypotension, but they do not cause levels of lipids, glucose, or uric acid to increase. ACE inhibitors that contain a sulfhydryl group (e.g., captopril) may cause taste disturbance, leukopenia, and a glomerulopathy with proteinuria. Because ACE inhibitors cause preferential vasodilation of the efferent arteriole in the kidney, worsening of renal function may occur in patients who have decreased renal perfusion or who have preexisting severe renal insufficiency. ACE inhibitors can cause hyperkalemia and should be used with caution in patients with a decreased glomerular filtration rate (GFR) who are taking potassium supplements or who are receiving potassium-sparing diuretics.
  - **ARBs** are a class of antihypertensive drugs that are effective in diverse patient populations (*N Engl J Med 1996;334:1649*). ARBs are useful alternatives in patients with HF who are unable to tolerate ACE inhibitors (*N Engl J Med 2001;345:1667*). **Side effects** of ARBs occur rarely but include angioedema, allergic reaction, and rash.
  - The **direct renin inhibitor** class consists of one agent, aliskiren, that is indicated solely for the treatment of hypertension (see Table 3-4). It may be used in combination with other antihypertensive agents; however, combined use with ACE inhibitors or ARBs is contraindicated in patients with diabetes (*Food and Drug Administration [FDA] Drug Safety Communication, April 2012*).

- **β-Adrenergic antagonists** (see Table 3-4) are part of medical regimens that have been proven to decrease the incidence of stroke, MI, and HF. β-Adrenergic antagonists work via competitive inhibition of the effects of catecholamines at β-adrenergic receptors, which decreases heart rate and cardiac output. These agents also decrease plasma renin and cause a resetting of baroreceptors to accept a lower level of BP. β-Adrenergic antagonists cause release of vasodilatory prostaglandins, decrease plasma volume, and may also have a CNS-mediated antihypertensive effect.
  - **Classes of β-adrenergic antagonists** can be subdivided into those that are cardioselective, with primarily β_1-blocking effects, and those that are nonselective, with β_1- and β_2-blocking effects. At low doses, the cardioselective agents can be given with caution to patients with mild chronic obstructive pulmonary disease, diabetes mellitus (DM), or peripheral vascular disease. At higher doses, these agents lose their β_1 selectivity and may cause unwanted effects in these patients. β-Adrenergic antagonists can also be categorized according to the presence or absence of partial agonist or intrinsic sympathomimetic activity (ISA). β-Adrenergic antagonists with ISA cause less bradycardia than do those without it. In addition, there are agents with mixed properties having both α- and β-adrenergic antagonist actions (labetalol and carvedilol). Nebivolol is a highly selective β-adrenergic antagonist that is vasodilatory through an unclear mechanism.
  - **Side effects** include high-degree atrioventricular (AV) block, HF, Raynaud phenomenon, and impotence. Lipophilic β-adrenergic antagonists, such as propranolol, have a

    higher incidence of CNS side effects including insomnia and depression. Propranolol can also cause nasal congestion. β-Adrenergic antagonists can cause adverse effects on the lipid profile; increased triglyceride and decreased high-density lipoprotein (HDL) levels occur mainly with nonselective β-adrenergic antagonists but generally do not occur when β-adrenergic antagonists with ISA are used. Pindolol, a selective β-adrenergic antagonist with ISA, may actually increase HDL and nominally increase triglycerides. Side effects of labetalol include hepatocellular damage, postural hypotension, a positive antinuclear antibody (ANA) test, a lupus-like syndrome, tremors, and potential hypotension in the setting of halothane anesthesia. Carvedilol appears to have a similar side effect profile to other β-adrenergic antagonists. Both labetalol and carvedilol have negligible effects on lipids. Rarely, reflex tachycardia may occur because of the initial vasodilatory effect of labetalol and carvedilol. Because β-receptor density is increased with chronic antagonism, abrupt withdrawal of these agents can precipitate angina pectoris, increases in BP, and other effects attributable to an increase in adrenergic tone.

- **Selective α-adrenergic antagonists** such as prazosin, terazosin, and doxazosin have replaced nonselective α-adrenergic antagonists such as phenoxybenzamine (see Table 3-4) in the treatment of essential hypertension. Based on the ALLHAT trial, these drugs appear to be less efficacious than diuretics, CCBs, and ACE inhibitors in reducing primary end points of cardiovascular disease

when used as monotherapy (*JAMA 2002;283:1967*; *JAMA 2002;288:2981*).

Side effects of these agents include a "first-dose effect," which results from a greater decrease in BP with the first dose than with subsequent doses. Selective α_1-adrenergic antagonists can cause syncope, orthostatic hypotension, dizziness, headache, and drowsiness. In most cases, side effects are self-limited and do not recur with continued therapy. Selective α_1-adrenergic antagonists may improve lipid profiles by decreasing total cholesterol and triglyceride levels and increasing HDL levels. Additionally, these agents can improve the negative effects on lipids induced by thiazide diuretics and β-adrenergic antagonists. Doxazosin specifically may be less effective at lowering SBP than thiazide diuretics and may be associated with a higher risk of HF and stroke in patients with hypertension and at least one additional risk factor for coronary artery disease (CAD) (*JAMA 2002;283:1967*).

- **Centrally acting adrenergic agents** (see Table 3-4) are potent antihypertensive agents. In addition to its oral dosage forms, clonidine is available as a transdermal patch that is applied weekly.

  Side effects may include bradycardia, drowsiness, dry mouth, orthostatic hypotension, galactorrhea, and sexual dysfunction. Transdermal clonidine causes a rash in up to 20% of patients. These agents can precipitate HF in patients with decreased left ventricular function, and abrupt cessation can precipitate an acute withdrawal syndrome (AWS) of elevated BP, tachycardia, and diaphoresis. Methyldopa produces a positive direct antibody (Coombs) test in up to 25% of patients, but significant hemolytic anemia is much less common. If hemolytic anemia develops secondary to methyldopa, the drug should be withdrawn. Severe cases of hemolytic anemia may require treatment with glucocorticoids. Methyldopa also causes positive ANA test results in approximately 10% of patients and can cause an inflammatory reaction in the liver that is indistinguishable from viral hepatitis; fatal hepatitis has been reported. Guanabenz and guanfacine decrease total cholesterol levels, and guanfacine can also decrease serum triglyceride levels.
- **Direct-acting vasodilators** are potent antihypertensive agents (see Table 3-4) now reserved for refractory hypertension or specific circumstances such as the use of hydralazine in pregnancy.
  - Hydralazine in combination with nitrates is useful in treating patients with hypertension and HF with reduced ejection fraction (see Chapter 5, Heart Failure and Cardiomyopathy). **Side effects** of hydralazine therapy may include headache, nausea,

    emesis, tachycardia, and postural hypotension. Asymptomatic patients may have a positive ANA test result, and a hydralazine-induced systemic lupus-like syndrome may develop in approximately 10% of patients. Patients at greater risk for the latter complication include those treated with excessive doses (e.g., >400 mg/d), those with impaired renal or cardiac function, and those with the slow acetylation phenotype. Hydralazine should be discontinued if clinical evidence of a lupus-like syndrome develops and a positive ANA test result is present. The syndrome usually resolves with discontinuation of the drug, leaving no adverse long-term effects.
  - **Side effects** of minoxidil include weight gain, hypertrichosis, hirsutism, ECG abnormalities, and pericardial effusions.
- **Reserpine, guanethidine, and guanadrel** (see Table 3-4) were among the first effective antihypertensive agents available. Currently, these drugs are not regarded as first- or second-line therapy because of their significant side effects.

  Side effects of reserpine include severe depression in approximately 2% of patients. Sedation and nasal stuffiness also are potential side effects. Guanethidine can cause severe postural hypotension through a decrease in cardiac output, a decrease in peripheral resistance, and venous pooling in the extremities. Patients who are receiving guanethidine with orthostatic hypotension should be cautioned to arise slowly and to wear support hose. Guanethidine can also cause ejaculatory failure and diarrhea.
- **Parenteral antihypertensive agents** are indicated for the immediate reduction of BP in patients with hypertensive emergencies. Judicious administration of these agents (Table 3-5) may also be appropriate in patients with hypertension complicated by HF or MI. These drugs are also indicated for individuals who have perioperative hypertensive urgency or are in need of emergency surgery. If possible, an accurate baseline BP should be determined before the initiation of therapy. In the setting of hypertensive emergency, the patient should be admitted to an intensive care unit (ICU) for close monitoring, and an intra-arterial monitor should be used when available. Although parenteral agents are indicated as a first-line treatment in hypertensive emergencies, oral agents may also be effective in this group; the choice of drug and route of administration must be individualized. If parenteral agents are used initially, oral medications should be administered shortly thereafter to facilitate rapid weaning from parenteral therapy.
  - **Sodium nitroprusside**, a direct-acting arterial and venous vasodilator, is the drug of choice for most hypertensive emergencies (see Table 3-5). It reduces BP rapidly and is easily titratable, and its action is short lived when discontinued. Patients should be monitored very closely to avoid an exaggerated hypotensive response. Therapy for more than 48-72 hours with a high cumulative dose or renal insufficiency may cause accumulation of thiocyanate, a toxic metabolite. Thiocyanate toxicity may cause paresthesias, tinnitus, blurred vision, delirium, or seizures. Serum thiocyanate levels should be kept at <10 mg/dL. Patients on high doses (>2-3 mg/kg/min) or those with renal dysfunction should have serum levels of thiocyanate drawn after 48-72 hours of therapy. In patients with normal renal function or those receiving lower doses, levels can be drawn after 5-7 days. Hepatic dysfunction may result in accumulation of cyanide, which can cause metabolic acidosis, dyspnea, vomiting, dizziness, ataxia, and syncope. Hemodialysis should be considered for thiocyanate poisoning. Nitrites and thiosulfate can be administered intravenously for cyanide poisoning.
  - **Nitroglycerin** given as a continuous IV infusion (see Table 3-5) may be appropriate in situations in which sodium nitroprusside is relatively contraindicated, such as in patients with severe coronary insufficiency or advanced renal or hepatic disease. It is the

preferred agent for patients with moderate hypertension in the setting of acute coronary ischemia or after coronary artery bypass surgery because of its more favorable effects on pulmonary gas exchange and collateral coronary blood flow. In patients with severely elevated BP, sodium nitroprusside remains the agent of choice. Nitroglycerin reduces

P.70

P.71

P.72

preload more than afterload and should be used with caution or avoided in patients who have inferior MI with right ventricular infarction and are dependent on preload to maintain cardiac output.

TABLE 3-5 Parenteral Antihypertensive Drug Preparations

Drug	Administration	Onset	Duration of Action	Dosage	Adverse Effects and Comments
Fenoldopam	IV infusion	<5 min	30 min	0.1-0.3 μg/kg/min	Tachycardia, nausea, vomiting
Sodium nitroprusside	IV infusion	Immediate	2-3 min	0.5-10 μg/kg/min (initial dose, 0.25 μg/kg/min for eclampsia and renal insufficiency)	Hypotension, nausea, vomiting, apprehension; risk of thiocyanate and cyanide toxicity is increased in renal and hepatic insufficiency, respectively; levels should be monitored; must shield from light
Diazoxide	IV bolus	15 min	6-12 h	50-100 mg q5-10min, up to 600 mg	Hypotension, tachycardia, nausea, vomiting, fluid retention, hyperglycemia; may exacerbate myocardial ischemia, heart failure, or aortic dissection
Labetalol	IV bolus IV infusion	5-10 min	3-6 h	20-80 mg q5-10min, up to 300 mg 0.5-2 mg/min	Hypotension, heart block, heart failure, bronchospasm, nausea, vomiting, scalp tingling, paradoxical pressor response; may not be effective in patients receiving α- or β-antagonists
Nitroglycerin	IV infusion	1-2 min	3-5 min	5-250 μg/min	Headache, nausea, vomiting. Tolerance may develop with prolonged use.
Esmolol	IV bolus IV infusion	1-5 min	10 min	500 μg/kg/min for first 1 min 50-300 μg/kg/min	Hypotension, heart block, heart failure, bronchospasm
Phentolamine	IV bolus	1-2 min	3-10 min	5-10 mg q5-15min	Hypotension, tachycardia, headache, angina, paradoxical pressor response
Hydralazine (for treatment of eclampsia)	IV bolus	10-20 min	3-6 h	10-20 mg q20min (if no effect after 20 mg, try another agent)	Hypotension, fetal distress, tachycardia, headache, nausea, vomiting, local thrombophlebitis. Infusion site should be changed after 12 h.
Methyldopate (for treatment of eclampsia)	IV bolus	30-60 min	10-16 h	250-500 mg	Hypotension

Nicardipine	IV infusion	1-5 min	3-6 h	5 mg/h, increased by 1.0-2.5 mg/h q15min, up to 15 mg/h	Hypotension, headache, tachycardia, nausea, vomiting
Enalaprilat	IV bolus	5-15 min	1-6 h	0.6255 mg q6h	Hypotension

- **Labetalol** can be administered parenterally (see Table 3-5) in hypertensive crisis, even in patients in the early phase of an acute MI, and is the drug of choice in hypertensive emergencies that occur during pregnancy. When given intravenously, the β-adrenergic antagonist effect is greater than the α-adrenergic antagonist effect. Nevertheless, symptomatic postural hypotension may occur with IV use; thus, patients should be treated in a supine position. Labetalol may be particularly beneficial during adrenergic excess (e.g., clonidine withdrawal, pheochromocytoma, post-coronary bypass grafting). Because the half-life of labetalol is 5-8 hours, intermittent IV bolus dosing may be preferable to IV infusion. IV infusion can be discontinued before oral labetalol is begun. When the supine DBP begins to rise, oral dosing can be initiated at 200 mg PO, followed in 6-12 hours by 200-400 mg PO, depending on the BP response.
- **Esmolol** is a parenteral, short-acting, cardioselective β-adrenergic antagonist (see Table 3-5) that can be used in the treatment of hypertensive emergencies in patients in whom β-blocker intolerance is a concern. Esmolol is also useful for the treatment of aortic dissection. β-Adrenergic antagonists may be ineffective when used as monotherapy in the treatment of severe hypertension and are frequently combined with other agents (e.g., with sodium nitroprusside in the treatment of aortic dissection).
- **Nicardipine** is an effective IV calcium antagonist preparation (see Table 3-5) approved for use in postoperative hypertension. Side effects include headache, flushing, reflex tachycardia, and venous irritation. Nicardipine should be administered via a central venous line. If it is given peripherally, the IV site should be changed q12h. Fifty percent of the peak effect is seen within the first 30 minutes, but the full peak effect is not achieved until after 48 hours of administration.
- **Enalaprilat** is the active de-esterified form of enalapril (see Table 3-5) that results from hepatic conversion after an oral dose. Enalaprilat (as well as other ACE inhibitors) has been used effectively in cases of severe and malignant hypertension. However, variable and unpredictable results have also been reported. ACE inhibition can cause rapid BP reduction in hypertensive patients with high renin states such as renovascular hypertension, concomitant use of vasodilators, and scleroderma renal crisis; thus, enalaprilat should be used cautiously to avoid precipitating hypotension. Therapy can be changed to an oral preparation when IV therapy is no longer necessary.
- **Diazoxide and hydralazine** are only rarely used in hypertensive crises and offer little or no advantage to the agents discussed previously. It should be noted, however, that hydralazine is a useful agent in pregnancy-related hypertensive emergencies because of its established safety profile.
- **Fenoldopam** is a selective agonist to peripheral dopamine-1 receptors, and it produces vasodilation, increases renal perfusion, and enhances natriuresis. Fenoldopam has a short duration of action; the elimination half-life is <10 minutes. The drug has important application as parenteral therapy for high-risk hypertensive surgical patients and the perioperative management of patients undergoing organ transplantation.

- **Oral loading of antihypertensive agents** has been used successfully in patients with hypertensive crisis when urgent but not immediate reduction of BP is indicated.
  - **Oral clonidine loading** is achieved by using an initial dose of 0.2 mg PO followed by 0.1 mg PO q1h to a total dose of 0.7 mg or a reduction in diastolic pressure of 20 mm Hg or more. BP should be checked at 15-minute intervals over the first hour, 30-minute intervals over the second hour, and then hourly. After 6 hours, a diuretic can be added, and an 8-hour clonidine dosing interval can be begun. Sedative side effects are significant.

  - Sublingual nifedipine has an onset of action within 30 minutes but can produce wide fluctuations and excessive reductions in BP. Because of the potential for adverse cardiovascular events (stroke/MI), sublingual nifedipine should be avoided in the acute management of elevated BP. Side effects include facial flushing and postural hypotension.

SPECIAL CONSIDERATIONS

- **Hypertensive crisis.** In hypertensive emergency, control of acute or ongoing end-organ damage is more important than the absolute level of BP. BP control with a rapidly acting parenteral agent should be accomplished as soon as possible (within 1 hour) to reduce the chance of permanent organ dysfunction and death. A reasonable goal is a 20-25% reduction of mean arterial pressure or a reduction of the diastolic pressure to 100-110 mm Hg over a period of minutes to hours. A precipitous fall in BP may occur in patients who are elderly, volume depleted, or receiving other antihypertensive agents. BP control in hypertensive urgencies can be accomplished more slowly. The initial goal of therapy in urgency should be to achieve a DBP of 100-110 mm Hg. Excessive or rapid

decreases in BP should be avoided to minimize the risk of cerebral hypoperfusion or coronary insufficiency. Normal BP can be attained gradually over several days as tolerated by the individual patient.

- **Aortic dissection** Acute proximal aortic dissection (type A) is a surgical emergency, whereas uncomplicated distal dissection (type B) can be treated successfully with medical therapy alone. All patients, including those treated surgically, require acute and chronic antihypertensive therapy to provide initial stabilization and to prevent complications (e.g., aortic rupture, continued dissection). Medical therapy of chronic stable aortic dissection should seek to maintain SBP at or below 130-140 mm Hg if tolerated. Antihypertensive agents with negative inotropic properties, including calcium channel antagonists, β-adrenergic antagonists, methyldopa, clonidine, and reserpine, are preferred for management in the postacute phase.
  - **Sodium nitroprusside** is considered the initial drug of choice because of the predictability of response and absence of tachyphylaxis. The dose should be titrated to achieve an SBP of 100-120 mm Hg or the lowest possible BP that permits adequate organ perfusion. Nitroprusside alone causes an increase in left ventricular contractility and subsequent arterial shearing forces, which contribute to ongoing intimal dissection. Thus, when using sodium nitroprusside, adequate simultaneous **β-adrenergic antagonist therapy** is essential, regardless of whether systolic hypertension is present. Traditionally, propranolol has been recommended. **Esmolol**, a cardioselective class intravenous β-adrenergic antagonist with a very short duration of action, may be preferable, especially in patients with relative contraindications to β-antagonists. If esmolol is tolerated, a longer acting β-adrenergic antagonist should be used.
  - **IV labetalol** has been used successfully as a single agent in the treatment of acute aortic dissection. Labetalol produces a dose-related decrease in BP and lowers contractility. It has the advantage of allowing for oral administration after the acute stage of dissection has been managed successfully.
- **The elderly hypertensive patient** (age >60 years) is generally characterized by increased vascular resistance, decreased plasma renin activity, and greater LVH than in younger patients. Often, elderly hypertensive patients have coexisting medical problems that must be considered when initiating antihypertensive therapy. Drug doses should be increased slowly to avoid adverse effects and hypotension. Diuretics as initial therapy have been shown to decrease the incidence of stroke, fatal MI, and overall mortality in this age group (*JAMA 1991;265:3255*). Calcium channel antagonists decrease vascular resistance, have no adverse effects on lipid levels, and are also good choices for elderly patients. ACE inhibitors and ARBs may be effective agents in this population.

  - **African American hypertensive patients** generally have a lower plasma renin level, higher plasma volume, and higher vascular resistance than do Caucasian patients. Thus, African American patients respond well to diuretics, alone or in combination with calcium channel antagonists. ACE inhibitors, ARBs, and β-adrenergic antagonists are also effective agents in this population, particularly when combined with a diuretic.
  - **The obese hypertensive patient** is characterized by more modest elevations in vascular resistance, higher cardiac output, expanded intravascular volume, and lower plasma renin activity at any given level of arterial pressure. Weight reduction is the primary goal of therapy and is effective in reducing BP and causing regression of LVH.
  - **The diabetic patient** with nephropathy may have significant proteinuria and renal insufficiency, which can complicate management (see Chapter 13, Renal Diseases). Control of BP is the most important intervention shown to slow loss of renal function. ACE inhibitors should be used as first-line therapy, because they have been shown to decrease proteinuria and to slow progressive loss of renal function independent of their antihypertensive effects. ACE inhibitors may also be beneficial in reducing the rates of death, MI, and stroke in diabetics who have cardiovascular risk factors but lack left ventricular dysfunction. Hyperkalemia is a common side effect in diabetic patients treated with ACE inhibitors, especially in those with moderate to severe impairment of their GFR. ARBs are also effective antihypertensive agents and have been shown to slow the rate of progression to ESRD, thus supporting a renal protective effect (*N Engl J Med 2001;345(12):861*).
  - **The patient with chronic renal insufficiency** has hypertension that usually is partially volume dependent. Retention of sodium and water exacerbates the existing hypertensive state, and diuretics are important in the management of this problem. When estimated GFR is <30-35 mL/min/1.73 m^2, loop diuretics are the most effective class. In the presence of proteinuria, ACE inhibitors/ARBs should be considered because higher urinary excretion of protein is associated with a more rapid decline in GFR, regardless of the cause of renal insufficiency.
  - **The hypertensive patient with LVH** is at increased risk for sudden death, MI, and all-cause mortality. Although there is no direct evidence, regression of LVH could be expected to reduce the risk for subsequent complications. ACE inhibitors appear to have the greatest effect on regression (*Am J Hypertens 1998;11(6 Pt 1):631*).
  - **The hypertensive patient with CAD** is at increased risk for UA and MI. β-Adrenergic antagonists can be used as first-line agents in these patients because they can decrease cardiac mortality and subsequent reinfarction in the setting of acute MI and can decrease progression to MI in those who present with UA. β-Adrenergic antagonists also have a role in secondary prevention of cardiac events and in increasing long-term survival after MI. Care should be exercised in those with cardiac conduction system disease. ACE inhibitors are beneficial in patients with CAD and decrease mortality in individuals who present with acute MI, especially those with left ventricular dysfunction (*Eur Heart J 1999;20(2):136*; *N Engl J Med 1991;325(5):293*; *Lancet 1995;345(8951):669*; *Lancet 1994;343(8906):1115*).

- **The hypertensive patient with HF** is at risk for progressive left ventricular dilatation and sudden death. In this population, ACE inhibitors decrease mortality (*N Engl J Med 1992;327:685*), and in the setting of acute MI, they decrease the risk of recurrent MI, hospitalization for HF, and mortality (*N Engl J Med 1992;327:669*). ARBs have similar beneficial effects, and they appear to be an effective alternative in patients who are unable to tolerate an ACE inhibitor (*N Engl J Med 2001;345:1667*). Nitrates and hydralazine also decrease mortality in patients with HF irrespective of hypertension, but hydralazine can cause reflex tachycardia and worsening ischemia in patients with unstable coronary syndromes and should be used with caution. Nondihydropyridine calcium channel antagonists should generally be avoided in patients in whom negative inotropic effects would affect their status adversely.

- **In the pregnant patient with hypertension**, there is concern for potential maternal and fetal morbidity and mortality associated with elevated BP and the clinical syndromes of preeclampsia and eclampsia. The possibility of teratogenic or other adverse effects of antihypertensive medications on fetal development also should be considered.
- **Classification of hypertension** during pregnancy has been proposed by the American College of Obstetrics and Gynecology (*Obstet Gynecol 2013;122(5):1122*).
  - **Preeclampsia-eclampsia.** Diagnosis is established if there is *new-onset* hypertension after 20 weeks of gestation and the presence of proteinuria. Elevated SBP ≥140 mm Hg or DBP ≥90 mm Hg on two occasions at least 4 hours apart or a one-time measurement of SBP ≥160 mm Hg or DBP ≥110 mm Hg qualifies as hypertension. If no proteinuria is present, then hypertension along with one of the following qualifies: platelets <100,000/μL, creatinine >1.1 mg/dL (or doubling from baseline), liver transaminases greater than twice the normal, pulmonary edema, or cerebral/visual symptoms. Eclampsia encompasses these parameters in addition to generalized seizures.
  - **Chronic (preexisting) hypertension.** This disorder is defined by a BP ≥140/90 mm Hg before the 20th week of pregnancy.
  - **Chronic hypertension with superimposed preeclampsia.** This classification is used when a woman with chronic hypertension develops worsening hypertension and new proteinuria and/or other features of preeclampsia as outlined previously.
  - **Gestational hypertension.** This disorder is defined by a BP ≥140/90 mm Hg after the 20th week of pregnancy without proteinuria or other features of preeclampsia.
- **Therapy.** Treatment of hypertension in pregnancy should begin if SBP is ≥160 mm Hg or DBP is ≥100 mm Hg.
  - Nonpharmacologic therapy, such as weight reduction and vigorous exercise, is not recommended during pregnancy.
  - Alcohol and tobacco use should be strongly discouraged.
  - Pharmacologic intervention with labetalol, nifedipine, or methyldopa is recommended as first-line therapy because of its proven safety. Other antihypertensives have theoretical disadvantages, but none except the ACE inhibitors have been proven to increase fetal morbidity or mortality.
  - If a patient is suspected of having preeclampsia or eclampsia, urgent referral to an obstetrician who specializes in high-risk pregnancy is recommended.
- **MAOIs.** MAOIs used in association with certain drugs or foods can produce a catecholamine excess state and accelerated hypertension. Interactions are common with tricyclic antidepressants, meperidine, methyldopa, levodopa, sympathomimetic agents, and antihistamines. Tyramine-containing foods that can lead to this syndrome include certain cheeses, red wine, beer, chocolate, chicken liver, processed meat, herring, broad beans, canned figs, and yeast. Nitroprusside, labetalol, and phentolamine have been used effectively in the treatment of accelerated hypertension associated with MAOI use (see Table 3-5).

COMPLICATIONS

Withdrawal syndrome associated with discontinuation of antihypertensive therapy. In substituting therapy in patients with moderate-to-severe hypertension, it is reasonable to increase doses of the new medication in small increments while tapering the previous medication to avoid excessive BP fluctuations. On occasion, an AWS develops, usually within the first 24-72 hours. Occasionally, BP rises to levels that are much higher than those of baseline values. The most severe complications of AWS include encephalopathy, stroke, MI, and sudden death. AWS is associated most commonly with centrally acting adrenergic agents (particularly clonidine) and β-adrenergic antagonists but has been reported with other agents as well, including diuretics. Discontinuation of antihypertensive medications should be done with caution in patients with preexisting cerebrovascular or

cardiac disease. Management of AWS by reinstitution of the previously administered drug is generally effective.

MONITORING/FOLLOW-UP

- BP measurements should be performed on multiple occasions under nonstressful circumstances (e.g., rest, sitting, empty bladder, comfortable temperature) to obtain an accurate assessment of BP in a given patient.

- Hypertension should not be diagnosed on the basis of one measurement alone, unless it is >210/120 mm Hg or accompanied by target organ damage. Two or more abnormal readings should be obtained, preferably over a period of several weeks, before therapy is considered.
- Care should also be used to exclude pseudohypertension, which usually occurs in elderly individuals with stiff, noncompressible vessels. A palpable artery that persists after cuff inflation (Osler sign) should alert the physician to this possibility.
- Home and ambulatory BP monitoring can be used to assess a patient's true average BP, which correlates better with target organ damage. Circumstances in which ambulatory BP monitoring might be of value include:
  - Suspected “white-coat hypertension” (increases in BP associated with the stress of physician office visits), which should be evaluated carefully.
  - Evaluation of possible drug resistance, where suspected.

Dyslipidemia

GENERAL PRINCIPLES

- Lipids are sparingly soluble molecules that include cholesterol, fatty acids, and their derivatives.
- Plasma lipids are transported by lipoprotein particles composed of **apolipoproteins**, **phospholipids**, **free cholesterol**, **cholesterol esters**, and **triglycerides**.
- Human plasma lipoproteins are separated into **five major classes** based on density:
  - Chylomicrons (least dense)
  - Very-low-density lipoproteins (VLDLs)
  - Intermediate-density lipoproteins (IDLs)
  - Low-density lipoproteins (LDLs)
  - High-density lipoproteins (HDLs)
- A sixth class, lipoprotein(a) [Lp(a)], resembles LDL in lipid composition and has a density that overlaps LDL and HDL.
- Physical properties of plasma lipoproteins are summarized in Table 3-6.
- Nearly 90% of patients with CHD have some form of dyslipidemia. Increased levels of LDL cholesterol, remnant lipoproteins, and Lp(a) and decreased levels of HDL cholesterol have all been associated with an increased risk of premature vascular disease (*Circulation 1992;85:2025*; *Circulation 1998;97:2519*).
- **Clinical dyslipoproteinemias**
  - Most dyslipidemias are multifactorial in etiology and reflect the effects of genetic influences coupled with diet, inactivity, smoking, alcohol use, and comorbid conditions such as obesity and DM.
  - Differential diagnosis of the major lipid abnormalities is summarized in Table 3-7.
  - The major genetic dyslipoproteinemias are reviewed in Table 3-8 (*Circulation 1974;49:476*; *J Lipid Res 1990;31:1337*; *Clin Invest 1993;71:362*).
    - Familial hypercholesterolemia and familial combined hyperlipidemia are disorders that contribute significantly to premature cardiovascular disease.

P.77

P.78

P.79

TABLE 3-6 Physical Properties of Plasma Lipoproteins[a]

Lipoprotein	Lipid Composition	Origin	Apolipoproteins
Chylomicrons	TG, 85%; chol, 3%	Intestine	A-I, A-IV; B-48; C-I, C-II, C-III; E
VLDL	TG, 55%; chol, 20%	Liver	B-100; C-I, C-II, C-III; E
IDL	TG, 25%; chol, 35%	Metabolic product of VLDL	B-100; C-I, C-II, C-III; E

LDL	TG, 5%; chol, 60%	Metabolic product of IDL	B-100
HDL	TG, 5%; chol, 20%	Liver, intestine	A-I, A-II; C-I, C-II, C-III; E
Lp(a)	TG, 5%; chol, 60%	Liver	B-100; Apo(a)

Chol, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TG, triglyceride; VLDL, very-low-density lipoprotein.

[a]Remainder of particle is composed of phospholipid and protein.

TABLE 3-7 Differential Diagnosis of Major Lipid Abnormalities

Lipid Abnormality	Primary Disorders	Secondary Disorders
Hypercholesterolemia	Polygenic, familial hypercholesterolemia, familial defective apo B-100	Hypothyroidism, nephrotic syndrome, anorexia nervosa
Hypertriglyceridemia	Lipoprotein lipase deficiency, apo C-II deficiency, apo A-V deficiency, familial hypertriglyceridemia, dysbetalipoproteinemia	Diabetes mellitus, obesity, metabolic syndrome, alcohol use, oral estrogen, renal failure, hypothyroidism, retinoic acid, lipodystrophies
Combined hyperlipidemia	Familial combined hyperlipidemia, dysbetalipoproteinemia	Diabetes mellitus, obesity, metabolic syndrome, nephrotic syndrome, hypothyroidism, lipodystrophies
Low HDL	Familial hypoalphalipoproteinemia, Tangier disease (ABCA1 deficiency), apoA1 mutations, lecithin:cholesterol acyltransferase (LCAT) deficiency	Diabetes mellitus, obesity, metabolic syndrome, hypertriglyceridemia, smoking, anabolic steroids

apo, apolipoprotein; HDL, high-density lipoprotein.

TABLE 3-8 Review of Major Genetic Dyslipoproteinemias

Type of Genetic Dyslipidemia	Typical Lipid Profile	Type of Inheritance	Pattern Phenotypic Features	Other Information
Familial hypercholesterolemia (FH)	▪ Increased LDL cholesterol (>190 mg/dL) cholesterol ▪ Homozygous form or compound heterozygous form (rare) can have LDL cholesterol >500 mg/dL	Autosomal dominant (prevalence of 1 in 200-500 for heterozygote form and 1 in 250,000 for homozygous form)	▪ Premature CAD ▪ Tendon xanthomas ▪ Premature arcus corneae (full arc before age 40) ▪ Homozygous form: planar and tendon xanthomas and CAD in childhood and adolescence	Mutations of the LDL receptor, apolipoprotein B-100, and gain-of-function mutations of proprotein convertase/kexin subtype 9 (PCSK9) lead to impaired uptake and degradation of LDL
Familial combined	▪ High levels of	Autosomal dominant	▪ Premature CAD	Genetic and

hyperlipidemia (FCH)	VLDL, LDL, or both ■ LDL apo B-100 level >130 mg/dL	(prevalence of 1-2%)	■ Patients do *not* develop tendon xanthomas	metabolic defects are not established
Familial dysbetalipoproteinemia	■ Symmetric elevations of cholesterol and triglycerides (300-500 mg/dL) ■ Elevated VLDL-totriglyceride ratio (>0.3)	Autosomal recessive	■ Premature CAD ■ Tuberous or tuberoeruptive xanthomas ■ Planar xanthomas of the palmar creases are essentially pathognomonic	Mutation of ApoE gene Many homozygotes are normolipidemic, and emergence of hyperlipidemia often requires a secondary metabolic factor such as diabetes mellitus, hypothyroidism, or obesity
Familial hypertriglyceridemia (can result in chylomicronemia syndrome)	■ Most patients have triglyceride levels in the range of 150-500 mg/dL ■ Clinical manifestations may occur when triglyceride levels exceed 1500 mg/dL	■ Familial hypertriglyceridemia is an autosomal dominant disorder caused by overproduction of VLDL triglycerides and manifests in adults	■ Eruptive xanthomas ■ Lipemia retinalis ■ Pancreatitis ■ Hepatosplenomegaly	Patients may develop the chylomicronemia syndrome in the presence of secondary factors such as obesity, alcohol use, or diabetes
Familial hyperchylomicronemia	■ Similar to familial hypertriglyceridemia	■ Onset before puberty indicates deficiency of lipoprotein lipase or apo C-II, both autosomal recessive	■ Similar to familial hypertriglyceridemia	Homozygosity for mutations in apoAV and GHIHBP1 also found (rare)

CAD, coronary artery disease; GHIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

- Familial hypercholesterolemia is an underdiagnosed, autosomal co-dominant condition with a prevalence of 1 in 200 to 1 in 500 people that causes elevated LDL cholesterol levels from birth (*Curr Opin Lipidol 2012;23:282*; *Eur Heart J 2013;34:3478*). It is associated with significantly increased risk of early cardiovascular disease when untreated (*J Clin Lipidol 2011;5:133*).
- Familial combined hyperlipidemia has a prevalence of 1-2% and typically presents in adulthood, although obesity and high dietary fat and sugar intake have led to increased presentation in childhood and adolescence (*J Clin Endocrinol Metab 2012;97:2969*).

- **Standards of care for hyperlipidemia**
  - LDL cholesterol-lowering therapy, particularly with hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as statins), lowers the risk of CHD-related death, morbidity, and revascularization procedures in patients ***with*** (secondary prevention) (*Lancet 1994;344:1383*; *N Engl J Med 1996;335:1001*; *N Engl J Med 1998;339:1349*; *Lancet 2002;360:7*) ***or without*** (primary prevention) (*Lancet 2002;360:7*; *N Engl J Med 1995;333:1301*; *JAMA 1998;279:1615*; *Lancet 2003;361:1149*; *Lancet 2004;364:685*) known CHD.
  - Prevention of atherosclerotic cardiovascular disease (ASCVD) is the primary goal of the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines. These guidelines address risk assessment (*Circulation 2014;129:S49*), lifestyle

modifications (*Circulation 2014;129:S76*), evaluation and treatment of obesity (*Circulation 2014;129:S102*), and evaluation and management of blood cholesterol (*Circulation 2014;129:S1*).

DIAGNOSIS

Screening

- Screening for hypercholesterolemia should be done **in all adults age 20 years or older** (*Circulation 2014;129:S49*).
- Screening is best performed with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) obtained after a 12-hour fast.
- If a fasting lipid panel cannot be obtained, total and HDL cholesterol should be measured. Non-HDL cholesterol ≥220 mg/dL may indicate a genetic or secondary cause. A fasting lipid panel is required if non-HDL cholesterol is ≥220 mg/dL or triglycerides are ≥500 mg/dL.
- If the patient does not have an indication for LDL-lowering therapy, screening can be performed every 4-6 years between ages 40-75 (*Circulation 2014;129:S49*).
- Patients hospitalized for an acute coronary syndrome or coronary revascularization should have a lipid panel obtained within 24 hours of admission if lipid levels are unknown.
- Individuals with hyperlipidemia should be evaluated for potential **secondary causes**, including hypothyroidism, DM, obstructive liver disease, chronic renal disease such as nephrotic syndrome, and medications such as estrogens, progestins, anabolic steroids/androgens, corticosteroids, cyclosporine, retinoids, atypical antipsychotics, and antiretrovirals (particularly protease inhibitors).

RISK ASSESSMENT

- The 2013 guidelines identify four groups in whom the benefits of LDL cholesterol-lowering therapy with HMG-CoA reductase inhibitors (statins) clearly outweigh the risks (*Circulation 2014;129:S1*):

1. Patients with clinical ASCVD
2. Patients with LDL cholesterol ≥190 mg/dL
3. Patients with DM age 40-75 years with LDL cholesterol between 70-189 mg/dL
4. Patients with a calculated ASCVD risk ≥7.5%

- For patients **without** clinical ASCVD or an LDL cholesterol ≥190 mg/dL, the guidelines advise calculating a patient's risk for ASCVD based on age, sex, ethnicity, total and HDL cholesterol, SBP (treated or untreated), presence of DM, and current smoking status (*Circulation 2014;129:S49*).
- The ACC/AHA risk calculator is available at http://my.americanheart.org/cvriskcalculator.
  - For patients of ethnicities other than African American or non-Hispanic white, risk cannot be as well assessed. Use of the non-Hispanic white risk calculation is suggested, with the understanding that risk may be lower than calculated in East Asian Americans and Hispanic Americans and higher in American Indians and South Asians.
  - Ten-year risk should be calculated beginning at age 40 in patients without ASCVD or LDL cholesterol ≥190 mg/dL.
  - Lifetime risk may be calculated in patients age 20-39 and patients age 40-59 with a 10-year risk <7.5% to inform decisions regarding lifestyle modification.

TREATMENT

- The 2013 guidelines recognize lifestyle factors, including diet (*Circulation 2014;129:S76*) and weight management (*Circulation 2014;129:S102*) as an important component of risk reduction for all patients.
- Patients should be advised to adopt a diet that is high in fruits and vegetables, whole grains, fish, lean meat, low-fat dairy, legumes, and nuts, with lower intake of red meat, saturated and trans fats, sweets, and sugary beverages (Table 3-9). Saturated fat should comprise no more than 5-6% of total calories (*Circulation 2014;129:S76*).
- Physical activity, including aerobic and resistance exercise, is recommended in all patients (*Circulation 2014;129:S76*).
- For all obese patients (body mass index ≥30) and for overweight patients (body mass index ≥25) who have additional risk factors, sustained weight loss of 3-5% or greater reduces ASCVD risk (*Circulation 2014;129:S102*).
- Consultation with a registered dietitian may be helpful to plan, start, and maintain a saturated fat-restricted and weight loss-promoting diet.

- Prior to the start of treatment, there should be a risk discussion between the patient and the clinician. Topics for discussion include:
  - Potential for ASCVD risk reduction benefits
  - Potential for adverse effects and drug-drug interactions
  - Heart-healthy lifestyle and management of other risk factors
  - Patient preferences
- **Clinical ASCVD**
  - Clinical ASCVD includes acute coronary syndromes, history of MI, stable angina, arterial revascularization (coronary or otherwise), stroke, transient ischemic attack, or atherosclerotic peripheral arterial disease.
  - Secondary prevention is an indication for high-intensity statin therapy, which has been shown to reduce events more than moderate-intensity statin therapy. Statin regimens are listed in Table 3-10.
  - If high-dose statin therapy is contraindicated or poorly tolerated or there are significant risks to high-intensity therapy (including age >75 years), moderate-intensity therapy is an option.
- **LDL cholesterol ≥190 mg/dL**
  - These individuals have elevated lifetime risk because of long-term exposure to very high LDL cholesterol levels, and the risk calculator does not account for this.
  - LDL cholesterol should be reduced by at least 50%, primarily with high-intensity statin therapy. If high-intensity therapy is not tolerated, maximum tolerated intensity should be used.

TABLE 3-9 Nutrient Composition of the Therapeutic Lifestyle Change Diet

Nutrient	Recommended Intake
Saturated fat[a]	<5-6% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate[b]	50-60% of total calories
Fiber	20-30 g/d
Protein	Approximately 15% of total calories
Cholesterol	<200 mg/d
Total calories (energy)[c]	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

[a]Trans fatty acids are another low-density lipoprotein-raising fat that should be kept at a low intake.

[b]Carbohydrates should be derived predominantly from foods rich in complex carbohydrates, including grains (especially whole grains), fruits, and vegetables.

[c]Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/d).

From *Circulation* 2014;129:S76.

- Even high-intensity statin therapy may not be sufficient to reduce LDL cholesterol by 50%, and nonstatin therapies are often required to achieve this goal (*J Clin Lipidol 2011;5:S18*).

- LDL apheresis is an optional therapy in patients with homozygous familial hypercholesterolemia and those with severe heterozygous familial hypercholesterolemia with insufficient response to medication. Lomitapide, a microsomal triglyceride transfer protein

inhibitor, and mipomersen, an apolipoprotein B antisense oligonucleotide, are new medications indicated for the treatment of patients with homozygous familial hypercholesterolemia (*Eur Heart J 2013;34:3478*).

TABLE 3-10 Statin Therapy Regimens by Intensity

High Intensity (↓ LDL ≥50%)	Medium Intensity (↓ LDL 30-50%)	Low Intensity (↓ LDL <30%)
Atorvastatin 40-80 mg	Atorvastatin 10-*20* mg	*Fluvastatin 20-40 mg*
Rosuvastatin 20-*40* mg	Fluvastatin 40 mg bid, *80 mg XL*	Lovastatin 20 mg
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Pitavastatin 2-4 mg	Pravastatin 10-20 mg
	Pravastatin 40-*80* mg	*Simvastatin 10 mg*
	Rosuvastatin *5*-10 mg	
	Simvastatin 20-40 mg	

LDL, low-density lipoprotein; ↓, decreased. Italicized doses have not been studied in randomized controlled trials but achieve this level of LDL reduction in clinical use. From *Circulation* 2014;129:S1.

- Because hyperlipidemia of this degree is often genetically determined, discuss screening of other family members (including children) to identify candidates for treatment. In addition, screen for and treat secondary causes of hyperlipidemia (*Curr Opin Lipidol 2012;23:282*).

- **Patients with diabetes, aged 40-75, LDL cholesterol between 70-189 mg/dL**
  - Using the AHA/ACC risk calculator, calculate 10-year risk of an ASCVD event in these patients (categories: ≥7.5% or <7.5%).
  - If the risk is ≥7.5%, consider high-intensity statin therapy. Otherwise, these patients have an indication for moderate-intensity statin therapy.
- **Patients without diabetes, aged 40-75, LDL cholesterol between 70-189 mg/dL**
  - Using the AHA/ACC risk calculator, calculate 10-year risk of an ASCVD event in these patients (categories: ≥7.5%, between 5.0-7.5%, and <5.0%).
  - A 10-year risk ≥7.5% is an indication for moderate- or high-intensity statin therapy. The decision between moderate- and high-intensity therapy should be made with the patient based on anticipated individualized risks and benefits.
  - A 10-year risk between 5.0-7.5% is reasonable for moderate-intensity statin therapy.
- **Other patient populations**
  - Some patients not described above may still benefit from statin therapy: if the decision on treatment is unclear, the guidelines offer assessment of family history, high-sensitivity C-reactive protein (hs-CRP), coronary artery calcium (CAC) score, or arterial-brachial index (ABI) as options to further define risk (*Circulation 2014;129:S49*; *Circulation 2014;129:S1*).
    - A family history of premature ASCVD is defined as an event in a first-degree male relative before age 55 or in a first-degree female relative before age 65.
    - Higher risk is also indicated by an hs-CRP ≥2 mg/L; CAC ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; or ABI ≤0.9.
    - The role of other biomarkers in risk assessment remains uncertain.
    - Depending on patient preference and assessment of risks and benefits, lower LDL cholesterol levels can be considered for treatment (particularly LDL cholesterol ≥160 mg/dL).
    - Patients with diabetes younger than 40 or older than 75 are reasonable candidates for statin therapy based on individual

evaluation.

- Use of statin therapy should be individualized for patients older than 75. In randomized controlled trials, patients older than 75 continued to have benefit from statin therapy, particularly for secondary prevention (*Lancet 2002;360:7*; *Lancet 2002;360:1623*). In addition, many ASCVD events occur in this age group, and patients without other comorbidities may benefit substantially from cardiovascular risk reduction.
- No official recommendation was made in the guidelines regarding initiation or continuation of statin therapy in patients on maintenance hemodialysis or with New York Heart Association class II-IV ischemic systolic HF. Evidence from randomized controlled trials has not shown a benefit from statin therapy in these subpopulations (*Circulation 2014;129:S1*).

- **Hypertriglyceridemia**
  - Hypertriglyceridemia may be an **independent cardiovascular risk factor** (*Circulation 2007;115:450*; *Ann Intern Med 2007;147:377*; *Circulation 2011;123:2292*).
  - Hypertriglyceridemia is often observed in the metabolic syndrome (*Circulation 2011;123:2292*), and there are many potential etiologies for hypertriglyceridemia, including obesity, DM, renal insufficiency, genetic dyslipidemias, and therapy with oral estrogen, glucocorticoids, β-blockers, tamoxifen, cyclosporine, antiretrovirals, and retinoids.

  - The classification of serum triglyceride levels is as follows (*Circulation 2011;123:2292*): normal: <150 mg/dL; borderline high: 150-199 mg/dL; high: 200-499 mg/dL; and very high: ≥500 mg/dL. The Endocrine Society has added two further categories: severe: 1000-1999 mg/dL (greatly increases the risk of pancreatitis); and very severe: ≥2000 mg/dL (*J Clin Endocrinol Metab 2012;97:2969*).
  - Treatment of hypertriglyceridemia depends on the degree of severity.
    - For patients with very high triglyceride levels, triglyceride reduction through a very low-fat diet (≤15% of calories), exercise, weight loss, and drugs (fibrates, niacin, ω-3 fatty acids) is the primary goal of therapy to prevent acute pancreatitis.
    - When patients have a lesser degree of hypertriglyceridemia, controlling the LDL cholesterol level is the primary aim of initial therapy. Lifestyle changes are indicated to lower triglyceride levels (*J Clin Endocrinol Metab 2012;97:2969*).

- **Low HDL cholesterol**
  - Low HDL cholesterol is an **independent ASCVD risk factor** that is identified as a non-LDL cholesterol risk and is included as a component of the ACC/AHA scoring algorithm (*Circulation 2014;129:S49*).
  - Etiologies for low HDL cholesterol include genetic conditions, physical inactivity, obesity, insulin resistance, DM, hypertriglyceridemia, cigarette smoking, high-carbohydrate (>60% of calories) diets, and certain medications (β-blockers, anabolic steroids/androgens, progestins).
  - Because therapeutic interventions for low HDL cholesterol are of limited efficacy, the guidelines recommend considering low HDL cholesterol as a component of overall risk, rather than a specific therapeutic target.
  - There are no clinical trial data showing a benefit of pharmacologic methods of elevating HDL cholesterol.

- **Starting and monitoring therapy**
  - Before starting therapy, guidelines recommend checking alanine aminotransferase (ALT), hemoglobin A1C (if diabetes status is unknown), labs for secondary causes (if indicated), and creatine kinase (if indicated).
  - Evaluate for patient characteristics that increase the risk of adverse events from statins, including impaired hepatic and renal function, history of statin intolerance, history of muscle disorders, unexplained elevations of ALT >3× the upper limit of normal, drugs affecting statin metabolism, Asian ethnicity, and age >75 years (*Circulation 2014;129:S1*).
  - **A repeat fasting lipid panel** is indicated 4-12 weeks after starting therapy to assess adherence, with reassessment every 3-12 months as indicated.
  - In contrast to previous guidelines, therapeutic targets are not recommended because specific targets and a “treat to target” strategy have not been evaluated in randomized controlled trials.
  - In patients without the anticipated level of LDL cholesterol reduction based on intensity of statin therapy (≥50% for high intensity, 30-50% for moderate intensity), assess adherence to therapy and lifestyle modifications, evaluate for intolerance, and consider secondary causes. After evaluation, if the therapeutic response is still insufficient on maximally tolerated statin therapy, it is reasonable to consider adding a nonstatin agent.
  - Creatine kinase should not be routinely checked in patients on statin therapy but is reasonable to measure in patients with muscle symptoms.
  - In 2012, the FDA stated that liver enzyme tests should be performed before starting statin therapy and only as clinically indicated thereafter. The FDA concluded that serious liver injury with statins is rare and unpredictable and that routine monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury. Elevations of liver transaminases 2-3× the upper limit of normal are dose dependent, may decrease on repeat testing even with continuation of statin therapy, and are

reversible with discontinuation of the drug.

P.85

Treatment of Elevated LDL Cholesterol

- **HMG-CoA reductase inhibitors (statins)**
  - Statins (see Table 3-10) are the treatment of choice for elevated LDL cholesterol and usually lower levels by 30-50% with moderate-intensity and ≥50% with high-intensity statin therapy (*J Clin Lipidol 2011;5:S18*; *N Engl J Med 1999;341:498*; *Circulation 2014;129:S1*).
  - The lipid-lowering effect of statins appears within the first week of use and becomes stable after approximately 4 weeks of use.
  - Common side effects (5-10% of patients) include gastrointestinal upset (e.g., abdominal pain, diarrhea, bloating, constipation) and muscle pain or weakness, which can occur without creatine kinase elevations. Other potential side effects include malaise, fatigue, headache, and rash (*N Engl J Med 1999;341:498*; *Ann Pharmacother 2002;36:1907*; *Circulation 2002;106:1024*).
  - Myalgias are the most common cause of statin discontinuation and are often dose dependent. They occur more often with increasing age and number of medications and decreasing renal function and body size (*Circulation 2002;106:1024*; *Endocrinol Metab Clin North Am 2009;38:121*).
    - The AHA/ACC guidelines recommend discontinuing statins in patients who develop muscle symptoms until they can be evaluated. For severe symptoms, evaluate for rhabdomyolysis (*Circulation 2014;129:S1*).
    - For mild to moderate symptoms, evaluate for conditions increasing the risk of muscle symptoms, including renal or hepatic impairment, hypothyroidism, vitamin D deficiency, rheumatologic disorders, and primary muscle disorders. Statin-induced myalgias are likely to resolve within 2 months of discontinuing the drug.
    - If symptoms resolve, the same or lower dose of the statin can be reintroduced.
    - If symptoms recur, use a low dose of a different statin and increase as tolerated.
    - If the cause of symptoms is determined to be unrelated, restart the original statin.
  - Statins have been associated with an increased incidence of DM. However, the total benefit of statin use usually outweighs the potential adverse effects from an increase in blood sugar (*Lancet 2010;375:735*).
  - Statins have very rarely been associated with reversible cognitive impairment and have not been associated with irreversible or progressive dementia.
  - Because some of the statins undergo metabolism by the cytochrome P450 enzyme system, taking these statins in combination with other drugs metabolized by this enzyme system increases the risk of **rhabdomyolysis** (*N Engl J Med 1999;341:498*; *Ann Pharmacother 2002;36:1907*; *Circulation 2002;106:1024*). Among these drugs are fibrates (greater risk with gemfibrozil), itraconazole, ketoconazole, erythromycin, clarithromycin, cyclosporine, nefazodone, and protease inhibitors (*Circulation 2002;106:1024*).
  - Statins may also interact with large quantities of grapefruit juice to increase the risk of myopathy.
  - Simvastatin can increase the levels of warfarin and digoxin and has significant doselimiting interactions with amlodipine, amiodarone, dronedarone, verapamil, diltiazem, and ranolazine. Rosuvastatin may also increase warfarin levels.
  - Because a number of drug interactions are possible depending on the statin and other medications being used, drug interaction programs and package inserts should be consulted (*J Clin Lipidol 2014;8:S30*).
  - The use of statins is contraindicated during pregnancy and lactation.
- **Bile acid sequestrant resins**
  - Currently available bile acid sequestrant resins include the following:
    - **Cholestyramine:** 4-24 g/d PO in divided doses before meals.
    - **Colestipol:** tablets, 2-16 g/d PO; granules, 5-30 g/d PO in divided doses before meals.
    - **Colesevelam:** 625-mg tablets, three tablets PO bid or six tablets PO daily (maximum of seven tablets daily) with food; or one packet of oral suspension daily.

P.86

  - Bile acid sequestrants typically lower LDL cholesterol levels by 15-30% and thereby lower the incidence of CHD (*N Engl J Med 1999;341:498*; *JAMA 1984;251:351*).
  - These agents should not be used as monotherapy in patients with triglyceride levels >250 mg/dL because they can raise triglyceride levels. They may be combined with nicotinic acid or statins.
  - Common side effects of resins include constipation, abdominal pain, bloating, nausea, and flatulence.
  - Bile acid sequestrants may decrease oral absorption of many other drugs, including warfarin, digoxin, thyroid hormone, thiazide diuretics, amiodarone, glipizide, and statins.
    - Colesevelam interacts with fewer drugs than do the older resins but can affect the absorption of thyroxine.

- Other medications should be given at least 1 hour before or 4 hours after resins.

- **Nicotinic acid (niacin)**
  - Niacin can lower LDL cholesterol levels by ≥15%, lower triglyceride levels by 20-50%, and raise HDL cholesterol levels by up to 35% (*Circulation 2007;115:450*; *Arch Intern Med 1994;154:1586*).
  - Crystalline niacin is given 1-3 g/d PO in two to three divided doses with meals. Extended-release niacin is dosed at night, with a starting dose of 500 mg PO, and the dose may be titrated monthly in 500-mg increments to a maximum of 2000 mg PO (administer dose with milk, applesauce, or crackers).
  - Common side effects of niacin include flushing, pruritus, headache, nausea, and bloating. Other potential side effects include elevation of liver transaminases, hyperuricemia, and hyperglycemia.
    - Flushing may be decreased with the use of aspirin 325 mg 30 minutes before the first few doses.
    - Hepatotoxicity associated with niacin is partially dose dependent and appears to be more prevalent with some over-the-counter time-release preparations.
  - Avoid use of niacin in patients with gout, liver disease, active peptic ulcer disease, and uncontrolled DM.
    - Niacin can be used with care in patients with well-controlled DM (hemoglobin A1C level ≤7%).
    - Serum transaminases, glucose, and uric acid levels should be monitored every 6-8 weeks during dose titration and then every 4 months.
  - The use of niacin in patients with well-controlled LDL cholesterol levels (with statins) has not been shown to be of benefit in clinical trials (*N Engl J Med 2011;365:2255*; *Eur Heart J 2013;34:1279*). Niacin can be useful as an additional agent in patients with severely elevated LDL cholesterol levels.

- **Ezetimibe**
  - Ezetimibe is currently the only available cholesterol-absorption inhibitor. It appears to act at the brush border of the small intestine and inhibits cholesterol absorption.
  - Ezetimibe may provide an additional 25% mean reduction in LDL cholesterol when combined with a statin and provides an approximately 18% decrease in LDL cholesterol when used as monotherapy (*Am J Cardiol 2002;90:1092*; *Eur Heart J 2003;24:729*; *Am J Cardiol 2002;90:1084*; *Mayo Clin Proc 2004;79:620*).
  - The recommended dosing is 10 mg PO once daily. No dosage adjustment is required for renal insufficiency and mild hepatic impairment or in elderly patients. It is not recommended for use in patients with moderate to severe hepatic impairment.
  - Side effects are infrequent and include gastrointestinal symptoms (e.g., diarrhea, abdominal pain) and myalgias.
  - In clinical trials, there was no excess of rhabdomyolysis or myopathy when compared with statin or placebo alone.

  - Liver enzymes should be monitored when used in conjunction with fenofibrate but are not required in monotherapy or with a statin.
  - A clinical outcome trial showed decreased reduction of cardiovascular events with the combination of simvastatin and ezetimibe compared to placebo in patients with chronic renal failure (*Lancet 2011;377:2181*). The recently completed IMPROVE-IT trial showed a reduction in cardiovascular end points when ezetimibe was added to simvastatin in high-risk patients with already low LDL levels (*American Heart Association Scientific Sessions 2014*).
  - Ezetimibe is useful in patients with familial hypercholesterolemia who do not achieve adequate LDL cholesterol reductions with statin therapy alone (*J Clin Lipidol 2011;5:S38*).

Treatment of Hypertriglyceridemia

- **Nonpharmacologic treatment**

  Nonpharmacologic treatments are important in the therapy of hypertriglyceridemia. Approaches include the following:
  - Changing oral estrogen replacement to transdermal estrogen
  - Decreasing alcohol intake
  - Encouraging weight loss and exercise
  - Controlling hyperglycemia in patients with DM
  - Avoiding simple sugars and very high-carbohydrate diets (*Circulation 2011;123:2292*; *J Clin Endocrinol Metab 2012;97:2969*)

- **Pharmacologic treatment**
  - Pharmacologic treatment of severe hypertriglyceridemia consists of a fibric acid derivative (fibrates), niacin, or ω-3 fatty acids.
  - Patients with severe hypertriglyceridemia (>1000 mg/dL) should be treated with pharmacotherapy in addition to reduction of dietary fat, alcohol, and simple carbohydrates to decrease the risk of pancreatitis.
  - Statins may be effective for patients with mild to moderate hypertriglyceridemia and concomitant LDL cholesterol elevation (*Circulation 2011;123:2292*; *J Clin Endocrinol Metab 2012;97:2969*; *N Engl J Med 2007;357:1009*).

- **Fibric acid derivatives**
  - Currently available fibric acid derivatives include the following:

    Gemfibrozil: 600 mg PO bid before meals

    Fenofibrate: available in several forms, dosage typically 48-145 mg/d PO
  - Fibrates generally lower triglyceride levels by 30-50% and increase HDL cholesterol levels by 10-35%. They can lower LDL cholesterol levels by 5-25% in patients with normal triglyceride levels but may actually increase LDL cholesterol levels in patients with elevated triglyceride levels (*N Engl J Med 2007;357:1009*; *Lancet 2005;366:1849*).
  - Common side effects include dyspepsia, abdominal pain, cholelithiasis, rash, and pruritus.
  - Fibrates may potentiate the effects of warfarin (*N Engl J Med 1999;341:498*). Gemfibrozil given in conjunction with statins may increase the risk of rhabdomyolysis (*Circulation 2002;106:1024*; *Am J Med 2004;116:408*; *Am J Cardiol 2004;94:935*; *Am J Cardiol 2005;95:120*).
- **ω-3 Fatty acids**
  - High doses of ω-3 fatty acids from fish oil can lower triglyceride levels (*J Clin Invest 1984;74:82*; *J Lipid Res 1990;31:1549*).
  - The active ingredients are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
  - To lower triglyceride levels, 1-6 g of ω-3 fatty acids, either EPA alone or with DHA, are needed daily.
  - Main side effects are burping, bloating, and diarrhea.

  - Prescription forms of ω-3 fatty acids are available and are indicated for triglyceride levels >500 mg/dL. One preparation contains EPA and DHA; four tablets contain about 3.6 g of ω-3 acid ethyl esters and can lower triglyceride levels by 30-40%. Other preparations contain only EPA or contain unesterified EPA and DHA.
  - In practice, ω-3 fatty acids are being used as an adjunct to statins or other drugs in patients with moderately elevated triglyceride levels.
  - The combination of ω-3 fatty acids plus a statin has the advantage of avoiding the risk of myopathy seen with statin-fibrate combinations (*Am J Cardiol 2008;102:429*; *Am J Cardiol 2008;102:1040*).

Treatment of Low HDL Cholesterol

- Low HDL cholesterol often occurs in the setting of hypertriglyceridemia and metabolic syndrome. Management of accompanying high LDL cholesterol, hypertriglyceridemia, and the metabolic syndrome may result in improvement of HDL cholesterol (*Circulation 2001;104:3046*).
- Nonpharmacologic therapies are the mainstay of treatment, including the following:
  - Smoking cessation
  - Exercise
  - Weight loss
- In addition, medications known to lower HDL levels, such as β-blockers (except carvedilol), progestins, and androgenic compounds, should be avoided.
- No clinical outcomes trials have shown a clear benefit to pharmacologic treatment for raising HDL cholesterol.

4
Ischemic Heart Disease

Marc A. Sintek

Philip M. Barger

Coronary Heart Disease and Stable Angina

GENERAL PRINCIPLES

Definition

- Coronary artery disease (CAD) refers to the luminal narrowing of a coronary artery, usually due to atherosclerosis. CAD is the leading contributor to ischemic heart disease (IHD). IHD includes angina pectoris, myocardial infarction (MI), and silent myocardial ischemia.
- Cardiovascular disease (CVD) includes IHD, cardiomyopathy, heart failure, arrhythmia, hypertension, cerebrovascular accident (CVA), diseases of the aorta, peripheral vascular disease (PVD), valvular heart disease, and congenital heart disease.
- Stable angina is defined as angina symptoms or angina equivalent symptoms that are reproduced by consistent levels of activity and relieved by rest.
- American Heart Association/American College of Cardiology (AHA/ACC) guidelines provide a more through overview of stable IHD (*J Am Coll Cardiol 2012;60:e44*; update *J Am Coll Cardiol 2014;64:1929*).

Epidemiology

- In the United States, IHD is the cause of one of every six deaths (*Circulation 2013;127:e6*).
- The lifetime risk of IHD at age 40 is one in two for men and one in three for women.
- There are more than 15 million Americans with IHD, 50% of whom have chronic angina.
- CVD has become an important cause of death worldwide, accounting for nearly 30% of all deaths, and has become increasingly significant in developing nations.
- Death due to CVD continues to decline in large part due to adherence to current guidelines.

Etiology

- CAD most commonly results from luminal accumulation of atheromatous plaque.
- Other causes of obstructive CAD include congenital coronary anomalies, myocardial bridging, vasculitis, and prior radiation therapy.
- Apart from obstructive CAD, other causes of angina include cocaine use, valvular and nonvalvular aortic stenosis, hypertrophic cardiomyopathy, left ventricular hypertrophy (LVH), malignant hypertension, dilated cardiomyopathy, spontaneous coronary dissection, and coronary vasospasm/Prinzmetal angina.
- Any factor that reduces myocardial oxygen supply or increases demand can cause or exacerbate angina (Table 4-1).

Pathophysiology

- Stable angina results from progressive luminal obstruction of angiographically visible epicardial coronary arteries or, less commonly, obstruction of the microvasculature, which results in a mismatch between myocardial oxygen supply and demand.
- Atherosclerosis is an inflammatory process, initiated by lipid deposition in the arterial intima layer followed by recruitment of inflammatory cells and proliferation of arterial smooth muscle cells to form an atheroma.
  - The coronary lesions responsible for stable angina differ from the vulnerable plaques associated with acute MI. The stable angina lesion is fixed and is less prone to fissuring, hence producing symptoms that are more predictable (*Circulation 2012;125:1147*).

TABLE 4-1 Conditions That May Provoke or Exacerbate Ischemia/Angina Independent of Worsening Atherosclerosis

Increased Oxygen Demand	Decreased Oxygen Supply
	Noncardiac
Hyperthermia	Anemia
Hyperthyroidism	Sickle cell disease
Sympathomimetic toxicity (i.e., cocaine use)	Hypoxemia
Hypertension	*Pneumonia*
Anxiety	*Asthma exacerbation*
	Chronic obstructive pulmonary disease
	Pulmonary hypertension
	Pulmonary fibrosis
	Obstructive sleep apnea
	Pulmonary embolus
	Sympathomimetic toxicity (i.e., cocaine use, pheochromocytoma)
	Hyperviscosity
	Polycythemia
	Leukemia
	Thrombocytosis
	Hypergammaglobulinemia
	Cardiac
Hypertrophic cardiomyopathy	Aortic stenosis
Aortic stenosis	Elevated left ventricular end-diastolic pressure
Dilated cardiomyopathy	Hypertrophic cardiomyopathy

Tachycardia	Microvascular disease
Ventricular Supraventricular	

Adapted from AHA/ACC Guidelines on Stable Ischemic Heart Disease. *J Am Coll Cardiol* 2012;60:e44.

- All coronary lesions are eccentric and do not uniformly alter the inner circumference of the artery.
- Epicardial coronary lesions causing less than 40% luminal narrowing generally do not significantly impair coronary flow.
- Moderate angiographic lesions (40-70% obstruction) may interfere with flow and are routinely underestimated on coronary angiograms given the eccentricity of CAD.

Risk Factors

- Of IHD events, >90% can be attributed to elevations in at least one major risk factor (*JAMA 2003;290:891*).
- Assessment of traditional CVD risk factors includes:
  - Age
  - Blood pressure (BP)
  - Blood sugar (Note: Diabetes is considered an IHD risk equivalent.)
  - Lipid profile (low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides); direct LDL for nonfasting samples or very high triglycerides

  - Tobacco use (Note: Smoking cessation restores the risk of IHD to that of a nonsmoker within approximately 15 years.) (*Arch Intern Med 1994;154(2):169*)
  - Family history of premature CAD: Defined as first-degree male relative with IHD before age 55 years or female relative before age 65 years
  - Measures for obesity, particularly central obesity; body mass index goal is between 18.5-24.9 kg/m^2; waist circumference goal is <40 inches for men and <35 inches for women
- As of 2013, AHA/ACC guidelines recommend assessing 10-year atherosclerotic cardiovascular disease (ASCVD) risk for patients age 40-79 years using new race and agespecific pooled cohort equations (*J Am Coll Cardiol 2014;63:2935*).
  - The ASCVD risk calculator is available online (*http://tools.cardiosource.org/ASCVD-Risk-Estimator/*).
  - If there remains uncertainty about lower risk estimates, high-sensitivity C-reactive protein (≥2 mg/dL), coronary artery calcium score (≥300 Agatston units or ≥75th percentile), or ankle-brachial index (<0.9) may be obtained to revise risk estimates upward.
  - Traditional risk factors noted above should be assessed in patients younger than age 40 and every 4-6 years after 40; 10-year ASCVD risk should be calculated every 4-6 years in patients 40-79 years of age.
  - Lifetime risk can be assessed using the ASCVD risk calculator and may be helpful in the setting of counseling patients about lifestyle modifications.

Prevention

Primary prevention: See Chapter 3, Preventive Cardiology

Clinical Presentation

History

- Angina: **Typical angina has three features**: (1) substernal chest discomfort with a characteristic quality and duration that is (2) provoked by stress or exertion and (3) relieved by rest or nitroglycerin.
  - **Atypical angina** has two of these three characteristics.
  - **Noncardiac chest pain** meets one or none of these characteristics.
- Chronic stable angina is reproducibly precipitated in a predictable manner by exertion or emotional stress and relieved within 5-10 minutes by sublingual nitroglycerin or rest.
- The severity of angina may be quantified using the Canadian Cardiovascular Society (CCS) classification system (Table 4-2).

TABLE 4-2 Canadian Cardiovascular Society (CCS) Classification System

Class	Definition
CCS 1	Angina with strenuous or prolonged activity
CCS 2	Angina with moderate activity (walking greater than two level blocks or one flight of stairs)
CCS 3	Angina with mild activity (walking less than two level blocks or one flight of stairs)
CCS 4	Angina that occurs with any activity or at rest

Anginal symptoms may include typical chest discomfort or anginal equivalents. From Sangareddi V, Anand C, Gnanavelu G, et al. Canadian Cardiovascular Society classification of effort angina: an angiographic correlation. *Coron Artery Dis* 2004;15:111-4.

TABLE 4-3 Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms

Age (y)	Asymptomatic		Nonanginal Chest Pain		Atypical/Probable Angina Pectoris		Typical/Definite Angina Pectoris	
Gender	Women	Men	Women	Men	Women	Men	Women	Men

30-39	<5	<5	2	4	12	34	26	76
40-49	<5	<10	3	13	22	51	55	87
50-59	<5	<10	7	20	31	65	73	93
60-69	<5	<5	14	27	51	72	86	94

Very Low <5%	Low <10%	Intermediate 10-80%	High >80%

Data from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106:1883.

- Associated symptoms may include dyspnea, diaphoresis, nausea, vomiting, dizziness, jaw pain, and left arm pain.
- Female patients and those with diabetes or chronic kidney disease may have minimal or atypical symptoms that serve as anginal equivalents. Such symptoms include dyspnea (most common), epigastric pain, and nausea.
- The clinician's assessment of the pretest probability of IHD is the important driver for further diagnostic testing in patients without known CAD and is largely ascertained from the clinical history (Table 4-3). Patients with a low pretest probability (<5%) of CAD are unlikely to benefit from further diagnostic testing aimed at detecting CAD.

Physical Examination

- Clinical exam should include measurement of BP, heart rate, and arterial pulses.
- Exam findings of a mitral regurgitation (MR) murmur or aortic stenosis murmur can alert the clinician to additional CVD that may be contributing to symptoms of angina.
- Stigmata of hyperlipidemia such as corneal arcus and xanthelasmas should be noted.
- Signs of heart failure, such as an S3 gallop, inspiratory crackles on lung exam, elevated jugular venous pulsation, and peripheral edema, are also high-risk exam findings.
- Vascular exam should include palpitation of radial, femoral, popliteal, posterior tibial, and dorsalis pedis pulses bilaterally to compare differences. Auscultation with the bell of the stethoscope should be performed to evaluate for femoral or carotid bruits.
- Pain that is reproducible on physical exam suggests a musculoskeletal cause of chest pain but does not exclude the presence of CAD.

Differential Diagnosis

- A wide range of disorders may manifest with chest discomfort and may include both cardiovascular and noncardiovascular etiologies (Table 4-4).
- A careful history focused on cardiac risk factors, physical exam, and initial laboratory evaluation usually

narrows the differential diagnosis.

- In patients with established IHD, always look for exacerbating factors that contribute to ischemia (see Table 4-1).

TABLE 4-4 Differential Diagnosis of Chest Pain Excluding Epicardial Atherosclerosis

Diagnosis	Comments
Cardiovascular	
Aortic stenosis	Anginal episodes can occur with severe aortic stenosis.
HCM	Subendocardial ischemia may occur with exercise and/or exertion.
Prinzmetal angina	Coronary vasospasm that may be elicited by exertion or emotional stress.
Pericarditis	Pleuritic chest pain associated with pericardial inflammation from infectious or autoimmune disease.
Aortic dissection	May mimic anginal pain and/or involve the coronary arteries.
Cocaine use	Results in coronary vasospasm and/or thrombus formation.
Other	
Anemia	Marked anemia can result in a myocardial O_2 supply-demand mismatch.
Thyrotoxicosis	Increase in myocardial demand may result in an O_2 supply-demand mismatch.
Esophageal disease	GERD and esophageal spasm can mimic angina (responsive to NTG).
Biliary colic	Gallstones can usually be visualized on abdominal sonography.
Respiratory diseases	Pneumonia with pleuritic pain, pulmonary embolism, pulmonary hypertension
Musculoskeletal	Costochondritis, cervical radiculopathy

GERD, gastroesophageal reflux disease; HCM, hypertrophic cardiomyopathy; NTG, nitroglycerin.

Diagnostic Testing

- **General diagnostic testing**
  - A resting ECG can be helpful in determining the presence of prior infarcts or conduction system disease and may alert the clinician to the possibility of CAD in patients with chest pain.
  - Chest radiography can be used to evaluate for cardiomegaly, heart failure, or vascular disease (pulmonary and aortic) that can be important in the management of patients with chest pain or IHD.
  - A transthoracic echocardiogram (TTE) can be useful in determining presence of left ventricular (LV) dysfunction or valvular heart disease that may affect the management and diagnosis of IHD. TTE can also be used to assess for resting wall motion abnormalities that may be the result of prior MI.
  - Evidence of vascular disease or prior MI on the diagnostic testing modalities noted above should raise the pretest probability of IHD in patients presenting with chest pain.

- **Stress testing overview**
  - All stress testing requires a cardiovascular stress and way of imaging cardiac changes consistent with ischemia; stress and imaging methods are chosen by the clinician to meet the diagnostic needs of the patient.
  - Many stress testing modalities provide not only detection of ischemia/CAD but also prognostic information based on the burden of ischemia.
  - Table 4-5 provides an overview of the sensitivity and specificity for each stress and imaging modality along with advantages and disadvantages for the clinician to consider.
- **Stress testing indications**
  - Patients without known CAD:
    - Not indicated in asymptomatic patients as a screening test
    - Patients with anginal symptoms who are intermediate risk
    - Asymptomatic intermediate-risk patients who plan on beginning a vigorous exercise program or those with high-risk occupations (e.g., airline pilot)
    - Atypical symptoms in patients with a high risk of IHD (i.e., diabetes or vascular disease patients)
  - Patients with known CAD:
    - Post-MI risk stratification (see section on ST-segment elevation MI)
    - Preoperative risk assessment if it will change management prior to surgery
    - Recurrent anginal symptoms despite medical therapy or revascularization
    - Routine screening in asymptomatic patients after revascularization is controversial
- **Contraindications to stress testing**
  - Acute MI within 2 days
  - Unstable angina not previously stabilized by medical therapy

- Cardiac arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Symptomatic heart failure
- Acute pulmonary embolus, myocarditis, pericarditis, or aortic dissection

- **Exercise stress testing**
  - The test of choice for evaluating most patients of intermediate risk for CAD (see Table 4-3).
  - Bruce protocol: Consists of 3-minute stages of increasing treadmill speed and incline. BP, heart rate, and ECG are monitored throughout the study and the recovery period.
  - The study is considered positive if:
    - New ST-segment depressions of >1 mm in multiple contiguous leads
    - Hypotensive response to exercise
    - Sustained ventricular arrhythmias are precipitated by exercise
  - The Duke Treadmill Score provides prognostic information for patients presenting with chronic angina (Table 4-6).
  - When exercise testing is combined with imaging (stress echocardiography or perfusion imaging) and the test is normal at the target heart rate for age, the risk of infarction or death from CVD is <1% annually in patients with no prior history of IHD. In patients who cannot exercise and require pharmacologic testing, the annual risk of infarction or death in a normal study doubles (2% per year), further underscoring the importance of the inability to perform physical activity as a contribution to increased cardiovascular risk.

- **Stress testing with imaging**
  - Recommended for patients with the following baseline ECG abnormalities:
    - Preexcitation (Wolf-Parkinson-White syndrome)
    - LVH
    - Left bundle branch block (LBBB) or paced rhythm

TABLE 4-5 Diagnostic Accuracy of Common Stress Testing Modalities in Patients Without Known Ischemic Heart Disease

Test Type	Sensitivity	Specificity	Advantages	Disadvantages
ECG				
Exercise Pharmacologic	61% —	70-77% —	▪ Easy to perform ▪ Inexpensive	▪ Less diagnostic accuracy; especially in women

				▪ No viability assessment
Echocardiography				
Exercise Pharmacologic (dobutamine)	70-85% 85-90%	77-89% 79-90%	▪ Gather other important information on diastolic function, valvular disorders, and pulmonary pressures ▪ Can assess viability with pharmacologic stress	▪ Limited by image quality ▪ Diagnostic accuracy reduced with resting wall motion abnormalities
Nuclear Perfusion Imaging				
Exercise Pharmacologic (adenosine, regadenoson, or dobutamine)	82-88% 82-91%	70-88% 75-90%	▪ More sensitive for small areas of ischemia/infarct ▪ Very accurate ejection fraction assessment ▪ Easy to compare to prior studies	▪ Significant radiation ▪ May underestimate severe balanced ischemia ▪ No other valve or other structural information ▪ Viability may require separate testing
Cardiac MRI				
Exercise Pharmacologic[a]	— 91%	— 81%	▪ Excellent assessment of viability ▪ Anatomic detail of heart and great vessels superb	▪ Expensive ▪ Requires closed MRI ▪ Exercise option not typically available

All diagnostic accuracies unadjusted for referral bias; data from *J Am Coll Cardiol* 2012;60:e44.

[a]Vasodilator stress only; dobutamine has sensitivity of 83% and specificity of 86%.

TABLE 4-6 Exercise Stress Testing: Duke Treadmill Score

Duke Treadmill Score (DTS) = Minutes exercised - [5 × maximum ST-segment deviation] - [4 × angina score]. Angina score: 0 = none, 1 = not test limiting, 2 = test limiting

DTS		
5	Annual mortality 0.25%	Low-risk study
-10 to 4	Annual mortality 1.25%	Intermediate-risk study
<-10	Annual mortality >5%	High-risk study

In general, β-blockers, other nodal blocking agents, and nitrates should be discontinued prior to stress testing.

Data from *N Engl J Med* 1991;325:849.

- Intraventricular conduction delay (IVCD)
- Resting ST-segment or T-wave changes
- Patients unable to exercise or who do not have an interpretable ECG at rest or with exercise
- May be considered in patients with high pretest probability of IHD who have not met the threshold of invasive angiography

- **Myocardial perfusion imaging:** Commonly uses tracers that emit radiation detected by a camera in conjunction with exercise or pharmacologic stress. Perfusion imaging compares rest perfusion to stress perfusion images to discern areas of ischemia or infarct. It can be limited by body habitus, breast attenuation, and quality of the acquisition and processing of images. Severe CAD may cause balanced reduction in perfusion and an underestimation of ischemic burden.
- **Echocardiographic imaging:** Exercise or dobutamine stress testing can be performed with echocardiography to aid in the diagnosis of CAD. Echocardiography adds to the sensitivity and specificity of the test by revealing areas with wall motion abnormalities. The technical quality of this study can be limited by imaging quality (i.e., obesity).
- **Magnetic resonance perfusion imaging:** MRI sequences obtained with contrast and vasodilator stress testing. Exercise testing requires an MRI-compatible ergometer and has been done in select cases with success. Advantage of having viability assessment without additional testing and provides evaluation for other causes of myocardial dysfunction that may mimic IHD (i.e., sarcoidosis or infiltrative cardiomyopathies). Cannot be performed in patients with implanted cardiac devices (i.e., defibrillators and pacemakers).

- **Pharmacologic stress testing**

- In patients who are unable to exercise, pharmacologic stress testing may be preferable.
- Dipyridamole, adenosine, and regadenoson are vasodilators that are commonly used in conjunction with myocardial perfusion scintigraphy. These are the agents of choice in patients with LBBB or paced rhythm on ECG due to the increased incidence of false-positive stress tests with either exercise or dobutamine infusion. Technically, these agents do not impose a physiologic stress. Relative ischemia across a coronary vascular bed is elucidated as healthy vessels dilate more than diseased vessels with fixed obstruction. This in turn leads to relative changes in perfusion that are reflected in the postvasodilator images.
- Dobutamine is a positive inotrope commonly used with echocardiographic stress tests and may be augmented with atropine to achieve target heart rate for age.

Diagnostic Procedures

- **Coronary angiography**
  - The gold standard for evaluating epicardial coronary anatomy because it quantifies the presence and severity of atherosclerotic lesions and provides prognostic information based on the extent and severity of CAD.
  - Coronary angiography is invasive and is associated with a small risk of death, MI, CVA, bleeding, arrhythmia, and vascular complications. Therefore, it is reserved for patients whose risk-benefit ratio favors an invasive approach such as:
    - ST-segment elevation MI (STEMI) patients
    - Most unstable angina (UA)/non-ST-segment elevation MI (NSTEMI) patients
    - Symptomatic patients with high-risk stress tests who are expected to benefit from revascularization
    - Class III and IV angina despite medical therapy (see Table 4-2)
    - Survivors of sudden cardiac death or those with serious ventricular arrhythmias
    - Signs or symptoms of heart failure or decreased LV function
    - Angina that is inadequately controlled with medical therapy for the patient's lifestyle
    - Previous coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)
    - Suspected/known left main (≥50% stenosis) or severe three-vessel CAD
    - To diagnose CAD in patients with angina who have not undergone stress testing due to a high pretest probability of having CAD (see Table 4-3)
  - Can be both diagnostic and therapeutic if PCI is needed.
  - Can be used to evaluate patients who are suspected of having a nonatherosclerotic cause of ischemia (e.g., coronary anomaly, coronary dissection, radiation vasculopathy).
  - Intravascular ultrasound (IVUS) can be used to directly visualize plaque burden and plaque anatomy.
  - Functional significance of intermediate stenotic lesions (50-70% narrowing) can further be assessed by fractional flow reserve (FFR).
    - FFR is calculated by determining the ratio of pressure distal to the coronary obstruction to that of the aortic pressure at maximal hyperemia (flow).
    - An FFR ≤0.8 is considered flow limiting, and PCI improves urgent revascularization for UA or MI and potentially improves cardiovascular mortality compared to medical therapy (*N Engl J Med 2014;371:1208*).

- Measurement of LV filling pressures (diastolic function) and aortic and mitral valve gradients, assessment of regional wall motion and LV function, and assessment for certain aortopathies can be accomplished by placing a catheter in the LV cavity or aorta directly and making the appropriate pressure measurements and/or injection of contrast.

- **Contrast-induced nephropathy (CIN)** occurs in up to 5% of patients undergoing coronary angiography and is more common in patients with baseline renal insufficiency and diabetics. In most patients, creatinine returns to baseline within 7 days. The following are considerations in the prevention of CIN:
  - The volume of contrast media used should be minimized, and patients with a creatinine clearance <60 mL/min should be considered for a staged procedure.
  - Adequate hydration with isotonic crystalloid should be given prior to angiography. We recommend 3 mL/kg bolus of normal saline at least 6 hours prior to the procedure with a 1-mL/kg continuous infusion rate until procedure start.
  - IV diuretics should be held if possible.
  - High-potency statins should be continued or initiated on the evening prior to and morning of the procedure (*J Am Coll Cardiol 2014;63:12S*). We recommend atorvastatin 40-80 mg or continuation of comparable home statin therapy.
  - All patients should receive some CIN prophylactic therapy: oral hydration, IV hydration, held diuretics, or statin therapy.

  - Nonionic low-osmolar contrast agents should be used.
  - *N*-Acetyl-L-cysteine may not be useful in the prevention of CIN.
  - National Cardiovascular Data Registry Acute Kidney Injury Risk Model is a robust risk stratification tool for acute kidney injury and the need for hemodialysis after cardiac catheterization (*J Am Heart Assoc 2014;3:e001380*) (Table 4-7).

- **Cardiac CT**
  - A noninvasive technique used to establish a diagnosis of CAD. Like cardiac angiography, it exposes the patient to both radiation and contrast material. CT has a high negative predictive value and hence is better suited for symptomatic patients with low to intermediate pretest probability for CAD to rule out disease, such as a patient with repeated emergency room admissions for chest pain or patients with equivocal stress test results.
  - Recent results from the PROMISE trial suggest no advantage of CT imaging over stress testing for patients with intermediate risk of IHD presenting with chest pain in reducing major adverse clinical events. Patients imaged with CT were less likely to have normal coronary angiography, and CT appears to be a safe diagnostic test when evaluating chest pain in this population (*N Engl J Med 2015;372:1291*).
  - May aid in identification of congenital anomalies of the coronary arteries.
  - Due to diminished study quality, it is not useful in patients with extensive coronary calcification, coronary stents, or small-caliber vessels.

TREATMENT

- The major goal of treatment is to reduce symptoms.

- An absolute reduction in incidence of MI or cardiac death in patients with stable IHD is accomplished mainly through medical therapy and not revascularization.
- A combination of lifestyle modification, medical therapy, and coronary revascularization can be used. A recommended strategy for the evaluation and management of the patient with stable angina can be found in Figure 4-1.
- **Medical treatment** is aimed at improving myocardial oxygen supply, reducing myocardial oxygen demand, controlling exacerbating factors (i.e., anemia), and limiting the development of further atherosclerotic disease.
- Medical treatment often is sufficient to control anginal symptoms in chronic stable angina.

Medications

- **Antiplatelet therapy**
  - **Acetylsalicylic acid (ASA)** (75-162 mg/d) reduces cardiovascular events, including repeat revascularization, MI, and cardiac death, by approximately 33% (*BMJ 1994;308:81*; *Lancet 1992;114:1421*).
  - ASA 81 mg appears to be sufficient for most patients (primary or secondary prevention for both IHD and CVA).
  - ASA desensitization may be performed in patients with ASA allergy.
  - **Clopidogrel** (75 mg/d) can be used in those allergic/intolerant of ASA.
- **Anti-ischemic therapy**
  - **β-Adrenergic antagonists** (Table 4-8) control anginal symptoms by decreasing heart rate and myocardial work, leading to reduced myocardial oxygen demand.
    - β-Blockers with intrinsic sympathomimetic activity should be avoided.
    - Dosage can be adjusted to result in a resting heart rate of 50-60 bpm.
    - Use with caution or avoid in patients with active bronchospasm, atrioventricular (AV) block, resting bradycardia, or poorly compensated heart failure (HF).

TABLE 4-7 NCDR AKI Risk Model: Risk of AKI and AKI Resulting in HD in Patients Undergoing PCI (points are determined by the points column and total points are converted to risk in the risk conversion column)

Points			Risk Conversion			
	AKI	AKI+HD	Points Total	Risk AKI (%)	Points Total	Risk HD (%)
Variables			0	1.9	≤6	<1
			5	2.6	7	1.5
Age ≤50	0		10	3.6	8	2.6

50-59	2		15	4.9	9	4.4
60-69	4		20	6.7	10	7.6
70-79	6		25	9.2	11	12.6
80-89	8		30	12.4	12	20.3
>90	10		35	16.5	13	31.0
Heart failure within 2 wk	11	2	40	21.7		
GFR ≤30	18	5	45	27.9		
GFR 31-44	8	3	50	35.1		
GFR 45-59	3	1	55	43		
Diabetes mellitus	7	1	>60	51.4		
Any prior heart failure	4	—				
Any prior cerebrovascular disease/stoke	4	—				
Anemia (Hgb <10 g/dL)	10	—				
NSTEMI/UA presentation	6	1				
STEMI presentation	15	2				
Shock prior to procedure	16	-				
Cardiac arrest prior to procedure	8	3				
IABP use	11	-				

AKI, acute kidney injury; GFR, glomerular filtration rate; HD, hemodialysis; Hgb, hemoglobin; IABP, intra-aortic balloon counterpulsation; NCDR, National Cardiovascular Data Registry; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina. GFR calculated using the Modification of Diet in Renal Disease (MDRD) formula; AKI defined as at least a ≥0.3 mg/dL increase or ≥1.5-fold relative increase in creatinine after procedure or initiation of dialysis (HD) after procedure. Patients were excluded if on dialysis at the time of the procedure.

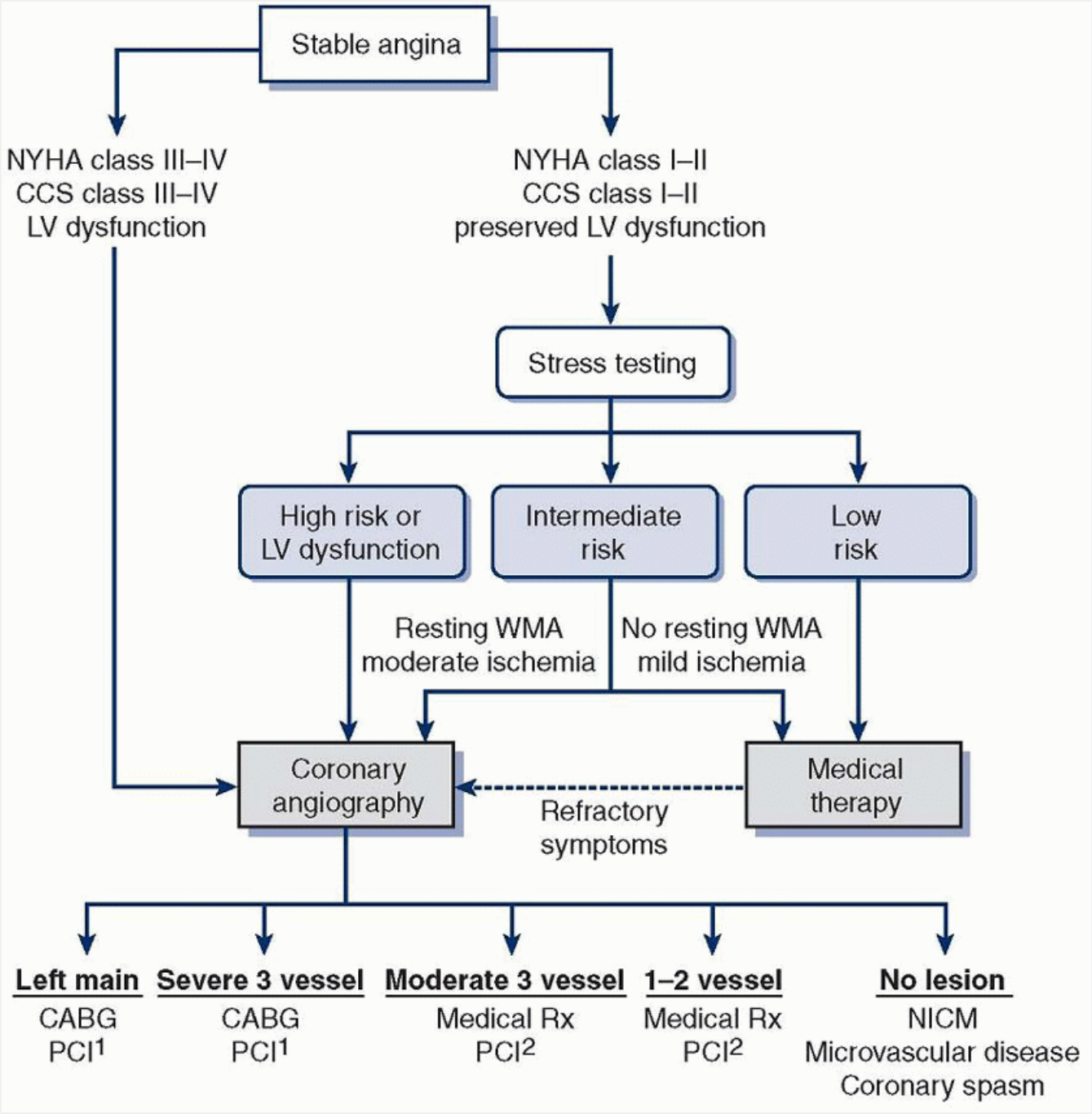


Figure 4-1. Approach to the evaluation and management of the patient with stable angina. Patients with clinical heart failure, severe limiting angina, and those with left ventricle (LV) dysfunction should undergo coronary angiography to define underlying coronary artery disease. Patients without these features may undergo further risk stratification with stress testing. Following stress testing, patients may undergo either coronary angiography or empiric medical therapy depending on their risk profile. Patients initially treated with medical therapy who have refractory symptoms should undergo angiography. [1]CABG generally preferred due to known survival advantage over medical therapy alone; however, if the coronary lesions are not complex, PCI may offer similar results to CABG but with a higher need for future revascularizations. [2]PCI should be reserved for patients who have high-grade lesions, have severe ischemia, and are refractory to medical therapy. CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society Classification (angina); NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; WMA,

wall motion abnormality.

- **Calcium channel blockers** can be used either in conjunction with or in lieu of β-blockers in the presence of contraindications or adverse effects as a second-line agent (Table 4-9).
  - Calcium antagonists are often used in conjunction with β-blockers if the latter are not fully effective at relieving anginal symptoms. Both long-acting dihydropyridines and nondihydropyridine agents can be used.

TABLE 4-8 β-Blockers Commonly Used for Ischemic Heart Disease

Drug	β-Receptor Selectivity	Dose
Propranolol	β_1 and β_2	20-80 mg bid
Metoprolol	β_1	50-200 mg bid
Atenolol	β_1	50-200 mg daily
Nebivolol	β_1	5-40 mg daily
Nadolol	β_1 and β_2	40-80 mg daily
Timolol	β_1 and β_2	10-30 mg tid
Acebutolol[a]	β_1	200-600 mg bid
Bisoprolol	β_1	10-20 mg daily
Esmolol (IV)	β_1	50-300 μg/kg/min
Labetalol	Combined α, β_1, β_2	200-600 mg bid
Pindolol[a]	β_1 and β_2	2.5-7.5 mg tid
Carvedilol	Combined α, β_1, β_2	3.125-25 mg bid

[a]β-blockers with intrinsic sympathomimetic activity.

TABLE 4-9 Calcium Channel Blockers Commonly Used for Ischemic Heart Disease

Drug	Duration of Action	Usual Dosage
Dihydropyridines		
Nifedipine	Long	30-180 mg/d
Amlodipine	Long	5-10 mg/d
Felodipine (SR)	Long	5-10 mg/d
Isradipine	Medium	2.5-10 mg/d
Nicardipine	Short	20-40 mg tid
Nondihydropyridines		
Diltiazem		
Immediate release	Short	30-90 mg qid
Slow release	Long	120-360 mg/d
Verapamil		
Immediate release	Short	80-160 mg tid
Slow release	Long	120-480 mg/d

TABLE 4-10 Nitrate Preparations Commonly Used for Ischemic Heart Disease

Preparation	Dosage	Onset (min)	Duration
Sublingual nitroglycerin	0.3-0.6 mg PRN	2-5	10-30 min
Aerosol nitroglycerin	0.4 mg PRN	2-5	10-30 min
Oral isosorbide dinitrate	5-40 mg tid	30-60	4-6 h
Oral isosorbide mononitrate	10-20 mg bid	30-60	6-8 h
Oral isosorbide mononitrate SR	30-120 mg daily	30-60	12-18 h

2% Nitroglycerin ointment	0.5-2.0 in. tid	20-60	3-8 h
Transdermal nitroglycerin patches	5-15 mg daily	>60	12 h
Intravenous nitroglycerin	10-200 µg/min	<2	During infusion

- Calcium channel blockers are effective agents for the treatment of coronary vasospasm.
- Nondihydropyridine agents (verapamil/diltiazem) should be avoided in patients with systolic dysfunction due to their negative inotropic effects.
- The use of short-acting dihydropyridines (nifedipine) should be avoided due to the potential to increase the risk of adverse cardiac events.

- **Nitrates**, either long-acting formulations for chronic use or sublingual/topical preparations for acute anginal symptoms. More often used as adjunctive antianginal agents (Table 4-10).
  - Sublingual preparations should be used at the first indication of angina or prophylactically before engaging in activities that are known to precipitate angina. Patients should seek prompt medical attention if angina occurs at rest or fails to respond to the third sublingual dose.
  - Nitrate tolerance resulting in reduced therapeutic response may occur with all nitrate preparations. The institution of a nitrate-free period of 10-12 hours (usually at night) can enhance treatment efficacy.
  - For patients with CAD, nitrates have not shown a mortality benefit.
  - Nitrates are contraindicated (even in patients with acute coronary syndrome [ACS]) for use in patients who are on phoshodiesterase-5 inhibitors due to risk of severe hypotension. A washout period of 24 hours for sildenafil and vardenafil and 48 hours for tadalafil is required prior to nitrate use.
- **Ranolazine** is indicated for angina refractory to standard medical therapy and has shown benefit in improving symptoms and quality of life. Ranolazine interacts with simvastatin metabolism and should not be used together.

- **Other secondary prevention medications**
  - **Angiotensin-converting enzyme inhibitors (ACE Inhibitors) and angiotensin receptor blockers (ARBs)** have cardiovascular protective effects that reduce the recurrence of ischemic events.
    - ACE inhibitor therapy, or ARBs in those intolerant to ACE inhibitors, should be used in all patients with an LV ejection fraction (EF) <40% and in those with hypertension, diabetes, or chronic kidney disease.
    - It is reasonable to use ACE inhibitor in all stable angina patients.
  - **Statins** have a marked effect in secondary prevention, and all patients with IHD who can tolerate therapy should be on a high-potency statin (see Chapter 3, Preventive Cardiology). Note, in secondary prevention of coronary heart disease, apart from statins, no other cholesterol agents have proven consistent mortality benefit.

    Ezetimibe can be safely used if statins cannot be tolerated or further reductions in LDL cholesterol are warranted.
  - **Influenza vaccination** is recommended for all patients with IHD.

Revascularization

- **Coronary revascularization**
  - In general, medical therapy with at least two classes of antianginal agents should be attempted before medical therapy is considered a failure and coronary revascularization pursued.
  - Relief of angina symptoms is the most common objective of all revascularization procedures.
  - The indication for all revascularization procedures should consider the acuity of presentation, the extent of ischemia, and the ability to achieve full revascularization. The selection of revascularization should be tailored to the individual patient and, in complex cases, include the use of a multidisciplinary heart team. The heart team includes but is not limited to a cardiac surgeon, interventional cardiologist, noninvasive cardiologist, primary care physician, and other important members of the patient's care.
  - The choice between PCI and CABG surgery is dependent on the coronary anatomy, medical comorbidities, and patient preference.
    - In general, patients with complex and diffuse disease do better with CABG, whereas PCI in select patients with the proper coronary anatomy can provide comparable results as CABG. Due to the more invasive nature of CABG, patient comorbidities often necessitate PCI for revascularization.
    - The Syntax Score is a validated angiographic model that can aid the clinician in determining outcomes after PCI or CABG. In general, patients with a low or intermediate Syntax Score do as well or better with PCI compared to CABG (*Eur Heart J 2011;32:2125*) (available at *http://www.syntaxscore.com/*).
    - The Society of Thoracic Surgeons (STS) score can help determine the risk of mortality and morbidity associated with CABG and should be determined for all patients when considering surgical revascularization (available at *http://riskcalc.sts.org/*).
  - Revascularization is shown to **improve survival** in the following circumstances as compared to medical therapy:
    - CABG for >50% left main coronary artery disease that has not been grafted (unprotected). PCI is a reasonable alternative for patients with left main disease if the patient is a poor surgical candidate (STS score >5) and has a favorable morphology for PCI (low Syntax Score). PCI, in the right clinical context, can offer rates of MI, CVA, or death similar to CABG (*N Engl J Med 2009;360:961*).
    - CABG for three-vessel disease or two-vessel disease that includes the proximal left anterior descending LAD (artery).
    - CABG for patients with two-vessel disease not including the LAD artery if there is extensive ischemia (>20% myocardium at risk) or in patients with isolated proximal LAD artery disease when an internal mammary artery revascularization is performed.
    - CABG, as compared to PCI or medical therapy, in patients with multivessel disease and diabetes, if a left internal mammary artery to the LAD artery can be placed (*N Engl J Med 1996;335:217*). PCI *may* offer similar survival outcomes in diabetics with multivessel disease and a low Syntax Score (<22) but does have a higher need for repeat revascularization (*J Am Coll Cardiol 2010;55:1067*).
    - PCI or CABG in patients who have survived sudden cardiac death due to ischemic ventricular tachycardia.
    - PCI or CABG in patients with ACS.
  - Due to the morbidity of a repeat CABG, PCI is often used to improve symptoms in patients with recurrent angina after CABG.

- The use of internal mammary artery grafts is associated with 90% graft patency at 10 years, compared with 40-50% for saphenous vein grafts. The long-term patency of a radial artery graft is 80% at 5 years. After 10 years of follow-up, 50% of patients develop recurrent angina or other adverse cardiac events related to late vein graft failure or progression of native CAD.
- The risks of elective PCI include <1% mortality, a 2-5% rate of nonfatal MI, and <1% need for emergent CABG for an unsuccessful procedure. Patients undergoing PCI have shorter hospitalizations but require more frequent repeat revascularization procedures compared to CABG.
- Elderly patients represent a unique population when considering revascularization due to comorbidities, frailty, the physiology of aging as it relates to drug metabolism and cardiopulmonary function, and concern over polypharmacy. In general, this population has been underrepresented in most trials but still derives benefit from revascularization to relieve symptoms. Frailty should be heavily considered when considering a procedure or counseling about the benefits of revascularization.
- It is reasonable to revascularize selected patients with severe LV dysfunction (EF <35%), but in general, there is no definitive clinical trial evidence that CABG or PCI will improve LV function or improve mortality compared to medical therapy (*N Engl J Med 2011;364:1407*).
- Viability testing (nuclear perfusion imaging or MRI) may provide some assistance to the clinician when trying to determine the possible benefit of revascularization in patients with prior MI or severe LV dysfunction but is still largely unproven.

PATIENT EDUCATION

- Compliance with medications, diet, and exercise should be stressed to patients. All patients should be encouraged to participate in cardiac rehab as well as meet with a registered dietician.
- Patients with known CAD should present for evaluation if any change in chest pain pattern, frequency, or intensity develops.
- Patients should also be reevaluated if they report the presence of any HF symptoms.

Monitoring/Follow-Up

- Close patient follow-up is a critical component of the treatment of CAD because lifestyle modification and secondary risk factor reduction require serial reassessment and interventions.
- All patients should be aggressively treated for the traditional risk factors mentioned above.
- Relatively minor changes in anginal symptoms can be safely treated with titration and/or addition of antianginal medications.
- Significant changes in anginal complaints (frequency, severity, or time to onset with activity) should be evaluated by either stress testing (usually in conjunction with an imaging modality) or cardiac angiography as warranted.
- Cardiac rehabilitation or an exercise program should be offered or instituted.

Acute Coronary Syndromes, Unstable Angina, and Non-ST-Segment Elevation Myocardial Infarction

GENERAL PRINCIPLES

Definition

- NSTEMI and UA are closely related conditions whose pathogenesis and clinical presentations are similar but differ in severity.

- If coronary flow is not severe enough or the occlusion does not persist long enough to cause myocardial necrosis (as indicated by positive cardiac biomarkers), the syndrome is labeled UA.
- NSTEMI is defined by an elevation of cardiac biomarkers and the absence of ST-segment elevation on the ECG.
- NSTEMI, like STEMI, can lead to cardiogenic shock.
- AHA/ACC guidelines provide a more through overview of NSTEMI/UA (*J Am Coll Cardiol 2014;65:e139*).

Epidemiology

- The annual incidence of ACS is >780,000 events, with 70% being NSTEMI/UA.
- Among patients with ACS, approximately 60% have UA and 40% have MI (one-third of MIs present with an acute STEMI).
- At 1 year, patients with UA/NSTEMI are at considerable risk for death (˜6%), recurrent MI (˜11%), and need for revascularization (˜50-60%). It is important to note that although the short-term mortality of STEMI is greater than that of NSTEMI, the long-term mortality is similar (*J Am Coll Cardiol 2007;50:e1*; *JAMA 1996;275:1104*).
- Patients with NSTEMI/UA tend to have more comorbidities, both cardiac and noncardiac, than STEMI patients.
- Women with NSTEMI/UA have worse short-term and long-term outcomes and more complications compared to men. Much of this has been attributed to delays in recognition of symptoms and underutilization of guideline-directed medical therapy and invasive management.

Etiology and Pathophysiology

- Myocardial ischemia results from decreased myocardial oxygen supply and/or increased demand. In the majority of cases, NSTEMI is due to a sudden decrease in blood supply via partial occlusion of the affected vessel. In some cases, markedly increased myocardial oxygen demand may lead to NSTEMI (demand ischemia), as seen in severe anemia, hypertensive crisis, acute decompensated HF, surgery, or any other significant physiologic stressor.
- UA/NSTEMI most often represents severe coronary artery narrowing or acute atherosclerotic plaque rupture/erosion and superimposed thrombus formation. Alternatively, it may also be due to progressive mechanical obstruction from advancing atherosclerotic disease, in-stent restenosis, or bypass graft disease.
- Plaque rupture may be triggered by local and/or systemic inflammation as well as shear stress. Rupture allows exposure of lipid-rich subendothelial components to circulating platelets and inflammatory cells, serving as a potent substrate for thrombus formation. A thin fibrous cap (thin-cap fibroatheroma) is felt to be more vulnerable to rupture and is most frequently represented as only moderate stenosis on angiography.
- Less common causes include dynamic obstruction of the coronary artery due to vasospasm (Prinzmetal angina, cocaine), coronary artery dissection (more common in women), coronary vasculitis, and embolus.

Clinical Presentation

History

- ACS symptoms include all the qualities of typical angina except the episodes are more severe, of longer duration, and may occur at rest.
- The three principal presentations for UA are **rest angina** (angina occurring at rest and prolonged, usually >20 minutes), **new-onset angina**, and **progressive angina** (previously diagnosed angina that has become more frequent, lasts longer, or occurs with less

exertion). New-onset and progressive angina should occur with at least mild to moderate activity, CCS class III severity.

TABLE 4-11 Killip Classification

Class	Definition	Mortality[a]
I	No signs or symptoms of heart failure	6%
II	Heart failure: S_3 gallop, rales, or JVD	17%
III	Severe heart failure: pulmonary edema	38%
IV	Cardiogenic shock: SBP <90 mm Hg and signs of hypoperfusion and/or signs of severe heart failure	81%

JDV, jugular venous distention; SBP, systolic blood pressure.

[a]In-hospital mortality of patients in 1965-1967 with no reperfusion therapy (n = 250).

Adapted from *Am J Cardiol* 1967;20:457.

- Female sex, diabetes, HF, end-stage kidney disease, and older age are traits that have been associated with a greater likelihood of atypical ACS symptoms. However, the most common presentation in these populations is still typical anginal chest pain.
- Jaw, neck, arm, back, or epigastric pain and/or dyspnea can be anginal equivalents.
- Pleuritic pain, pain that radiates down the legs or originates in the mid/lower abdomen, pain that can be reproduced by extremity movement or palpation, and pain that lasts seconds in duration are unlikely to be related to ACS.

Physical Examination

- Physical examination should be directed at identifying hemodynamic instability, pulmonary congestion, and

other causes of acute chest discomfort.

- Objective evidence of HF, including peripheral hypoperfusion, heart murmur (particularly MR murmur), elevated jugular venous pulsation, pulmonary edema, hypotension, and peripheral edema worsen the prognosis.
- Killip classification can be useful to risk stratify and identify patients with features of cardiogenic shock (Table 4-11).
- Examination may also give clues to other causes of ischemia such as thyrotoxicosis or aortic dissection (see Table 4-4).

Diagnostic Testing

Electrocardiography

- Prior to or immediately on arrival to the emergency department, a baseline ECG should be obtained in all patients with suspected ACS. A normal tracing does not exclude the presence of disease.
- The presence of Q waves, ST-segment changes, or T-wave inversions is suggestive of CAD.
- Isolated Q waves in lead III only are a normal finding.
- Serial ECGs should be obtained to assess for dynamic ischemic changes.
- Comparison to prior ECGs is important when evaluating an ECG for dynamic changes.
- The posterior circulation (i.e., circumflex coronary artery distribution) is poorly assessed with standard ECG lead placement and should always be considered when evaluating patients with ACS. Posterior placed leads or urgent echocardiography may more accurately assess the presence of ischemia when the suspicion is high.

- Approximately 50% of patients with UA/NSTEMI have significant ECG abnormalities, including transient ST-segment elevations, ST depressions, and T-wave inversions (*J Am Coll Cardiol 2007;50:e1*).
  - ST-segment depression in two contiguous leads is a sensitive indicator of myocardial ischemia, especially if dynamic and associated with symptoms.
    - Threshold value for abnormal J-point depression should be 0.5 mm in leads V_2 and V_3 and 1 mm in all other leads.
    - ST-segment depression in multiple leads plus ST-segment elevation in aVR and/or V_1 suggests ischemia due to multivessel or left main disease.
  - Deeply inverted T waves (>5 mm) with QT prolongation in leads V_2 to V_4 (Wellens waves) are suggestive of a critical lesion in the LAD artery distribution.
  - Nonspecific ST-segment changes or T-wave inversions (those that do not meet voltage criteria) are nondiagnostic and unhelpful in management of acute ischemia but are associated with a higher risk for future cardiac events.

Laboratories

- A complete blood count, basic metabolic panel, fasting glucose, and lipid profile should be obtained in all patients with suspected CAD. Other conditions may be found to be contributing to ischemia (e.g., anemia) or mimicking ischemia (e.g., hyperkalemia-related ECG changes) or may alter management (e.g., severe thrombocytopenia).

- Cardiac biomarkers are essential in the diagnosis of UA/NSTEMI and should be obtained in all patients who present with chest discomfort suggestive of ACS. In patients with negative cardiac markers within 6 hours of the onset of pain, a second sample should be drawn 8-12 hours after symptom onset. Troponin is the recommended biomarker for assessment of myocardial necrosis.
  - Troponin T and I assays are highly specific and sensitive markers of myocardial necrosis. Serum troponin levels are usually undetectable in normal individuals, and any elevation is considered abnormal.
  - MI size and prognosis are directly proportional to magnitude of increase in troponin (*N Engl J Med 1996;335:1333*; *Circulation 1998;98:1853*).
- Creatine kinase (CK)-MB is also an acceptable marker of myocardial necrosis, but lacks specificity because it is present in both skeletal and cardiac muscle cells.
  - Specificity can be improved by using the CK-MB/total CK fraction. A CK-MB fraction >5% is suggestive of myocardial injury.
  - CK-MB is a useful assay for detecting postinfarct ischemia because a fall and subsequent rise in enzyme levels suggest reinfarction, especially if accompanied by recurrent ischemic symptoms or ECG changes.
  - CK-MB and troponin levels should not routinely be measured after PCI or cardiac surgery because their prognostic value is uncertain. Patients who have symptoms should be assessed with appropriate tests including biomarkers.
- Brain natriuretic peptide (BNP) can be a useful biomarker of myocardial stress in patients with ACS, and elevations are associated with worse outcomes (*Circulation 2002;105:1760*). Severe elevations of BNP in the setting of ACS in patients without known HF should raise concern for a large infarction and urgent angiography.

TREATMENT

- Acute treatment should be aimed at reducing the symptoms of chest pain.
- Risk stratification can be helpful in determining the appropriate testing, pharmacologic interventions, and timing or need for coronary angiography.

- Risk of death or MI progression is elevated with the following **high-risk ACS characteristics**:
  - Recurrent/accelerating angina despite adequate medical therapy
  - Signs or symptoms of new HF, pulmonary edema, or shock (high Killip Classification)
  - New or worsening MR
  - New LBBB
  - Ventricular tachycardia noted on monitoring
- These findings (on presentation **or anytime during the index hospitalization**) should prompt the performance of **urgent** coronary angiography with intention to offer revascularization.
- Several clinical tools can estimate a patient's risk of recurrent MI and cardiac mortality, such as the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) risk scores. The TIMI risk score can be used to determine the risk of death or nonfatal MI up to 1 year after an ACS event and, given the ease of use, is our recommended risk stratification tool. Patients can be classified as low, intermediate, or high risk on the basis of their clinical profile (Figure 4-2).

- Patients with a TIMI risk of 0 and negative troponins have a very low 30-day rate of major adverse cardiac events.
- Patients with a TIMI risk score of ≥3 benefit from aggressive medical therapy and invasive evaluation.

- In the stabilized patient, two treatment strategies are available: the **ischemia-driven approach** (formerly termed *conservative*) versus the **routine invasive approach** (*early* defined as <24 hours of presentation or *delayed* >24 hours). The planned approach should always be individualized to the patient (Figure 4-3). All patients should receive aggressive antithrombotic, antiplatelet, and ischemic medical therapy no matter the final revascularization strategy. Table 4-12 summarizes the selection approach.
  - In the ischemia-driven approach, if the patient does not develop high-risk ACS features, has normal subsequent cardiac enzymes, has no dynamic ECG changes, and responds to medical therapy, a noninvasive stress test should be obtained for further risk stratification.
    - Patients should be angina free for at least 12 hours prior to stress testing.
    - If a patient with positive cardiac enzymes is selected for noninvasive testing, a submaximal or pharmacologic stress test 72 hours after the peak value may be performed.
    - Coronary angiography is reserved for patients who develop high-risk ACS features, have a high-risk stress test, develop angina at low levels of stress, or are noted to have an LVEF <40%.
  - In the **routine invasive strategy**, the patient is planned for a coronary angiography with intent to revascularize. An early (<24 hours from presentation) invasive approach is recommended for patients with high-risk scores or other high-risk features (see Table 4-12).
  - Note: Refractory chest pain, hemodynamic instability, or serious ventricular arrhythmias are indications for an urgent/emergent invasive strategy similar to STEMI; this is not to be confused with a routine invasive strategy.
  - An early invasive strategy is also warranted in low- or intermediate-risk patients with repeated ACS presentations despite appropriate therapy.
  - A routine invasive strategy is not recommended for the following:
    - Patients with severe comorbid illnesses such as chronic kidney disease, end-stage liver or lung disease, or metastatic/uncontrolled cancer whereby the benefits of the procedure are likely outweighed by the risk from the routine invasive procedure
    - Acute chest pain with a low likelihood of ACS and negative biomarkers, especially in women
  - As opposed to stable IHD, a routine invasive approach with possible PCI has been shown to **reduce the incidence of recurrent MI, hospitalizations, and death**. In general, patients with ACS should undergo a routine invasive strategy unless it is clear that the risk outweighs the possible benefit in a given patient.

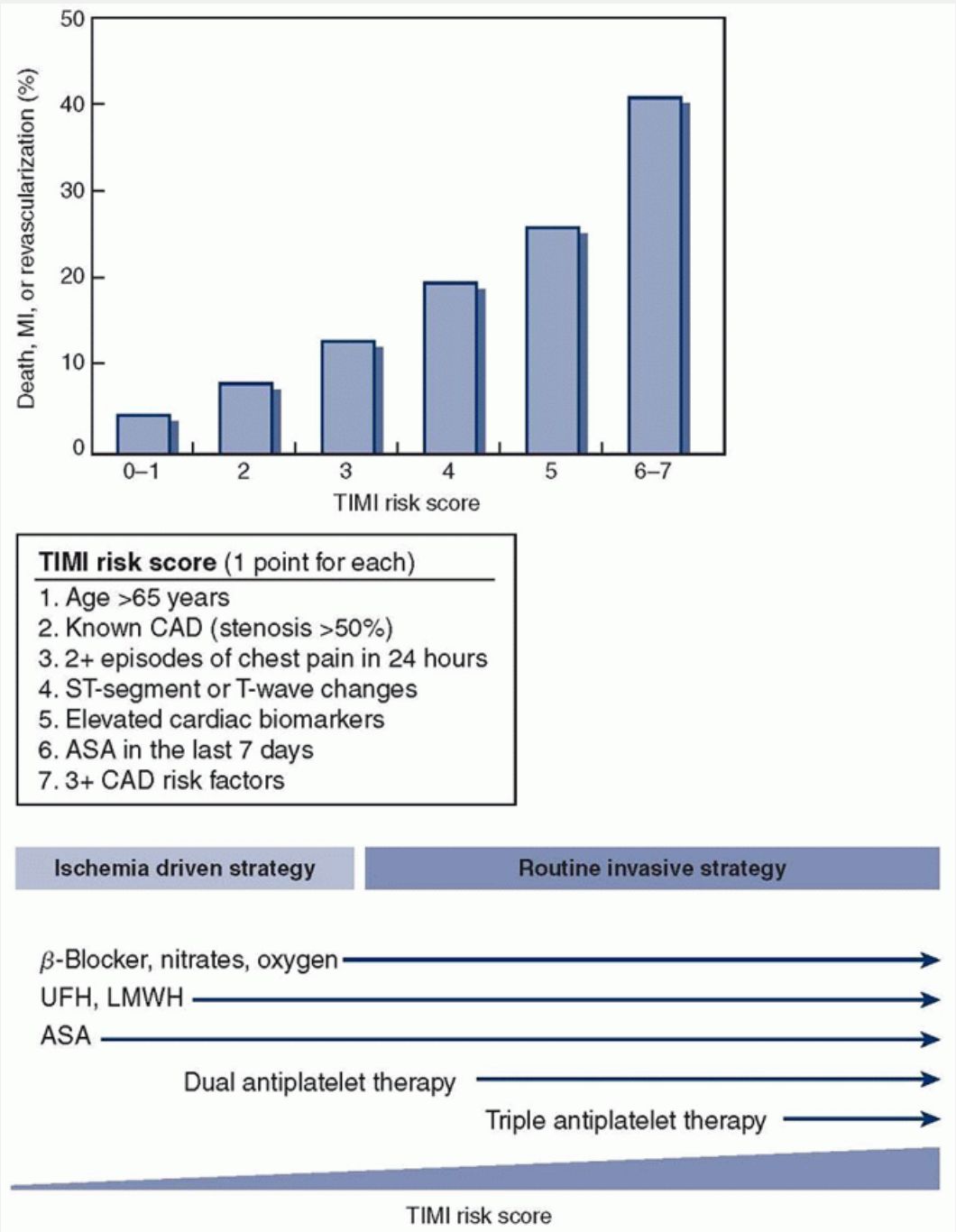


Figure 4-2. Fourteen-day rates of death, MI, or urgent revascularization from the TIMI 11B and ESSENCE trials based on increasing TIMI risk score. Coronary artery disease (CAD) risk factors include family history of CAD, diabetes, hypertension, hyperlipidemia, and tobacco use. ASA, aspirin; LMWH, low-molecular-weight heparin; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin. (Data from *JAMA* 2000;284:835-42.)

Medications

Patients presenting with UA/NSTEMI should receive medications that reduce myocardial ischemia through reduction in myocardial oxygen demand, improvement in coronary perfusion, and prevention of further thrombus formation.

- This approach should include antiplatelet, anticoagulant, and antianginal medications.
- Supplemental oxygen should be provided if the patient is hypoxemic (<90%) or having difficulty breathing. Routine use of oxygen is not needed and possibly harmful (*Heart 2009;95:198*).

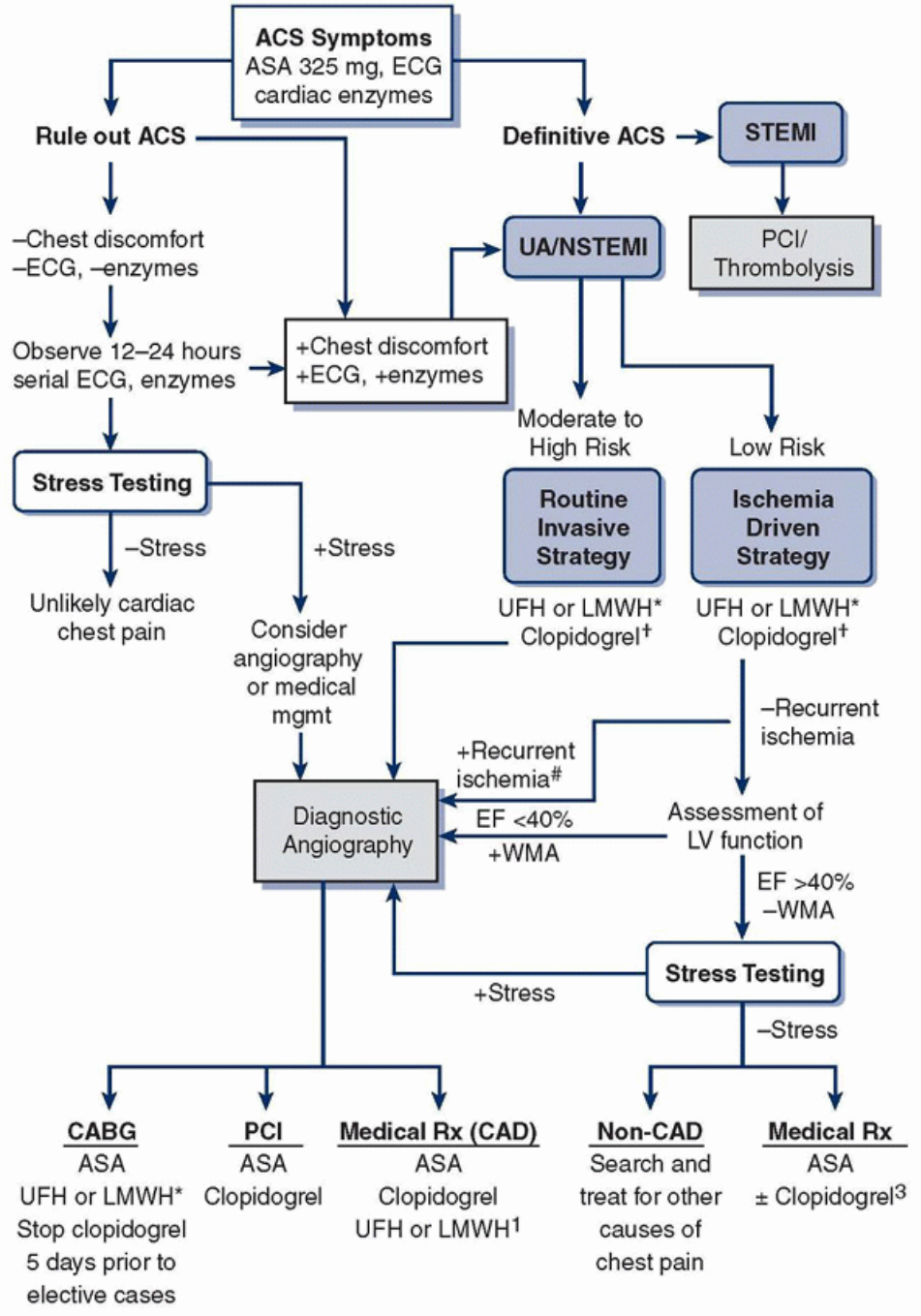


Figure 4-3. Diagnostic and therapeutic approach to patients presenting with acute coronary syndrome (ACS) focusing on antiplatelet and antithrombotic therapy. *Bivalirudin is an appropriate alternative to UFH and LMWH, or at time of PCI, patients on UFH may be switched to bivalirudin. †Choose either clopidogrel, ticagrelor, or prasugrel as the second antiplatelet agent. #Indicators of recurrent ischemia include worsening chest pain, increasing cardiac enzymes, heart failure signs/symptoms, arrhythmia (VT/VF), and dynamic ECG changes. [1]UFH for 48 hours or LMWH until discharge or up to 8 days and clopidogrel or ticagrelor for 1 year. P2Y12 inhibitor includes antiplatelet agents clopidogrel, ticagrelor, or prasugrel. ASA, aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EF, ejection fraction; glycoprotein IIb/IIIa inhibitor; LMWH, low-molecular-weight heparin; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; Rx, treatment; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UFH, unfractionated heparin; VT/VF, ventricular tachycardia/ventricular fibrillation; WMA, wall motion abnormality. (Data from the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction.)

TABLE 4-12 Appropriate Selection of Routine Invasive Versus Ischemia-Driven Revascularization Strategy in Patients with NSTEMI/UA

Immediate/urgent invasive (within 2 h)	Refractory angina Worsening signs or symptoms of heart failure or mitral regurgitation Hemodynamic instability or shock Sustained VT or VF
Ischemia-driven	Low-risk score (TIMI ≤1 or GRACE <109) Low-risk biomarker-negative female patients Patient or clinician preference in the absence of highrisk features
Early invasive (within 24 h)	None of the above but a high-risk score (TIMI ≥3 or GRACE >140) Rapid rate of rise in biomarkers New or presumably new ST depressions
Delayed invasive (24-72 h)	None of the above but presence of diabetes Renal insufficiency (GFR <60) LV ejection fraction <40% Early postinfarction angina Prior PCI within 6 months Prior CABG TIMI score ≥2 or GRACE score 109-140 and no indication for early invasive strategy

CABG, coronary artery bypass graft; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; LV, left ventricular; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; VF, ventricular fibrillation; VT, ventricular tachycardia.

- **Antiplatelet therapy**
  - Table 4-13 summarizes available agents and dosing recommendations for use in ACS.
  - Dual antiplatelet therapy is recommended for patients with NSTEMI/UA.
  - **Aspirin** blocks platelet aggregation within minutes.
    - A chewable 162-325-mg dose of ASA should be administered immediately at symptom onset or at first medical contact, unless a contraindication exists. This should be followed by ASA 81 mg daily indefinitely.

TABLE 4-13 Antiplatelet Agents in UA/NSTEMI

Medication	Dosage	Comments
Aspirin (ASA)	162-325 mg initial, then 75-100 mg	In patients taking ticagrelor, the maintenance dose of ASA *should not* exceed 100 mg.

Clopidogrel	300-600 mg loading dose, 75 mg daily	In combination with ASA, clopidogrel (300-600 mg loading dose, then 75 mg/d) decreased the composite end point of cardiovascular death, MI, or stroke by 18-30% in patients with UA/NSTEMI (*N Engl J Med 2001;345:494*; *Lancet 2001;358:527*; *JAMA 2002;288:2411*).
Ticagrelor	180 mg loading dose, then 90 mg bid	Ticagrelor reduced incidence of vascular death, MI, or CVA (9.8% vs. 11.0%) but with higher major bleeding not related to CABG (4.5% vs. 3.8%) as compared to clopidogrel (*N Engl J Med 2009;361:1045*).
Prasugrel	60 mg loading dose, 10 mg daily	Prasugrel has increased antiplatelet potency compared to clopidogrel. Prasugrel reduced the incidence of cardiovascular death, MI, and stroke (9.9% vs. 12.1%) at the expense of increased major (2.4% vs. 1.1%) and fatal bleeding (0.4% vs. 0.1%), compared to clopidogrel (*N Engl J Med 2007;357:2001*).
Eptifibatide	180 µg/kg IV bolus, 2 µg/kg/min[a]	Eptifibatide reduces the risk of death or MI in patients with ACS undergoing either invasive or noninvasive therapy in combination with ASA and heparin (*N Engl J Med 1998;339:436*; *Circulation 2000;101:751)*. Compared to abciximab and tirofiban, eptifibatide has the most consistent effects on platelet inhibition with shortest on-time and drug half-life (*Circulation 2002;106:1470-6*).
Tirofiban	0.4 µg/kg IV bolus, 0.1 µg/kg/min[a]	Tirofiban reduces the risk of death or MI in patients with ACS undergoing either invasive or noninvasive therapy in combination with ASA and heparin (*Circulation 1997;96:1445*; *N Engl J Med 1998;338:1498*; *N Engl J Med 1998;338:1488*).
Abciximab	0.25 mg/kg IV bolus, 10 µg/min[b]	Abciximab reduces the risk of death or MI in patients with ACS undergoing coronary intervention (*N Engl J Med 1994;330:956*; *Lancet 1997;349:1429*; *N Engl J Med 1997;336:1689*). It should not be used in patients in whom percutaneous intervention is not planned (*Lancet 2001;357:1915*). Platelet inhibition may be reversed by platelet transfusion.

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina.

[a]Infusion doses should be decreased by 50% in patients with a GFR <30 mL/min and avoided in patients on HD.

[b] Abciximab may be used in patients with ESRD because it is not cleared by the kidney.

- If an ASA allergy is present, clopidogrel may be substituted. An allergy consultation should be obtained for possible desensitization, preferably prior to the need for a coronary stent.
- After PCI, ASA 81 mg is the current recommended dose in the setting of dual antiplatelet therapy.

- **Clopidogrel** is a prodrug whose metabolite blocks the P2Y12 receptor and inhibits platelet activation and aggregation by blocking the adenosine diphosphate receptor site on platelets.
  - The addition of clopidogrel to ASA reduced cardiovascular mortality and recurrent MI both acutely and at 11 months of follow-up (*N Engl J Med 2001;345:494*).
  - A loading dose should always be given in naïve patients.
  - In patients unable to take oral medications or unable to absorb oral medications due to ileus, rectal administration is unproven but has been reported. This may be particularly important after PCI when dual antiplatelet therapy is critical.
  - Can be used as part of the protocol in both the ischemia-driven and early invasive strategies.
- **Prasugrel** is also a prodrug that blocks the P2Y12 adenosine receptor; its conversion to its active metabolite occurs faster and to a greater extent than clopidogrel.
  - Results in faster, greater, and more uniform platelet inhibition compared to clopidogrel at the expense of higher risk of bleeding (*Circulation 2007;116:2923*).
  - It decreases risk of CVD death, MI, CVA, and acute stent thrombosis as compared to clopidogrel in ACS patients, including STEMI patients.
  - It should be used with caution or avoided in patients older than 75 years and who weigh less than 60 kg. It is **contraindicated** in those with prior stroke or transient ischemic attack.
  - Used only in the **invasive approach of ACS** and **only after coronary anatomy is known and PCI is planned**. There is no benefit over clopidogrel when tested before initiation of PCI.
- **Ticagrelor** is not a prodrug and blocks the P2Y12 adenosine receptor directly.
  - Reduces the risk of death, MI, CVA, and stent thrombosis as compared to clopidogrel in ACS patients, including STEMI patients (*N Engl J Med 2009;361:1045*).

  - After the loading dose of ASA, the maintenance dose of ASA **must be <100 mg** (*Circulation 2011;124:544*).
  - Can be used as part of the protocol in both the ischemia-driven and early invasive strategies.
- Use of **proton pump inhibitors (PPIs)** with P2Y12 receptor antagonists.
  - PPIs should be used in patients who will require both ASA therapy and a P2Y12 antagonist with prior history of gastrointestinal bleeding and may be considered in those at increased risk of bleeding (such as older individuals, patients with known ulcers or *Helicobacter pylori* infection, and patients also on warfarin, steroids, or NSAIDs) (*Circulation 2010;122:2619*).
  - Pharmacologic studies have raised concerns about the potential of PPIs to blunt the efficiency of clopidogrel. However, in a prospective randomized trial, no apparent cardiovascular interaction was noted between PPIs and clopidogrel (*N Engl J Med 2010;363:1909*).
- **Glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists** (abciximab, eptifibatide, or tirofiban) block the interaction between platelets and fibrinogen, thus targeting the final common pathway for platelet

aggregation.

- GPIIb/IIIa inhibitors play a limited role in ACS management with the introduction of more potent oral antiplatelet agents.
- Routine use of GPIIb/IIIa antagonists on initial presentation, before angiography, in patients undergoing the invasive approach *should be avoided* due to increased risk of major bleeding and a lack of improvement in outcomes.
- GPIIb/IIIa agents may be considered in the following:

  Patients who require add-on therapy for *worsening* ischemia any time prior to angiography or as part of conservative therapy even if the patient is already being treated with dual oral antiplatelet therapy and anticoagulation.

  Discretional use during PCI due to the presence of complex coronary lesions or coronary thrombus.
- Abciximab is reserved for use only during PCI and started no sooner than 4 hours prior to the planned procedure.
- Eptifibatide has been used as a bridging, short-acting antiplatelet agent in patients who have had recent PCI and require surgery where dual antiplatelet therapy is prohibited. An infusion is started to bridge in absence of oral therapy, stopped before surgery, and promptly restarted after surgery when deemed safe. Although common practice, this strategy is of unproven benefit.
- Thrombocytopenia, which can be severe, is an uncommon complication of these agents and should prompt discontinuation.

- **Antiplatelet agents and timing of CABG**
  - Due to increased risk of bleeding, it is currently recommended that clopidogrel be withheld for at least 5 days prior to CABG, prasugrel 7 days prior, and ticagrelor 5 days prior.
  - GPIIb/IIIa antagonists can be an alternative to clopidogrel, ticagrelor, and prasugrel for upstream use (prior to angiography) in appropriate patients with UA/NSTEMI who are known to require surgical revascularization.
  - In general, dual antiplatelet therapy should not be withheld during the initial management of ACS for concern over need for surgical revascularization. There is a larger risk of withholding beneficial therapy to patients in this setting than causing harm by complicating surgical revascularization.

- **Anticoagulant therapy**
  - See Table 4-14 for recommended use and dosing in ACS.
  - Anticoagulation accompanied by dual antiplatelet therapy is required for all UA/NSTEMI patients, whether along the early invasive or conservative pathway.

TABLE 4-14 Anticoagulant Medications

Medication	Dosage	Comments
Heparin (UFH)	60 units/kg IV bolus	Heparin therapy, when used in conjunction with ASA, has been shown to reduce the early rate of death or MI by up to 60% (*JAMA 1996;276:811*). The aPTT should be adjusted to

	(maximum dose: 4000 units), 12-14 units/kg/h	maintain a value of 1.5-2.0 times control.
Enoxaparin (LMWH)	1 mg/kg SC bid[a]	LMWH is at least as efficacious as UFH and may further reduce the rate of death, MI, or recurrent angina (*N Engl J Med 1997;337:447*). LMWH may increase the rate of bleeding (*JAMA 2004;292:45*) and cannot be reversed in the setting of refractory bleeding. LMWH does not require monitoring for clinical effect.
Fondaparinux	2.5 mg SC daily	Fondaparinux has efficacy similar to that of LMWH with possibly reduced bleeding rates (*N Engl J Med 2006;354:1464*).
Bivalirudin[b]	0.75 mg/kg IV bolus, 1.75 mg/kg/h	When used in conjunction with ASA and clopidogrel, bivalirudin is at least as effective as the combination of ASA, UFH, clopidogrel, and GPIIb/IIIa antagonists with decreased bleeding rates (*N Engl J Med 2006;355:2203*). May increase risk for stent thrombosis. Monitoring is required with a goal aPTT of 1.5-2.5 times control.

aPTT, activated partial thromboplastin time; ASA, aspirin; GFR, glomerular filtration rate; GP, glycoprotein; LMWH, low-molecular-weight heparin; MI, myocardial infarction; UFH, unfractionated heparin.

[a]LMWH should be given at reduced dose (50%) in patients with a serum creatinine >2 mg/dL or GFR <30 mL/min.

[b]Bivalirudin requires dosage adjustment in patients with a GFR less than 30 mL/min or those on hemodialysis.

- **Unfractionated heparin (UFH)** works by binding antithrombin III, which catalyzes the inactivation of thrombin and other clotting factors.
  - Most commonly used and easily monitored but also most inconsistent in its anticoagulation and metabolism.
  - Heparin-induced thrombocytopenia (HIT) is a concern with prior use.
  - Easily reversed in the event of a severe hemorrhagic complication.
  - Always requires aggressive bolus dosing and anticoagulation monitoring in the setting of ACS.
  - Recommended anticoagulant to be used in the setting of ACS.
- **Low-molecular-weight heparin (LMWH)** inhibits mostly factor Xa but also affects thrombin activity and offers an ease of administration (weight-based, twice-daily subcutaneous dose). The risk of HIT is

lower but not absent.

- As compared to UFH, LMWH has a more predictable anticoagulant effect.
- It has a similar efficacy as UFH but is associated with a higher risk of postprocedural bleeding (*JAMA 2004;292:45*).
- LMWH must be adjusted for renal dysfunction and should be avoided in patients with severe impairments.
- Enoxaparin 0.3 mg/kg IV should be administered at the time of PCI in patients who have received less than two therapeutic doses or if the last dose was received more than 8 hours before PCI.

- **Fondaparinux** is a synthetic polysaccharide that selectively inhibits factor X and can be subcutaneously administered on a daily routine.
  - Associated with less bleeding and similar major adverse cardiovascular outcomes when compared to enoxaparin.
  - Associated with an increased risk of thrombosis during PCI and should not be used without additional antithrombin anticoagulation; as such, it is not recommended for the routine management of ACS.
  - In patients not undergoing invasive management, fondaparinux may significantly reduce bleeding and improve outcomes compared to LMWH (*JAMA 2015;313:707*).
- **Bivalirudin** is a direct thrombin inhibitor given as a continuous IV infusion and requires partial thromboplastin time (PTT) monitoring when used for >4 hours.
  - It does not cause HIT and is used in the treatment of patients who develop HIT or patients with ACS who have history of HIT.
  - Bivalirudin can be given in conjunction with ASA and clopidogrel in patients presenting with UA/NSTEMI who will undergo a routine invasive strategy.
  - Bivalirudin alone compared to UFH/LMWH + GPIIb/IIIa inhibitor was associated with less bleeding (*N Engl J Med 2006;355:2203*). Recent evidence has shown that in ACS without significant GPIIb/IIIa inhibitor use, bivalirudin is associated with increased risk of stent thrombosis and target lesion revascularization (*Lancet 2014;384:1849*).
  - Caution should be used with routine use of bivalirudin in ACS unless there is a high risk of bleeding.

- **Anti-ischemic therapy** (please also refer to Treatment section of stable angina)
  - **Nitroglycerin**
    - Treatment can be initiated at the time of presentation with sublingual nitroglycerin. **NOTE:** 40% of patients with chest pain *not* due to CAD will get relief with nitroglycerin (*Ann Intern Med 2003;139:979*) (see Table 4-10).
    - Patients with ongoing ischemic symptoms or those who require additional agents to control significant hypertension can be treated with IV nitroglycerin until pain relief, hypertension control, or both are achieved.
    - Rule out right ventricular (RV) infarct prior to administration of nitrates because this can precipitate profound hypotension.
  - **β-Adrenergic blockers (BBs)** (please also refer to the Treatment section for stable angina)
    - Oral therapy should be started early in the absence of contraindications.

- Treatment with an IV preparation should be reserved for treatment of arrhythmia, ongoing chest pain, or advanced hypertension rather than routine use.
- Routine use of IV BBs is associated with increased risk of cardiogenic shock and should be avoided.
- Contraindications to BB therapy include advanced AV block, active bronchospasm, decompensated HF, cardiogenic shock, hypotension, and bradycardia.

◦ **Morphine** 2-4 mg IV may be used as an adjunct to BB, nitrates, and calcium channel blockers. Care must be used not to mask further clinical evaluation by heavy use of narcotic medications.

- **Adjunctive medical therapy**
  - **ACE inhibitors** (refer to Treatment section for stable angina) are effective antihypertensive agents and have been shown to reduce mortality in patients with CAD and LV systolic dysfunction. ACE inhibitors should be used in patients with LV dysfunction (EF <40%), hypertension, or diabetes presenting with ACS. **ARBs** are appropriate in patients who cannot tolerate ACEIs.
  - **Aldosterone antagonists** should be added, if there are no contraindications (potassium >5 mEq/L or creatinine clearance [CrCl] <30 mL/min), after initiation of ACE inhibitors to patients with diabetes or who have an LVEF <40%.
  - **3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins)** are potent lipid-lowering agents that reduce the incidence of ischemia, MI, and death in patients with CAD. High-dose statins should be routinely administered within 24 hours of presentation in patients presenting with ACS. A lipid profile should be obtained in all patients.
    - Statin therapy reduces adverse outcomes through lipid lowering and potentially through pleiotropic effects (anti-inflammatory/atherosclerotic plaque-stabilizing effects).
    - Aggressive statin therapy reduces the risk of recurrent ischemia, MI, and death in patients presenting with ACS (*JAMA 2001;285:1711*).
    - A reduction in adverse CVD outcomes following early initiation of a high-dose statin with achievement of an LDL <70 mg/dL can be seen as early as 30 days following initial presentation with ACS (*N Engl J Med 2004;350:1495*). Aggressive LDL lowering also reduces the incidence of periprocedural MI following PCI (*J Am Coll Cardiol 2007;49:1272*).
  - **NSAIDs** are associated with an increased risk of death, MI, myocardial rupture, hypertension, and HF in large meta-analyses (*Circulation 2006;113:2906*). Adverse outcomes have been observed for both nonselective and cyclooxygenase-2 (COX-2) selective agents.
    - NSAIDs should be discontinued in patients presenting with UA/NSTEMI.
    - Acetaminophen is an acceptable alternative for the treatment of osteoarthritis and other musculoskeletal pain.
  - **Blood glucose** should not be tightly controlled in diabetic patients who have suffered ACS because it may increase mortality. Goal is <180 mg/dL while avoiding hypoglycemia at all costs.

Revascularization

- **PCI**

  See "Revascularization" section on pp. 103-104 for invasive management strategies.

- **CABG**
  - The indications for PCI and CABG in patients with UA/NSTEMI are similar to those for individuals with chronic stable angina (please see section on revascularization on pp. 103-104).

- The urgency of revascularization should weigh heavily in the decision for CABG; patients in cardiogenic shock may benefit from PCI and mechanical support compared to emergency cardiac surgery.
- NSTEMI in the setting of critical left main coronary artery disease should prompt urgent surgical revascularization and consideration of intra-aortic balloon counterpulsation (IABP) for stabilization prior to the induction of anesthesia.

Monitoring/Follow-Up

The highest rate of progression to MI or development of recurrent MI is in the first 2 months after presentation with the index episode. Beyond that time, most patients have a clinical course similar to those with chronic stable angina.

- Patients should be discharged on dual antiplatelet, BB, and statin therapy.
- Most patients should be discharged on ACE inhibitors.

- Patients should be evaluated for the need of aldosterone antagonists.
- Screen for life stressors and depression. Refer for depression treatment as needed.
- Smoking cessation and risk factor modification should be stressed.
- Referral to cardiac rehabilitation should also be pursued.

ST-Segment Elevation Myocardial Infarction

GENERAL PRINCIPLES

Definition

- STEMI is defined as a clinical syndrome of myocardial ischemia in association with persistent ECG ST elevations (see ECG section) and subsequent release of biomarkers of necrosis.
- STEMI is a medical emergency.
- Compared to UA/NSTEMI, STEMI is associated with a higher in-hospital and 30-day morbidity and mortality. Left untreated, the mortality rate of STEMI can exceed 30%, and the presence of mechanical complications (papillary muscle rupture, ventricular septal defect [VSD], and free wall rupture) increases the mortality rate to 90%.
- Ventricular fibrillation accounts for approximately 50% of mortality and often occurs within the first hour from symptom onset.
- Keys to treatment of STEMI include rapid recognition and diagnosis, coordinated mobilization of health care resources, and prompt reperfusion therapy.
- Mortality is directly related to total ischemia time.
- AHA/ACC guidelines provide a more thorough overview of STEMI (*J Am Coll Cardiol 2013;61:e78*).

Epidemiology

- STEMI accounts for approximately 25-30% of ACS cases annually, and the incidence has been declining.
- Over the last several decades, there has been a dramatic improvement in short-term mortality to the current rate of 6-10%.

- Approximately 30% of STEMI presentations occur in women, but outcomes and complications continue to be worse compared with male counterparts.

Pathophysiology

- STEMI is caused by acute, total occlusion of an epicardial coronary artery, most often due to atherosclerotic plaque rupture/erosion and subsequent thrombus formation.
- As compared to NSTEMI/UA, thrombotic occlusion is complete such that there is total transmural ischemia/infarct in the distribution of the large occluded artery.

DIAGNOSIS

Clinical Presentation

History

- Chest pain from STEMI resembles angina but lasts longer, is more intense, and is not relieved by rest or sublingual nitroglycerin. Chest discomfort may be accompanied by dyspnea, diaphoresis, palpitations, nausea, vomiting, fatigue, and/or syncope.
- Severe tearing chest pain or focal neurologic deficits should raise concern for aortic dissection. Aortic dissection can mimic ACS; in addition, dissections of the ascending aorta may involve the right coronary artery and cause ST elevations on the ECG.
- It is imperative to determine the time of symptom onset because this is critical in determining the appropriate means of reperfusion.

- STEMI may have an atypical presentation particularly in female, elderly, and postoperative patients, as well as those with diabetes and chronic or end-stage kidney disease. Such patients may experience atypical or no chest pain and may instead present with confusion, dyspnea, unexplained hypotension, or HF.
- STEMI should always be considered as an etiology when any patient is hemodynamically compromised (i.e., postoperative, delirium, or shock).
- The initial history by the clinician should always include an inquiry about prior cardiac procedures or surgery. Prior PCI or CABG can have profound implications for acute revascularization management.
- The clinician should assess for absolute and relative contraindications to thrombolytic therapy (see the following text) and potential issues complicating primary PCI (IV contrast allergy, PVD/peripheral revascularization, renal dysfunction, central nervous system [CNS] disease, pregnancy, bleeding diathesis, or severe comorbidity).
- Inquire about recent cocaine use. In this setting, aggressive medical therapy with nitroglycerin, coronary vasodilators, and benzodiazepines should be administered before reperfusion therapy is considered.

Physical Examination

Physical examination should be directed at identifying hemodynamic instability, pulmonary congestion, mechanical complications of MI, and other causes of acute chest discomfort.

- The Killip classification (see Table 4-11) can be a useful guide when evaluating patients with ACS. The Forrester classification uses hemodynamic data to risk stratify patients and is less frequently used.
- The identification of a new systolic murmur may suggest the presence of ischemic MR or a VSD.

- A limited neurologic exam to detect baseline cognitive and motor deficits and a vascular examination (lower extremity pulses and bruits) will aid in determining candidacy and planning for reperfusion treatment.
- Cardiogenic shock due to right ventricular MI (RVMI) may be clinically suspected by the presence of hypotension, elevated jugular venous pressure, and absence of pulmonary congestion.
- Bilateral arm BPs should be obtained to assess for the presence of aortic dissection.

DIAGNOSTIC TESTING

Electrocardiography

The ECG is paramount to the diagnosis of STEMI and should be obtained within 10 minutes of presentation. If the diagnosis of STEMI is in doubt, serial ECGs may help elucidate the diagnosis. Classic findings include:

- Peaked upright T waves are the first ECG manifestation of myocardial injury.
- ST elevations correlate with the territory of injured myocardium (Table 4-15).
- **Diagnostic ECG criteria for STEMI** (*J Am Coll Cardiol 2009;53:1003*)
  - When ST elevations reach threshold values in two or more anatomically contiguous leads, a diagnosis of STEMI can be made.
  - In men >40 years of age, threshold value for abnormal ST-segment elevation at the J point is ≥2 mm in leads V_2 and V_3 and >1 mm in all other leads. In men <40 years of age, threshold value for abnormal ST-segment elevation at the J point in leads V_2 and V_3 is >2.5 mm.
  - In women, the threshold value of abnormal ST-segment elevation at the J point is >1.5 mm in leads V_2 and V_3 and >1 mm in all other leads.
  - In right-sided leads (V_3R and V_4R), the threshold for abnormal ST elevation at the J point is 0.5 mm, except in males <30 years in whom it is 1 mm. Right-sided leads

should be obtained in all patients with evidence of inferior wall ischemia to rule out RV ischemia. RV infarction can occur with proximal right coronary artery (RCA) lesions.

TABLE 4-15 Electrocardiogram-Based Anatomic Distribution

ST Elevation	Myocardial Territory	Coronary Artery
V_1-V_6 or LBBB	Anterior and septal walls	Proximal LAD or left main
V_1-V_2	Septum	Proximal LAD or septal branch
V_2-V_4	Anterior wall	LAD
V_5-V_6	Lateral wall	LCX

II, III, aVF	Inferior wall	RCA or LCX
I, aVL	High lateral wall	Diagonal or proximal LCX

LAD, left anterior descending artery; LBBB, left bundle branch block; LCX, left circumflex artery; RCA, right coronary artery.

- In posterior leads (V_7, V_8, and V_9), the threshold for abnormal ST elevation at the J point is 0.5 mm.
  - All patients with ST-segment depression in leads V_1 to V_3, inferior wall ST elevation, or tall R waves in V_1 to V_3 should have posterior leads placed in order to diagnose a posterior wall MI. Posterior STEMIs are usually due to occlusion of the circumflex artery and are often misdiagnosed as UA/NSTEMI. R waves in V_1 or V_2 represent Q waves of the posterior territory.
  - Ischemia of the circumflex artery may also be electrocardiographically silent.
- The presence of reciprocal ST-segment depression opposite of the infarct territory increases the specificity for acute MI.
- New LBBB suggests a large anterior wall MI with a worse prognosis.
- ECG criteria for STEMI in patients with preexisting LBBB or RV pacing can be found in Table 4-16. Above criteria do not apply.
- **ECG changes that mimic MI.** ST-segment elevation and Q waves may result from numerous etiologies other than acute MI, including prior MI with aneurysm formation, aortic dissection, LV hypertrophy, pericarditis, myocarditis, or pulmonary embolism, or they may be a normal finding (Table 4-17). It is critical to obtain prior ECGs to clarify the diagnosis.

TABLE 4-16 Criteria for ST-segment Elevation for Prior LBBB or RV-Paced Rhythm

ECG Change
ST-segment elevation >1 mm in the presence of a positive QRS complex (concordant with the QRS)
ST-segment elevation >5 mm in the presence of a negative QRS complex (disconcordant with the QRS)
ST-segment depression >1 mm in V_1-V_3

LBBB, left bundle branch block; RV, right ventricular.

Sgarbossa's (GUSTO) criteria: *Am J Cardiol* 1996;77:423; *N Engl J Med* 1996;334:481; *Pacing Clin Electrophysiol* 2001;24:1289.

TABLE 4-17 Differential Diagnosis of ST-Segment Elevation on ECG Excluding STEMI

Cardiac Etiologies	Other Etiologies
Prior MI with aneurysm formation	Pulmonary embolism
Aortic dissection with coronary involvement	Hyperkalemia
Pericarditis	
Myocarditis	
LV hypertrophy or aortic stenosis (with strain)[a]	
Hypertrophic cardiomyopathy	
Coronary vasospasm (cocaine, Prinzmetal angina)	
Early repolarization (normal variant)	
Brugada syndrome	

LV, left ventricular; MI, myocardial infarction; ST-segment elevation myocardial infarction.

[a]Strain may occur in numerous settings including systemic hypertension, hypotension, tachycardia, exercise, and sepsis.

- **Q waves.** Development of new pathologic Q waves is considered diagnostic for transmural MI but may occur in patients with prolonged ischemia or poor collateral supply. The presence of Q waves only is not an indication for acute reperfusion therapy; however, it is very helpful to have an old ECG to compare to in order to determine chronicity. Diagnostic criteria include:
  - In leads V_2 and V_3, a pathologic Q wave is ≥0.02 second or a QS complex in V_2 or V_3. An isolated Q wave in lead V_1 or lead III is normal.
  - In leads other than V_1 through V_3, presence of a Q wave ≥0.03 second and ≥0.1 mV deep or a QS complex in any two contiguous leads suggests prior MI.
  - R wave ≥0.04 second in V_1 and V_2 and R/S ratio ≥1 with a positive T wave suggest prior posterior MI (in the absence of RV hypertrophy or right bundle branch block [RBBB]).

Laboratories and Imaging

- STEMI diagnosis and initiation of treatment are done in a patient who reports prolonged chest discomfort or anginal equivalent with qualifying ECG findings. Attempting to wait for results of cardiac biomarkers will add

unnecessary delay.

- Blood samples should be sent for cardiac enzymes (troponin, CK-MB), complete blood cell count, coagulation studies (PTT, prothrombin time [PT], international normalized ratio [INR]), creatinine, electrolytes including magnesium, and type and screen. A fasting lipid profile should be obtained in all patients with STEMI for secondary prevention (note, however, that lipid levels may be falsely lowered during the acute phase of MI).
- Initial cardiac enzymes (including troponin assays) may be normal, depending on the time in relation to symptom onset. Myoglobin is the first enzyme to rise.
- CK-MB can be used to confirm that myocardial injury occurred within the previous 48 hours because troponin levels may remain elevated for up to 2 weeks after MI.
- The risk of subsequent cardiac death is directly proportional to the increase in cardiacspecific troponins, even when CK-MB levels are not elevated. Measuring enzymes until the peak level has been attained can be used to determine infarct size.
- Routine use of cardiac noninvasive imaging is not recommended for the initial diagnosis of STEMI. When the diagnosis is in question, a TTE can be performed to document regional wall motion abnormalities. If not adequately evaluated by TTE, a transesophageal echocardiogram (TEE) can be obtained to assess for acute complications of MI and presence of aortic dissection.

- A portable chest radiograph is useful to assess for pulmonary edema and evaluate for other causes of chest pain including aortic dissection. Importantly, a normal mediastinal width does not exclude aortic dissection, especially if clinically suspected.

TREATMENT

- **Before presentation to the hospital.** The general public should be informed of the signs and symptoms consistent with an acute MI that should lead them to seek urgent medical care. Availability of “911” access and emergency medical services facilitates delivery of patients to emergency medical care.
- **Acute management.** Prompt treatment should be initiated as soon as the diagnosis is suspected, as mortality and risk of subsequent HF are directly related to ischemia time (Figure 4-4).

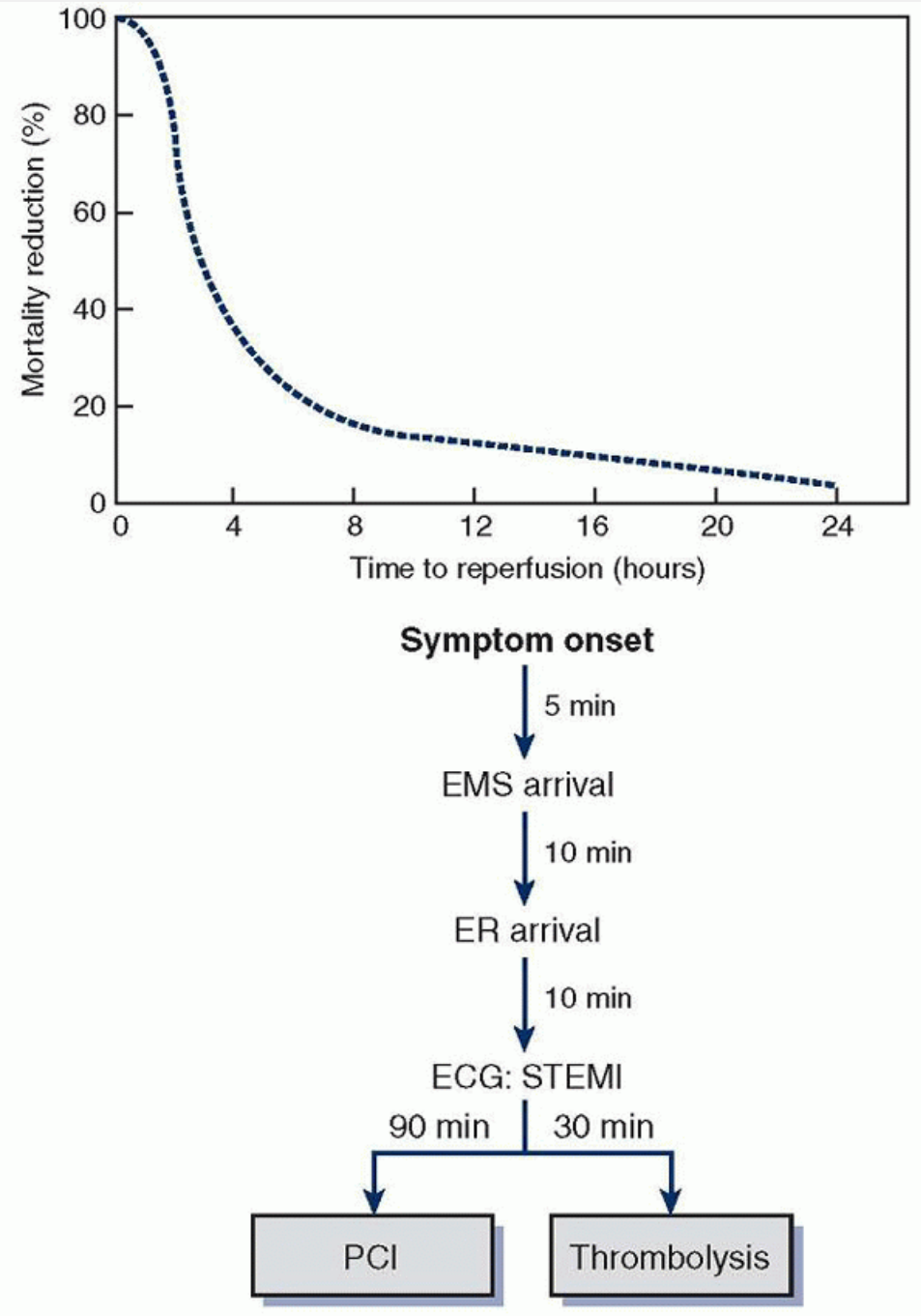


Figure 4-4. The benefit of coronary reperfusion is inversely related to ischemia time. **Top.** Graphic representation of mortality benefit of coronary reperfusion as a function of ischemia time. (Data from *JAMA 2005;293:979.*) **Bottom.** Recommended timeline of events following chest pain onset according to AHA/ACC guidelines (Data from *Circulation 2008;117:296*). AHA/ACC, American Heart Association/American College of Cardiology; ECG, electrocardiogram; EMS, emergency medical service; ER, emergency room; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

- All medical centers should have in place and use an AHA/ACC guideline-based STEMI protocol. Centers that are not primary PCI capable should have protocols in place to meet accepted time-to-therapy guidelines, with either rapid transfer to a PCI-capable facility or administration of thrombolytics with subsequent transfer to a PCI center.
- **In the emergency department**, an acute MI protocol should be activated that includes a targeted clinical examination and a 12-lead ECG completed within 10 minutes of arrival.

- **Immediate management.** The goal of immediate management in patients with STEMI is to identify candidates for reperfusion therapy and to immediately initiate that process. Other priorities include relief of ischemic pain, as well as recognition and treatment of hypotension, pulmonary edema, and arrhythmia.
- **General measures**
  - Supplemental oxygen should be administered if saturations are <90%. If necessary, institution of mechanical ventilation decreases the work of breathing and reduces myocardial oxygen demand.
  - Two peripheral IV catheters should be inserted upon arrival.
  - Serial ECGs should be obtained for patients who do not have ST-segment elevation on the initial ECG but experience ongoing chest discomfort as they may have an evolving STEMI. Telemetry should be placed to monitor for arrhythmias.

Medications

Upstream medical therapy should include administration of ASA and anticoagulants as well as agents that reduce myocardial ischemia (Table 4-18).

- Chewable **ASA** 162-325 mg should be given immediately to *all* patients with suspected acute MI; 325 mg is preferred for those who are ASA naïve. After PCI, the subsequent dose of ASA is 81 mg/d and is to be given indefinitely (*Eur Heart J 2009;30:900*).
- A loading dose of a **P2Y12 inhibitor** should be given to all STEMI patients, as part of dual antiplatelet therapy, as soon as possible after presentation. Cost and bleeding risk can be taken into consideration when choosing which agent. *Please also refer to the antiplatelet section on UA/NSTEMI for background information and dosing on agents listed in the following text.*
  - If the patient is to receive fibrinolytic therapy, along with ASA and an anticoagulant, patients should receive:
    - Clopidogrel 300-mg loading dose if given during the first 24 hours of therapy; if started 24 hours after administration of fibrinolytics, a 600-mg loading dose is preferred. Maintenance is 75 mg/d.
    - Patients older than 75 years should not be given the loading dose.
  - If the patient is going for PCI, **one** of the following should be added to ASA and anticoagulant:
    - **Clopidogrel** 600-mg loading, then 75 mg daily for 12 months.
    - **Prasugrel** 60-mg loading, then 10 mg daily for minimum of 12 months (contraindicated in patients with prior CVA and avoided in those >75 years and with weight <60 kg). Prasugrel generally should be given after diagnostic angiography (or within an hour of PCI) when it is certain the patient will not need CABG surgery given a higher incidence of bleeding related to surgery as compared to clopidogrel (*Lancet 2009;373:723*).
    - **Ticagrelor** 180-mg loading dose, then 90 mg bid (Note: maintenance ASA is 81 or 100 mg daily **only**) for a minimum of 12 months.
- **GPIIb/IIIa inhibitors** do not have a routine role in the initial presentation of STEMI patients or as part of adjunctive therapy with thrombolytics.
  - It may be reasonable to use GPIIb/IIIa inhibitors as an alternative to a P2Y12 antagonist in patients who present with acute complications of MI requiring surgery (ischemic MR, ruptured papillary muscle, or VSD).
  - In general, GPIIb/IIIa use should be left to the discretion of the invasive cardiologist.

TABLE 4-18 Upstream Medical Therapy

Medication	Dosage	Comments
Aspirin (ASA)	162-325 mg	Non-enteric-coated formulations (chewed or crushed) given orally or rectally facilitate rapid drug absorption and platelet inhibition.
Clopidogrel	600 mg loading dose, 75-150 mg/d	600 mg loading dose followed by 150 mg maintenance dose for 7 d may reduce the incidence of stent thrombosis and MI compared to the standard 300 mg loading dose and 75 mg maintenance dose. Caution should be used in the elderly because clinical trials validating clopidogrel use in STEMI either did not include elderly patients or did not use a loading dose.
Prasugrel	60 mg loading dose, 10 mg/d	Compared to clopidogrel, prasugrel is a quicker acting and more potent antiplatelet agent with improved efficacy but did significantly increase CABG bleeding rates. Prasugrel should not be used in patients >75 y old, <60 kg, or with a history of stroke/TIA.
Ticagrelor	180 mg loading, then 90 mg bid	ASA dose should not exceed 100 mg. Ticagrelor has shown mortality benefit over clopidogrel at the expense of higher bleeding rates.
Unfractionated heparin (UFH)	60 units/kg IV bolus, 12 units/kg/h	UFH should be given to all patients undergoing PCI and those receiving thrombolytics with the exception of streptokinase. The maximum IV bolus is 4000 units.
Enoxaparin (LMWH)	30 mg IV bolus, 1 mg/kg SC bid	Patients >75 y old should not be given a loading dose and receive 0.75 mg/kg SC bid. An additional loading dose of 0.3 mg/kg should be given if the last dose of LMWH was >8 h prior to PCI. The use of LMWH is only validated in thrombolysis and rescue PCI.
Bivalirudin	0.75 mg/kg IV bolus, 1.75 mg/kg/h	Bivalirudin has been validated in patients undergoing PCI and has not been studied in conjunction with thrombolysis. Patients who received a heparin bolus prior to bivalirudin had a lower incidence of stent thrombosis than those who only received bivalirudin.
Fondaparinux	2.5 mg IV bolus, 2.5 mg	Shown to be superior to UFH when used during thrombolysis with decreased bleeding rates. Fondaparinux increases the risk of catheter thrombosis when used during PCI (*JAMA*

	SC daily	*2006;295:1519*).
Nitroglycerin	0.4 mg SL or aerosol infusion; 10-200 µg/min IV	Sublingual or aerosol nitroglycerin can be given every 5 min for a total of three doses in the absence of hypotension. IV nitroglycerin can be used for uncontrolled chest discomfort.
Metoprolol	25 mg PO qid, uptitrate as needed	β-Blockers should be avoided in patients with evidence of heart failure, hemodynamic instability, marked first-degree AV block, advanced heart block, and bronchospasm.

AV, atrioventricular; CABG, coronary artery bypass graft; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; SL, sublingual; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

- **Anticoagulant therapy** should be initiated on presentation in all patients with STEMI regardless of the choice of PCI or thrombolytic therapy. *Please also refer to the medication section for UA/NSTEMI for background information on agents listed in the following text.*
  - **Patients who will receive fibrinolytic therapy should be started on either:**
    - **UFH** with monitoring to ensure the activated PTT is twice the upper limit of normal. UFH should be continued for at least 48 hours after fibrinolysis. If angiography with intent to perform PCI is anticipated to occur early after fibrinolysis, then UFH may be preferable.

      Dosing for UFH: bolus dose of 60 units/kg (maximum 4000 units), then 12 units/kg/h (maximum 1000 units/h) to keep PTT at 50-70 seconds.
    - **Enoxaparin**, if the serum creatinine is <2.5 mg/dL in men or 2.0 mg/dL in women, an initial 30-mg IV bolus is given followed 15 minutes later with 1 mg/kg SC bid. Give for the entirety of the index hospitalization but not to exceed 8 days.

      In patients 75 years or older, no bolus is given and subcutaneous dose is 0.75 mg/kg bid.

      If CrCL <30 mL/min, the subcutaneous dose is 1 mg/kg daily.
    - **Fondaparinux** with an initial IV dose is 2.5 mg, followed by subcutaneous 2.5 mg daily. Agent should not be used if CrCl <30 mL/min. Give for the entirety of the index hospitalization but not to exceed 8 days.
    - **Bivalirudin** can be used for HIT-positive patients but has not been studied extensively in STEMI patients and patient with fibrinolysis.
  - **Anticoagulant choice for patients who will receive primary PCI:**
    - **UFH** is often preferred during PCI by many operators due to the availability and realtime therapeutic monitoring with activating clotting times (ACTs) in the catheterization laboratory. Additional bolus doses of UFH are given at PCI, with the dose and ACT goal dependent on whether a GPIIb/IIIa antagonist has been given.

- **Enoxaparin** use in STEMI patients as an anticoagulant for PCI is unclear.

  Additional IV dose may be needed at PCI depending on timing of the last dose and total number of doses given.

  Patients on therapeutic enoxaparin should not be given UFH.

- **Bivalirudin** can be given to patients already treated with ASA and clopidogrel on presentation.

  Bivalirudin is an acceptable alternative to the use of combined heparin and GPIIb/IIIa inhibitor during PCI with lower bleeding rates but higher rate of stent thrombosis (*N Engl J Med 2008;358:2218*; *JAMA 2003;19:853*).

  It is the agent of choice in patients with known HIT.

  It can be given with or without prior treatment with UFH. If patient is being treated with UFH, discontinue UFH for 30 minutes prior to starting bivalirudin.

  Dose is 0.75 mg/kg bolus, then 1.75 mg/kg/h infusion.

- **Fondaparinux** is not indicated for use in STEMI patients as a sole anticoagulant and has to be given along with UFH due to risk of catheter-related thrombosis.

- **Anti-ischemic therapy** (also refer to the Medications section for UA/NSTEMI for background information on agents listed here)
  - **Nitroglycerin** should be administered to patients with ischemic chest pain, to aid in control of hypertension, or as part of the management of HF. Nitroglycerin should either be avoided or used with caution in patients with:
    - Hypotension (systolic BP [SBP] <90 mm Hg)
    - RV infarct
    - Heart rate >100 bpm or <50 bpm
    - Documented use of phosphodiesterase inhibitors in previous 48 hours
  - **Morphine** (2-4 mg IV) can be used for refractory chest pain that is not responsive to nitroglycerin. Adequate analgesia decreases levels of circulating catecholamines and reduces myocardial oxygen consumption.
  - **BBs** improve myocardial ischemia, limit infarct size, and reduce major adverse cardiac events including mortality, recurrent ischemia, and malignant arrhythmias.
    - Oral BBs should be started in all patients with STEMI within the first 24 hours who do not have signs of new HF, evidence of cardiogenic shock (Killip class II or greater), age older than 70 years, SBP <120 mm Hg, pulse >110 or <60 bpm, or advanced heart block (*Lancet 2005;366:1622*).
    - IV BBs can increase mortality in patients with STEMI and should be reserved for management of arrhythmias or acute treatment of accelerated hypertension in patients without the earlier mentioned features. Sinus tachycardia in the setting of a STEMI may be a compensatory response to maintain cardiac output and should not prompt IV BB use.

Acute Coronary Reperfusion

- The majority of patients who suffer an acute STEMI have thrombotic occlusion of a coronary artery. Early restoration of coronary perfusion limits infarct size, preserves LV function, and reduces mortality.
- All other therapies are secondary and should not delay the timely goal of achieving coronary reperfusion.
- Unless spontaneous resolution of ischemia occurs (as determined by resolution of chest discomfort and

normalization of ST elevation), the choice of reperfusion strategy includes thrombolysis, primary PCI, or emergent CABG (Figure 4-5).

- Normalization of the ECG and symptoms should not preclude the patient being referred for urgent diagnostic angiography. Morphine may mask ongoing ischemic symptoms.
- Note: Ongoing symptoms are not criteria for treatment of STEMI in the first 12 hours of symptom onset. Patients who arrive within 12 hours of their symptoms, despite symptom resolution, but with continued ECG changes of STEMI are still candidates for immediate reperfusion (either primary PCI or fibrinolytics). We recommend angiography with intent for PCI/CABG in such a circumstance.

- The choice of reperfusion therapy should be considered of secondary importance to the overall goal of achieving reperfusion in a timely manner.
  - **Primary PCI**
    - Primary PCI is the preferred reperfusion strategy when available within 90 minutes of first medical contact. Compared to fibrinolytic therapy, PCI offers superior vessel patency and perfusion (TIMI 3 flow) with less reinfarction, less risk of

intracranial hemorrhage, and improved survival regardless of lesion location or patient age. STEMI patients with symptom onset <12 hours prior have a better prognosis and outcome after PCI. PCI should still be routinely offered to patients with STEMI who have ongoing symptoms that began 12-24 hours prior to presentation.

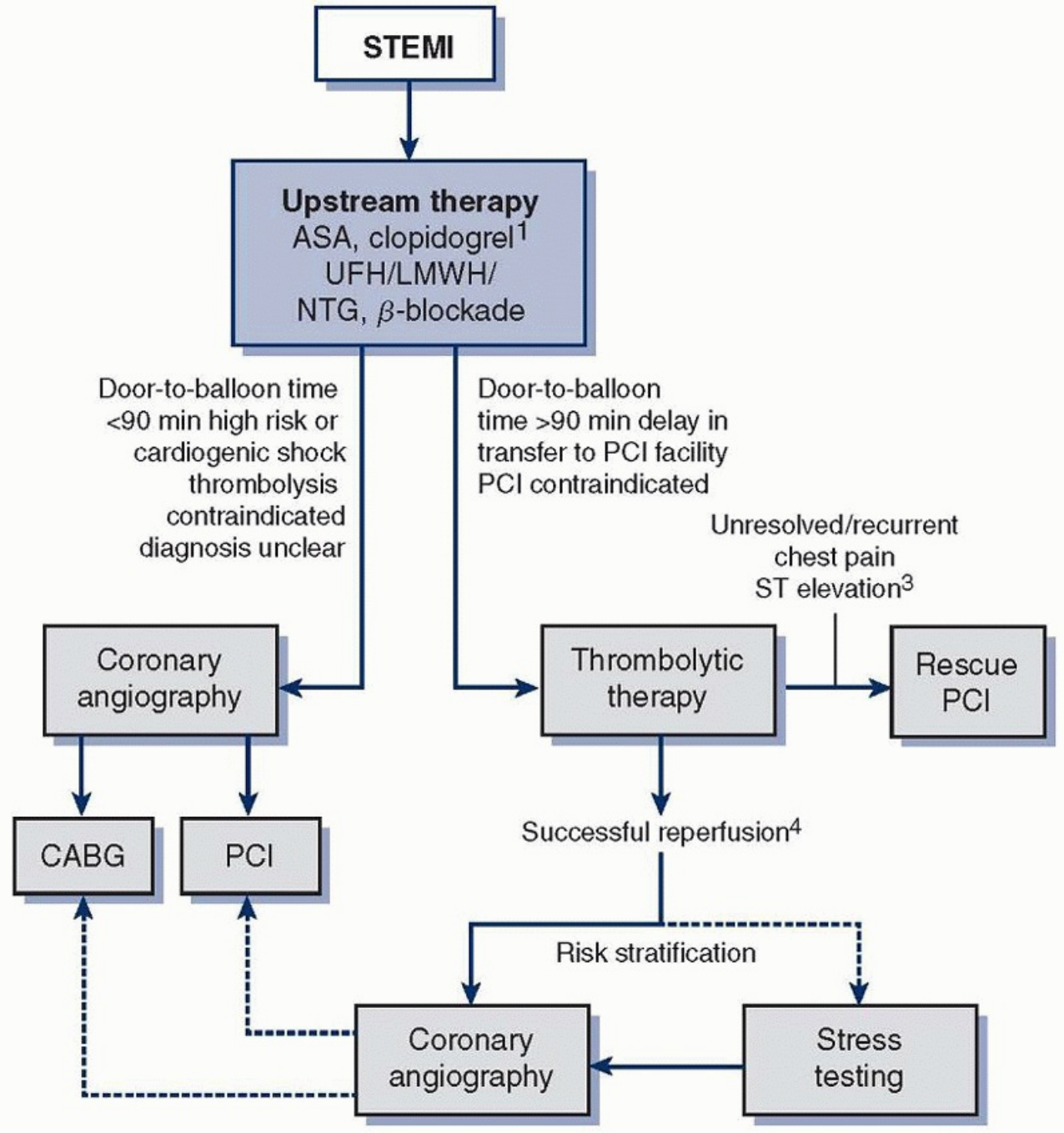


Figure 4-5. Strategies for coronary reperfusion and risk assessment. [1]If fibrinolytics are to be given, use clopidogrel only. If primary PCI is planned, give ticagrelor, prasugrel, or clopidogrel. [2]UFH may be used with either PCI or thrombolytic therapy, whereas bivalirudin has only been studied with PCI and LMWH has only been validated for fibrinolytic therapy and rescue PCI. In patients who are to receive fibrinolysis, LMWH and fondaparinux are preferred to UFH. [3]Patients who do not experience chest pain relief, have recurrent chest pain, have unstable arrhythmias, develop heart failure, or have ST-segment elevations that do not normalize 60-90 minutes following fibrinolysis should undergo rescue PCI. [4]Signs of successful reperfusion include chest pain relief, 50% reduction in ST-segment elevation, and idioventricular rhythm. P2Y12 inhibitors include antiplatelet agents: clopidogrel, prasugrel, and ticagrelor. ASA, aspirin; CABG, coronary artery bypass graft; LMWH, low-molecular-weight heparin; NTG, nitroglycerin; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

- PCI may also be considered, although evidence of benefit is limited, in patients who are now asymptomatic but had symptoms in the previous 12- to 24-hour period.

- Asymptomatic patients who are hemodynamically and electrically stable without evidence of ischemia and whose symptoms began more than 24 hours prior should not be offered PCI of a totally occluded infarct artery (*Circulation 2011;22:2320*).
- **PCI** is always preferred over fibrinolysis in the following situations:

  Patients who present with severe HF or cardiogenic shock should receive primary PCI (even if transfer to a PCI center may cause delays beyond current time goals for reperfusion). Patients with Killip class III/IV or TIMI risk score ≥5 represent high-risk groups where PCI is preferred despite a potential time delay (*Eur Heart J 2010;31:676*; *Circulation 2005;112:2017*).

  Have a contraindication to fibrinolytic therapy.

  Have had recent PCI or prior CABG.

  PCI is generally preferred to fibrinolysis in patients with symptom onset >12 hours prior (*N Engl J Med 1997;336:1621*; *Lancet 2003;361:13*).
- Coronary stenting is superior to balloon angioplasty alone and reduces the rates of target vessel revascularization.
- Drug-eluting stents further reduce the need for target vessel revascularization without increasing the incidence of stent thrombosis.
- If the infarct-related artery is successfully treated and patients have lesions in non-infarct-related arteries that are amenable to PCI, there may be a benefit for death or recurrent nonfatal MI to undergo revascularization at the time of STEMI (*N Engl J Med 2013;369:1115*).
- Patients in shock should have significant lesions in non-infarct-related arteries intervened on if feasible.
- Transradial approach in STEMI reduces bleeding and may have a mortality benefit compared to transfemoral access.
- Facilitated PCI, a strategy of reduced dose of GPIIb/IIIa inhibitors and/or fibrinolytic agent just prior to PCI, should not be routinely used because it does not improve efficacy and significantly increases bleeding rates.

- **Fibrinolytic therapy**
  - Fibrinolytic therapy has the main advantages of widespread availability and ease of delivery. The primary disadvantage of fibrinolytic therapy is the risk of intracranial hemorrhage, uncertainty of whether normal coronary flow has been restored, and risk of reocclusion of the infarct-related artery.
  - Fibrinolysis is indicated when primary PCI is not available in a timely fashion (i.e., delay >120 minutes).
  - Fibrinolytic therapy is indicated for use if given within 12 hours of the symptom onset with qualifying ECG changes of ST elevation, new LBBB, or true posterior MI. When given, it should be administered within 30 minutes of initial patient contact. Fibrinolytic therapy is most successful when given in the first 3 hours of symptom onset, after which the benefit tapers.
  - Patients presenting to a hospital without PCI capability should be transferred for primary PCI, rather than being given fibrinolytics, if time from first medical contact to PCI will not be >120 minutes. This seems particularly relevant to patients arriving 3-12 hours from symptom onset.
  - In patients transferred for PCI, primary PCI significantly lowered the incidence of death, MI, or stroke compared to on-site thrombolysis (*N Engl J Med 2003;249:733*; *J Am Coll Cardiol 2002;39:1713*; *Eur Heart J 2000;21:823*).

- All patients should be transferred to a PCI-capable facility after fibrinolysis (early routine angiography); this should occur urgently if patients are in shock or have failed reperfusion.
- Rescue PCI is PCI in the setting of failed fibrinolysis and has shown benefit over conservative management. Given the risk of bleeding, this decision must be tailored to the individual patient and clinical status (e.g., amount of myocardium in jeopardy, shock, other comorbid illness).

- Available thrombolytic agents include the fibrin-selective agents such as **alteplase (recombinant tissue plasminogen activator [rt-PA])**, **reteplase** (r-PA), and **tenecteplase** (TNK-tPA). **Streptokinase** is the only nonselective agent in use. Further details and dosing information can be found in Table 4-19.

  TNK-tPA is the current agent of choice due to similar efficacy, lower risk of bleeding, and convenient single bolus administration as compared to rt-PA. Streptokinase is the cheapest and still widely used worldwide.

TABLE 4-19 Fibrinolytic Agents

Medication	Dosage	Comments
Streptokinase (SK)	1.5 million units IV over 60 min	Produces a generalized fibrinolytic state (not clot specific). SK reduces mortality following STEMI: 18% relative risk reduction and 2% absolute risk reduction (*Lancet 1987;2:871*). Allergic reactions including skin rashes, fever, and anaphylaxis may be seen in 1-2% of patients. Isolated hypotension occurs in 10% of patients and usually responds to volume expansion. Because of the development of antibodies, patients who were previously treated with SK should be given an alternate thrombolytic agent.
Recombinant tissue plasminogen activator (rt-PA)	15 mg IV bolus 0.75 mg/kg over 30 min (maximum 50 mg) 0.50 mg/kg over 60 min (maximum 35 mg)	Fibrin-selective agent with improved clot specificity compared to SK. Does not cause allergic reactions or hypotension. Mortality benefit compared to SK at the expense of an increased risk of intracranial hemorrhage (*N Engl J Med 1993;329:673*).
Reteplase (r-PA)	Two 10-unit IV boluses administered 30 min apart	Fibrin selective agent with a longer half-life but reduced clot specificity compared to rt-PA. Mortality benefit equivalent to that of rt-PA (*N Engl J Med 1997;337:1118*).

Tenecteplase (TNK-tPA)	0.50 mg/kg IV bolus (total dose 30-50 mg)	Genetically engineered variant of rt-PA with slower plasma clearance, improved fibrin specificity, and higher resistance to PAI-1. Mortality benefit equivalent to that of rt-PA with reduced bleeding rates (*Lancet 1999;354:716*). Monitoring is required with a goal aPTT of 1.5-2.5 times control.

aPTT, activated partial thromboplastin time; PAI-1, plasminogen activator inhibitor-1; STEMI, ST-segment elevation myocardial infarction.

Fibrin-selective agents should be used in combination with anticoagulant therapy, ASA, and clopidogrel (see earlier). GPIIb/IIIa inhibitors should not be used in conjunction. Prasugrel and ticagrelor have not been studied for use with fibrinolytics.

- Fibrinolytic therapy is contraindicated:

  In patients with ECG evidence of ST-segment depressions (unless posterior MI suspected).

  In those who are asymptomatic with initial symptoms occurring >24 hours prior (*this is in contrast to patients who are asymptomatic with symptom onset <12 hours prior; see earlier*).

  In patients with other contraindications to fibrinolysis (Table 4-20).

  In patients with presence of five or more risk factors for intracranial hemorrhage.

- The most common complication of fibrinolytic therapy is bleeding. Intracranial hemorrhage occurs in >4% of patients with five or more of the following risk factors for intracranial hemorrhage (*Stroke 2000;31:1802*).

  Age ≥75 years

  Weight ≤65 kg in women and ≤80 kg in men

  Female gender

  African American race

  Prior history of stroke

  SBP ≥160 mm Hg

  INR >4 or PT >24

  Use of alteplase

- Any patient who experiences a sudden change in neurologic status should undergo urgent head CT, and all anticoagulant and thrombolytic therapies should be discontinued. Fresh frozen plasma should be given to patients with intracerebral hemorrhage. Cryoprecipitate may also be used to replenish fibrinogen and factor VIII levels. Platelet transfusions and protamine can be useful in patients with markedly prolonged bleeding times. Neurologic and neurosurgical consultation should be obtained immediately.
- Major bleeding complications that require blood transfusion occur in approximately 10% of patients.

TABLE 4-20 Contraindications to Thrombolytic Therapy

Absolute Contraindications	Relative Contraindications
History of intracranial hemorrhage or hemorrhagic stroke Ischemic stroke within 3 mo Known structural cerebrovascular lesion (AVMs, aneurysms, tumor) Closed head injury within 3 mo Aortic dissection Severe uncontrolled hypertension (SBP >180 mm Hg, DBP >110 mm Hg) Active bleeding or bleeding diathesis Acute pericarditis	Prior ischemic stroke >3 mo ago Allergy or previous use of streptokinase (>5 d ago)[a] Recent internal bleeding (2-4 wk) Prolonged/traumatic CPR more than 10 min Major surgery within 3 wk Active peptic ulcer disease Noncompressible vascular punctures History of intraocular bleeding Pregnancy Uncontrolled hypertension Use of oral anticoagulants

AVM, arteriovenous malformation; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Thrombolytics other than streptokinase may be used.

- **Postfibrinolysis care**

  All patients should receive appropriate dual antiplatelet therapy and at least 48 hours of anticoagulation after fibrinolysis.

  Routine coronary angiography within 24 hours of thrombolysis has reduced adverse cardiac events compared to rescue PCI (*Lancet 2004;264:1045*). Immediate transfer for angiography (3-24 hours after fibrinolysis) at a PCI-capable facility is also proven to be beneficial (*Lancet 2008;371:559*).

  Evidence for successful fibrinolysis includes:

  - Relief of chest pain or angina symptoms

  - >50% reduction in ST-segment elevations at 90 minutes

  - Reperfusion arrhythmia (i.e., accelerated idioventricular rhythm) up to 2 hours after completion of infusion

- **Rescue PCI after failed fibrinolysis**

  Thrombolytic therapy does not achieve coronary artery patency in 30% of patients. In contrast, primary PCI results in restoration of normal coronary flow (TIMI 3) in >95% of cases.

  Rescue PCI reduces the incidence of death, reinfarction, and HF by nearly 50% (*Circulation 1994;90:2280*; *N Engl J Med 2005;353:2758*).

  Evidence of failed fibrinolysis includes:

  - Persistence or reoccurrence of ischemic symptoms

  - ST segments resolve <50% 90 minutes after fibrinolysis

- Electrical or hemodynamic instability
- Development of HF symptoms

- **Emergency CABG** is a high-risk procedure that should be considered only if the patient has severe left main disease or refractory ischemia in the setting of failed PCI or coronary anatomy that is not amenable to PCI. Emergency surgery should also be considered for patients with acute mechanical complications of MI including papillary muscle rupture, severe ischemic MR, VSD, ventricular aneurysm formation in the setting of intractable ventricular arrhythmias, or ventricular free wall rupture.

Peri-Infarct Management

- **The coronary care unit (CCU)** was the first major advance in the modern era of treatment of acute MI. All patients with STEMI should be observed in a specialized CCU or intensive care unit setting for at least 24 hours after MI.
- Bed rest is appropriate intermediate care for the first 24 hours after presentation with an acute MI. After 24 hours, clinically stable patients can progressively advance their activity as tolerated.
- Patients should have continuous telemetry monitoring to detect for recurrent ischemia and arrhythmias.
- Daily evaluation should include assessment for recurrent chest discomfort, new HF symptoms, and routine ECGs. Physical exam should focus on new murmurs and any evidence of HF.
- A baseline echocardiogram should be obtained to document EF, wall motion abnormalities, valvular lesions, and presence of ventricular thrombus.
- **Cardiac pacing** may be required in the setting of an acute MI. Rhythm disturbance may be transient in nature, in which case temporary pacing is sufficient until a stable rhythm returns (see the following text). As compared to inferior wall MIs where AV block is transient and stable, AV block with anterior wall MIs can be unstable with wide QRS escape rhythms with 80% mortality and usually requires temporary and then permanent pacemakers.

Post-STEMI Medical Therapy

- See also Medications section for UA/NSTEMI.
- **ASA** should be continued indefinitely. Dose of 81 mg/d has been shown to be effective after PCI; however, the range of 75-162 mg/d has also been endorsed.

- **Clopidogrel** (75 mg/d), **prasugrel** (10 mg/d), or **ticagrelor** (90 mg bid) should be given for a minimum of 12 months regardless of whether a bare metal stent (BMS) or drugeluting stent was used (*this is in contrast to non-ACS patients who receive a BMS and the minimum duration of therapy is 1 month*).
- **BBs** confer a mortality benefit following acute MI. Treatment should begin as soon as possible (preferably within the first 24 hours) and continued indefinitely unless contraindicated.
- **ACE inhibitors** provide a reduction in short-term mortality, incidence of HF, and recurrent MI when initiated within the first 24 hours of an acute MI (*Lancet 1994;343:1115*; *Lancet 1995;345:669*).
  - Patients with EF <40%, large anterior MI, and prior MI derive the most benefit from ACE inhibitor therapy.
  - Contraindications include hypotension, history of angioedema with use, pregnancy, acute renal failure, and hyperkalemia.
  - ARBs can be used in patients who are intolerant of ACE inhibitors.
- **HMG-CoA reductase inhibitors** should be started in all patients in the absence of contraindications. Several trials have shown the benefit of early and aggressive use of high-dose statins following acute MI.

The goal is at least 50% reduction in LDL or LDL <70 mg/dL.

- **Aldosterone receptor antagonists (spironolactone and eplerenone)** have shown benefit in post-MI patients with LVEF <40% and in diabetics (*N Engl J Med 1999;341:709*; *N Engl J Med 2003;348:1309*). Caution should be used in patients with hyperkalemia and renal insufficiency.
- **Warfarin** should not be routinely prescribed to patients with apical hypokinesis in the setting of an anterior MI in the absence of LV thrombus or other indications for anticoagulation. Such therapy is associated with increased bleeding and death. The actual risk of developing LV thrombus is low because many patients will have recovery of hypokinesis (*J Am Coll Cardiol 2015;8:155*).

SPECIAL CONSIDERATIONS

Risk Assessment

- Asymptomatic patients who present >24 hours after symptom onset, patients who receive medical therapy alone, and patients who receive an incomplete revascularization should undergo further risk assessment. Patients may be evaluated using either noninvasive stress testing or an invasive (coronary angiography) strategy.
- **Stress testing** can be used to determine prognosis, residual ischemia, and functional capacity. Patients who are successfully revascularized do not need stress testing prior to discharge unless needed for referral to cardiac rehabilitation.
  - A submaximal exercise stress test can be performed as early as 2-3 days following MI in stable patients who have had no further ischemic signs/symptoms or signs of HF.
  - Alternatively, stress testing can be performed after hospital discharge (2-6 weeks) for low-risk patients and for patients starting cardiac rehabilitation.
  - Coronary angiography should be performed in patients with limiting angina, significant ischemic burden, and poor functional capacity.
- Patients treated medically or with fibrinolytics who experience complications of MI, including recurrent angina/ischemia, HF, significant ventricular arrhythmia, or a mechanical complication of the MI, should proceed directly to coronary angiography to define their anatomy and offer an appropriate revascularization strategy.
- **Special clinical situations**
  - **RVMI** is seen in patients with an acute inferior MI secondary to complete occlusion of the proximal RCA. RV function is very preload dependent, and frequently, hypotension responds to fluid resuscitation.
    - The clinical triad of hypotension, elevated jugular venous pressure, and clear lung fields in the setting of STEMI should prompt an evaluation for RV infarct.

    - One-mm ST elevations in the V_1 or V_4R leads are the most sensitive marker of RV involvement.
    - LV filling pressures are typically normal or decreased, the right atrial pressures are elevated (>10 mm Hg), and the cardiac index is depressed. In some patients, elevated right atrial pressures may not be evident until IV fluids are administered.
    - Initial therapy is IV fluids. If hypotension persists, inotropic support with dobutamine and/or IABP may be necessary. Right-sided mechanical support devices are available when pharmacologic support fails.

- Invasive hemodynamic monitoring is critical in the persistently hypotensive patient because it guides volume status and the need for inotropic and mechanical support.
- In patients with heart block and AV dyssynchrony, sequential AV pacing has a marked beneficial effect.

- **Restenosis and stent thrombosis** are disease entities unique to patients who have previously undergone PCI.
  - Restenosis is a result of neointimal hyperplasia and occurs more frequently in patients with BMS placement, diabetics, patients with long areas of prior stenting, and patients with stenting in small arteries. Restenosis presents most frequently as stable progressive angina and is not affected by the discontinuation of dual antiplatelet therapy.
  - Stent thrombosis is the thrombotic occlusion of a previously placed coronary stent and presents as ACS or sudden cardiac death. Stent thrombosis is associated with a high mortality rate and poor prognosis (*JAMA 2005;293:2126*; *J Am Coll Cardiol 2009;53:1399*).

    Acute stent thrombosis occurs within 24 hours and is due to mechanical procedural complications as well as inadequate anticoagulation and antiplatelet therapies.

    Subacute stent thrombosis (24 hours to 30 days) is a consequence of inadequate platelet inhibition and mechanical stent complications. Cessation of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) therapy during this time yields a 30- to 100-fold risk of stent thrombosis.

    Late (30 days to 1 year) stent thrombosis and very late stent thrombosis occur principally with drug-eluting stents.

    Neoatherosclerosis is atherosclerotic plaque unique to prior PCI, occurs in previously placed stents, and can predispose a patient to angina or plaque rupture with subsequent ACS.

- **Ischemic MR** is a poor prognostic indicator following MI. Papillary muscle rupture is associated with inferior and posterior infarcts. The anterior papillary muscle has a dual blood supply and is less vulnerable to rupture. The mechanism of chronic MR after STEMI includes papillary muscle dysfunction or leaflet tethering due to posterior wall akinesis.
  - Acute MR from papillary muscle rupture is a severe complication of MI associated with high mortality (see below).
  - Progressive MR following MI may develop as a result of LV chamber dilation, apical remodeling, or posterior wall dyskinesis. These changes lead to leaflet tethering or mitral annular dilation.
  - Echocardiography is the diagnostic modality of choice.
  - Transient ischemic MR occurs secondary to papillary muscle ischemia and results in transient severe MR and pulmonary edema. It can be hard to detect on exam or imaging when ischemia is not induced.
  - Initial treatment of MR involves aggressive afterload reduction and revascularization. *Stable* patients should receive a trial of medical therapy and undergo surgery only if they fail to improve.

- **STEMI** in the setting of recent **cocaine use** presents a unique and challenging management situation (*Circulation 2008;117:1897-907*). ST elevation can result from

myocardial ischemia due to coronary vasospasm, in situ thrombus formation, and/or increased myocardial oxygen demand. The common pathophysiology is excessive stimulation of α- and β-adrenergic receptors. Chest pain due to cocaine use usually occurs within 3 hours but may be seen several days following use.

- Oxygen, ASA, and heparin (UFH or LMWH) should be administered to all patients with cocaine-associated STEMI.
- Nitrates should be used preferentially to treat vasospasm. Additionally, benzodiazepines may confer additional relief by decreasing sympathetic tone.
- **BBs** are contraindicated; both selective and nonselective BBs should be avoided.
- Phentolamine (α-adrenergic antagonist) and calcium channel blockers may reverse coronary vasospasm and are recommended as second-line agents.
- The use of reperfusion therapy is controversial and should be reserved for those patients whose symptoms persist despite initial medical therapy.

  Primary PCI is the preferred approach for the patient with persistent symptoms and ECG changes despite aggressive medical therapy. It is important to note that coronary angiography and intervention carry a significant risk of worsening vasospasm.

  Fibrinolytic therapy should be reserved for patients who are clearly having a STEMI and who cannot undergo PCI.

COMPLICATIONS

Myocardial damage predisposes the patient to several potential adverse consequences and complications that should be considered if the patient experiences new clinical signs and/or symptoms. These include recurrent chest pain, cardiac arrhythmias, cardiogenic shock, and mechanical complications of MI.

- **Recurrent chest pain** may be due to ischemia in the territory of the original infarction, pericarditis, myocardial rupture, or pulmonary embolism.
  - Recurrent angina is experienced by 20-30% of patients after MI who receive fibrinolytic therapy and up to 10% of patients in the early time period following percutaneous revascularization. These symptoms may represent recurrence of ischemia or infarct extension.
    - Assessment of the patient may include evaluation for new murmurs or friction rubs, ECG to assess for new ischemic changes, cardiac enzymes (troponin and CK-MB), echocardiography, and repeat coronary angiography if indicated.
    - Patients with recurrent chest pain should continue to receive ASA, P2Y12 inhibition, heparin, nitroglycerin, and BB therapy.
    - If recurrent angina is refractory to medical treatment, urgent repeat coronary angiography and intervention should be considered.
  - **Acute pericarditis** occurs 24-96 hours after MI in approximately 10-15% of patients. The associated chest pain is often pleuritic and may be relieved in the upright position. A friction rub may be noted on clinical examination, and the ECG may show diffuse ST-segment elevation and PR-segment depression. Lead AVR may have PR elevation. Treatment is directed at pain management.
    - High-dose ASA (up to 650 mg qid maximum) is generally considered a first-line agent. NSAIDs such as ibuprofen may be used if ASA is not effective but should be avoided early after acute MI.
    - Colchicine along with ASA may also be beneficial for recurrent symptoms and may also be superior to each agent alone.
    - Glucocorticoids (prednisone 1 mg/kg daily) may be useful if symptoms are severe and refractory to initial therapy. Steroids should be used sparingly because they may lead to an increased risk of

recurrence of pericarditis. Use should also be deferred until at least 4 weeks after acute MI due to their adverse impact on infarct healing and risk of ventricular aneurysm.

    - Heparin should be avoided in the setting of pericarditis with or without pericardial effusion because it may lead to pericardial hemorrhage.
  - **Dressler syndrome** is thought to be an autoimmune process characterized by malaise, fever, pericardial pain, leukocytosis, elevated erythrocyte sedimentation rate, and often a pericardial effusion. In contrast to acute pericarditis, Dressler syndrome occurs 1-8 weeks after MI. Treatment is identical to acute pericarditis.
- **Arrhythmias.** Cardiac rhythm abnormalities are common following MI and may include conduction block, atrial arrhythmias, and ventricular arrhythmias. Arrhythmias that result in hemodynamic compromise require prompt, aggressive intervention. If the arrhythmia precipitates refractory angina or HF, urgent therapy is warranted. For all rhythm disturbances, exacerbating conditions should be addressed, including electrolyte imbalances, hypoxia, acidosis, and adverse drug effects. Details on specific arrhythmias can be found in Table 4-21.
  - **Atropine** should be attempted for all bradyarrhythmias in the setting of STEMI. Bradycardia is a common complication of intense vagal input to the AV node as a result of baroreceptor activation in the myocardium (also called Bezold-Jarisch reflex).
  - **Transcutaneous and transvenous pacing.** Conduction system disease that progresses to complete heart block or results in symptomatic bradycardia can be effectively treated with cardiac pacing. A transcutaneous pacing device can be used under emergent circumstances; however, a temporary transvenous system should be used for longer duration therapy.
    - Absolute indications for temporary transvenous pacing include asystole, symptomatic bradycardia, recurrent sinus pauses, complete heart block, and incessant polymorphic ventricular tachycardia (VT).
    - Temporary transvenous pacing may also be warranted for new trifascicular block, new Mobitz II block, and patients with LBBB who require a pulmonary artery catheter, given the risk of developing complete heart block.
  - **Implantable cardioverter-defibrillators (ICDs)** should not routinely be implanted in patients with reduced LV function following MI or those with VT/ventricular fibrillation (VF) in the setting of ischemia or immediately following reperfusion.
    - Routine insertion of ICDs into patients with reduced LV function immediately following MI does not improve outcomes (*N Engl J Med 2004;351:2481*).
    - In contrast, patients who continue to have depressed LV function (EF <35% and New York Heart Association [NYHA] class II or III or EF <30% regardless of NYHA class) >40 days following MI benefit from ICD therapy (*N Engl J Med 2005;352:225*; *N Engl J Med 2002;346:877*).
    - ICD therapy is also indicated for patients with recurrent episodes of sustained VT or VF despite coronary reperfusion.
- **Cardiogenic shock** is an infrequent, but serious, complication of MI and is defined as hypotension in the setting of inadequate ventricular function to meet the metabolic needs of the peripheral tissue. Risk factors include prior MI, older age, diabetes, and anterior infarction. Organ hypoperfusion may manifest as progressive renal failure, dyspnea, diaphoresis, or mental status changes. Hemodynamic monitoring reveals elevated filling pressures (wedge pressure >20 mm Hg), depressed cardiac index (<2.5

L/kg/min), and hypotension.

- Patients with cardiogenic shock in the setting of MI have a mortality rate in excess of 50%. Such patients require invasive hemodynamic monitoring and advanced therapeutic modalities including inotropic and mechanical support.
- **Dobutamine and milrinone** are the most frequently used medications for inotropic support. They both possess vasodilatory properties (i.e., afterload reducing) and are arrhythmogenic. Milrinone should be avoided in the setting of renal insufficiency.
- **Dopamine** can be used as both a vasopressor and inotrope but increases the risk of atrial arrhythmias in patients with shock and is not a preferred first-line agent.

TABLE 4-21 Arrhythmias Complicating Myocardial Infarction

Arrhythmia	Treatment	Comments
Intraventricular conduction delays	None	The left anterior fascicle is most commonly affected because of isolated coronary blood supply. Bifascicular and trifascicular block may progress to complete heart block and other rhythm disturbances.
Sinus bradycardia	None Atropine 0.5 mg Temporary pacing[a]	Sinus bradycardia is common in patients with RCA infarcts. In the absence of hypotension or significant ventricular ectopy, observation is indicated.
AV block	Temporary pacing[a]	First-degree AV block usually does not require specific treatment. Mobitz I second-degree block occurs more often with inferior MI. The block is usually within the His bundle and does not require treatment unless symptomatic bradycardia is present. Mobitz II second-degree AV block originates below the His bundle and is more commonly associated with anterior MI. Because of the significant risk of progression to complete heart block, patients should be observed in the CCU and treated with temporary pacing if symptomatic. Third-degree AV block complicates large anterior and RV infarcts. In patients with anterior MI, third-degree heart block often occurs 12-24 h after initial presentation and may appear suddenly. Temporary pacing is recommended because of the risk of progression to ventricular asystole.
Sinus tachycardia	None[b]	Sinus tachycardia is common in patients with acute MI and is often due to enhanced sympathetic activity

		resulting from pain, anxiety, hypovolemia, anxiety, heart failure, or fever. Persistent sinus tachycardia suggests poor underlying ventricular function and is associated with excess mortality.
Atrial fibrillation and flutter	β-Blockers Anticoagulation Cardioversion	Atrial fibrillation and flutter are observed in up to 20% of patients with acute MI. Because atrial fibrillation and atrial flutter are usually transient in the acute MI period, longterm anticoagulation is often not necessary after documentation of stable sinus rhythm.
Accelerated junctional rhythm	None	Accelerated junctional rhythm occurs in conjunction with inferior MI. The rhythm is usually benign and warrants treatment only if hypotension is present.
Ventricular premature depolarizations (VPDs)	β-Blockers if symptomatic[c]	VPDs are common in the course of an acute MI. Prophylactic treatment with lidocaine or other antiarrhythmics has been associated with increased overall mortality and is not recommended (*N Engl J Med 1989;321:406*).
Accelerated idioventricular rhythm (AIVR)	None	Commonly seen within 48 h of successful reperfusion and is not associated with an increased incidence of adverse outcomes. If hemodynamically unstable, sinus activity may be restored with atropine or temporary atrial pacing.
Ventricular tachycardia (VT)	Cardioversion for sustained VT Lidocaine or amiodarone for 24-48 h[d]	Nonsustained ventricular tachycardia (NSVT, <30 s) is common in the first 24 h after MI and is only associated with increased mortality when occurring late in the post-MI course. Sustained VT (>30 s) during the first 48 h after acute MI is associated with increased in-hospital mortality.
Ventricular fibrillation (VF)	Unsynchronized cardioversion Lidocaine or amiodarone for 24-48 h[d]	VF occurs in up to 5% of patients in the early post-MI period and is life threatening.

AV, atrioventricular; CCU, coronary care unit; MI, myocardial infarction; RCA, right coronary artery; RV, right ventricular.

[a]Atropine and temporary pacing should only be used for symptomatic or hemodynamically unstable patients.

[b]The use of β-blockers in the setting of sinus tachycardia and poor left ventricular function may result in decompensated heart failure.

[c]β-Blockers should be used with caution in the setting of bradycardia and frequent VPDs as they may increase the risk of polymorphic VT.

[d]Lidocaine should be used as a 1 mg/kg bolus followed by a 1-2 mg/kg/h infusion. Amiodarone should be given as a 150-300 mg bolus followed by an infusion of 1 mg/kg/h for 6 h and then 0.5 mg/kg/h for 18 h.

- **Norepinephrine and phenylephrine** may be required to maintain systemic BP. The use of any vasoconstrictive agents in the setting of cardiogenic shock should prompt an evaluation for mechanical circulatory support
- **Epinephrine** is a potent vasopressor and inotrope and is frequently used as an adjunct to other medical therapies. There may be some preferential benefit to RV function, and thus, epinephrine may be used for shock secondary to RV infarct or severe RV dysfunction.
- **Mechanical circulatory support** includes both temporary and durable support devices. Temporary support devices include IABP, Impella catheter, TandemHeart System, or extracorporeal membrane oxygenation. Temporary support is offered as bridge to recovery or as bridge to decision about long-term durable mechanical support such as an LV assist device (see Chapter 5, Heart Failure and Cardiomyopathy). The choice of

temporary support device is not always clear and should be made by a team familiar with the management of cardiogenic shock.
- All patients with cardiogenic shock should undergo echocardiography to evaluate for mechanical complications of MI (see the following text).
- **LV thrombus** occurs most often in setting of anterior MI and should be treated with anticoagulation. Warfarin is the recommended long-term anticoagulation agent; novel oral anticoagulants such as dabigatran should be avoided because there have been no studies documenting safety in this setting. Patients should receive warfarin for 3-6 months unless other indications warrant its continued use.

- **Mechanical complications**
  - **Aneurysm.** After MI, the affected area of the myocardium may undergo infarct expansion and thinning, forming an aneurysm. The wall motion may become dyskinetic, making the endocardial surface susceptible to mural thrombus formation.
    - LV aneurysm is suggested by persistent ST elevation on the ECG and may be diagnosed by imaging studies including ventriculography, echocardiography, and MRI.
    - Anticoagulation is warranted to lower the risk of embolic events, especially if a mural thrombus is present.
    - Surgical intervention may be appropriate if the aneurysm results in HF or ventricular arrhythmias that are not satisfactorily managed with medical therapy.
  - **Ventricular pseudoaneurysm.** Incomplete rupture of the myocardial free wall can result in formation of a ventricular pseudoaneurysm. In this case, blood escapes through the myocardial wall and is

contained within the visceral pericardium. In the post-CABG patient, hemorrhage from frank ventricular rupture may be contained within the fibrotic pericardial space producing a pseudoaneurysm.

- Echocardiography (TTE with contrast or TEE) is the preferred diagnostic test to assess for a pseudoaneurysm, often allowing differentiation from a true aneurysm.
- Prompt surgical intervention for pseudoaneurysms is advised because of the high incidence of myocardial rupture.

- **Free wall rupture** represents a catastrophic complication of acute MI, accounting for 10% of early deaths. Rupture typically occurs within the first week after MI and presents with sudden hemodynamic collapse. This complication can occur after anterior or inferior MI and is more commonly seen in hypertensive women with their first large transmural MI, in patients receiving late therapy with fibrinolytics, and patients given NSAIDs or glucocorticoids.
  - Echocardiography may identify patients with particularly thinned ventricular walls at risk for rupture.
  - Emergent surgical correction is necessary.
  - Despite optimal intervention, mortality of free wall rupture remains >90%.
- **Papillary muscle rupture** (*please also refer to earlier MR section*) is a rare complication after MI and is associated with abrupt clinical deterioration. The posterior medial papillary muscle is most commonly affected due to its isolated vascular supply, but anterolateral papillary muscle rupture has been reported. Of note, papillary muscle rupture may be seen in the setting of a relatively small acute MI or even NSTEMI.
  - The diagnostic test of choice is echocardiography with Doppler imaging and/or TEE because physical exam reveals a murmur in only ˜50% of cases.
  - Initial medical therapy should include aggressive afterload reduction. Patients with refractory HF and those with hemodynamic instability may require inotropic support with dobutamine and/or IABP. Surgical repair is indicated in the majority of patients.
- **Ventricular septal rupture** is most commonly associated with anterior MI occurring 3-5 days after MI. The perforation may follow a direct course between the ventricles or a serpiginous route through the septal wall.
  - Diagnosis can be made by echocardiography with Doppler imaging and often requires TEE.

  - Diagnosis should be suspected in the postinfarct patient who develops HF symptoms and a new holosystolic murmur.
  - Stabilization with afterload reduction, inotropic support, and/or IABP may be necessary for hemodynamically unstable patients until definitive therapy with surgical repair can be performed.
  - In hemodynamically stable patients, surgery is best deferred for at least a week to improve patient outcome. Left untreated, mortality approaches 90%.
  - Percutaneous device closure in the cardiac catheterization laboratory can be performed in select patients with an unacceptable surgical risk.

MONITORING/FOLLOW-UP

Routine office visits 1 month after discharge and every 3-12 months thereafter are suggested for the patient presenting with an acute MI.

- Patients should be instructed to seek more frequent or urgent follow-up evaluation if they experience any noticeable changes in their clinical status.
- Specific plans for long-term follow-up care should be individualized based on clinical status, anatomy, prior interventions, and change in symptoms.
- All patients should be referred for cardiac rehabilitation.

5
Heart Failure and Cardiomyopathy

Shane J. LaRue

Justin M. Vader

HEART FAILURE

General Principles

DEFINITION

Heart failure (HF) is a **clinical syndrome** in which either structural or functional abnormalities of the heart impair its ability to fill with or eject blood, resulting in dyspnea, fatigue, and fluid retention (*Circulation 2013;128:e240-e327*). HF is a progressive disorder and is associated with extremely high morbidity and mortality.

CLASSIFICATION

- HF may be due to abnormalities in myocardial contraction (systolic dysfunction), relaxation and filling (diastolic dysfunction), or both.
- Left ventricular (LV) ejection fraction (EF) is used to subdivide HF patients into groups for therapeutic and prognostic purposes. These groups are:
  - EF <40%: HF with reduced EF (HFrEF)
  - EF 40-50%: HF with borderline EF
  - EF >50%: HF with preserved EF (HFpEF)
- HF is classified in terms of natural history by American College of Cardiology/American Heart Association (ACC/AHA) HF stage and in terms of symptom status by New York Heart Association (NYHA) Functional Class (Tables 5-1 and 5-2).

EPIDEMIOLOGY

- In the United States, over 5.7 million people are living with HF (*Circulation 2014;131: e29-e322*).
- Approximately 870,000 new cases of HF are diagnosed each year.
- HF accounts for over 1 million hospitalizations per year.
- Estimated 1- and 5-year mortality are 30% and 50%, respectively (*Circulation 2010;123(4): 410-528*).

ETIOLOGY

- Coronary artery disease (CAD) is the most frequent cause of HF in the United States. Other risk factors with high population attributable risk include tobacco use, hypertension, diabetes, and obesity (*Circulation 2014;131:e29-e322*).
- Other causes include valvular heart disease, toxin induced (alcohol, cocaine, chemotherapy), myocarditis (infectious or autoimmune), familial cardiomyopathy, infiltrative disease (amyloidosis, sarcoidosis, hemochromatosis), peripartum cardiomyopathy (PPCM), hypertrophic cardiomyopathy (HCM), constrictive

(i.e., arteriovenous malformation or fistula), generalized myopathy (Duchenne or Becker muscular dystrophy), tachycardia-induced cardiomyopathy, and idiopathic cardiomyopathy.

TABLE 5-1 American College of Cardiology/American Heart Association Guidelines of Evaluation and Management of Chronic Heart Failure in Adults

Stage	Description	Treatment
A	No structural heart disease and no symptoms but risk factors: CAD, HTN, DM, cardio toxins, familial cardiomyopathy	Lifestyle modification—diet, exercise, smoking cessation; treat hyperlipidemia and use ACE inhibitor for HTN
B	Abnormal LV systolic function, MI, valvular heart disease, but no HF symptoms	Lifestyle modifications, ACE inhibitor, β-adrenergic blockers
C	Structural heart disease and HF symptoms	Lifestyle modifications, ACE inhibitor, β-adrenergic blockers, diuretics, digoxin
D	Refractory HF symptoms to maximal medical management	Therapy listed under A, B, and C, and mechanical assist device, heart transplantation, continuous IV inotropic infusion, hospice care in selected patients

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; LV, left ventricular; MI, myocardial infarction.

From Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Am Coll Cardiol* 2005;46:1116-43.

- HF exacerbations may be precipitated by dietary and medication noncompliance; however, myocardial ischemia, hypertension, arrhythmias (particularly atrial fibrillation), infection, volume overload, alcohol/toxins, thyroid disease, drugs (NSAIDs calcium channel blockers, doxorubicin), and pulmonary embolism are also potential triggers.

TABLE 5-2 New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I (mild)	No symptoms or limitation while performing ordinary physical activity (walking, climbing

	stairs, etc.).
II (mild)	Mild symptoms (mild shortness of breath, palpitations, fatigue, and/or angina) and slight limitation during ordinary physical activity.
III (moderate)	Marked limitation in activity due to symptoms, even during less than ordinary activity (walking short distances [20-100 m]). Comfortable only at rest.
IV (severe)	Severe limitations with symptoms even while at rest. Mostly bedbound patients.

PATHOPHYSIOLOGY

- HF begins with an initial insult leading to myocardial injury.
- Regardless of etiology, the myocardial injury leads to a pathologic remodeling, which manifests as an increase in LV volume (dilatation) and/or mass (hypertrophy).
- Compensatory adaptations initially maintain cardiac output; specifically, there is activation of the renin-angiotensin-aldosterone system (RAAS) and vasopressin (antidiuretic hormone), which lead to increased sodium retention and peripheral vasoconstriction. The sympathetic nervous system is also activated, with increased levels of circulating catecholamines, resulting in increased myocardial contractility. Over time, these neurohormonal pathways result in direct cellular toxicity, fibrosis, arrhythmias, and pump failure.
- Cardiac dysfunction and pathologic remodeling alter the ventricular pressure-volume relationship, leading to an increase in chamber pressures, resulting in pulmonary and systemic venous congestion.

Diagnosis

CLINICAL PRESENTATION

History

- Affected patients most commonly present with symptoms of HF, including:
  - Dyspnea (on exertion and/or at rest)
  - Fatigue
  - Exercise intolerance
  - Orthopnea, paroxysmal nocturnal dyspnea
  - Systemic or pulmonary venous congestion (lower extremity swelling or cough/wheezing)
  - Presyncope, palpitations, and angina may also be present
- Other possible presentations include incidental detection of asymptomatic cardiomegaly or symptoms related to coexisting arrhythmia, conduction disturbance, thromboembolic complications, or sudden death.
- Clinical manifestations of HF vary depending on the severity and rapidity of cardiac decompensation, underlying etiology, age, and comorbidities of the patient.
- Extreme decompensation may present as cardiogenic shock (resulting from both low arterial and high venous pressures), characterized by hypoperfusion of vital organs, leading to renal failure (decreased

urine output), mental status changes (confusion and lethargy), or “shock liver” (elevated liver function tests).

Physical Examination

- The goal of the physical exam in HF is to estimate intracardiac pressures, ventricular compliance, cardiac output, and end-organ perfusion.
- Elevated right-sided pressures result in lower extremity edema, jugular venous distension (JVD), abdominojugular reflux, pleural and pericardial effusions, hepatic congestion, and ascites.
  - JVD is the most specific and reliable physical exam indicator of right-sided volume overload and is representative of left-sided filling pressures except in cases of disproportionate right heart dysfunction (e.g., pulmonary hypertension, severe tricuspid regurgitation, and pericardial disease).
  - JVD is best visualized with oblique light and the patient at 45 degrees. Venous pulsations are differentiated from carotid pulsation by their biphasic nature, respiratory variability, and compressibility.
  - Abdominojugular reflux suggests an impaired ability of the right ventricle to handle augmented preload and may be due to constriction or pulmonary hypertension in addition to myocardial disease.

- Elevated left-sided pressures may result in pulmonary rales, but rales are absent in the majority of HF patients with elevated left-sided filling pressures.
- In the setting of systolic dysfunction, a third (S_3) or fourth (S_4) heart sound as well as the holosystolic murmurs of tricuspid or mitral regurgitation (MR) may be present; carotid upstrokes may also be diminished.
- Low cardiac output is suggested by a proportional pulse pressure (pulse pressure/diastolic blood pressure) ≤25%, diminished carotid upstroke, and cool extremities.

DIAGNOSTIC TESTING

Laboratories

- Initial laboratory studies should include complete blood count (CBC), urinalysis, serum electrolytes, blood urea nitrogen (BUN), creatinine, calcium, magnesium, fasting glucose, liver function tests, fasting lipid profile, and thyroid function tests.
- B-type natriuretic peptide (BNP) and the biologically inactive cleavage product N-terminal prohormone BNP (NT-proBNP) are released by myocytes in response to stretch, volume overload, and increased filling pressures. Elevated BNP/NT-proBNP is present in patients with asymptomatic LV dysfunction as well as symptomatic HF.
- BNP and NT-proBNP levels have been shown to correlate with HF severity and to predict survival (*N Engl J Med 2002;347:161*; *Eur Heart J 2006;27(3):330*). A serum BNP >400 pg/mL is consistent with HF; however, specificity is reduced in patients with renal dysfunction. A serum BNP level <100 pg/mL has a good negative predictive value to exclude HF in patients presenting with dyspnea (*Curr Opin Cardiol 2006;21:208*). Age-specific cut points have also been identified, for example, NT-proBNP levels of 450 pg/mL, 900 pg/mL, and 1800 pg/mL optimally identified acute HF for patients age <50, 50-75, and >75, respectively (*Eur Heart J 2006;27(3):330*).
- Additional laboratory testing in a patient with new-onset HF without CAD may include diagnostic tests for HIV, hepatitis, and hemochromatosis. When clinically suspected, serum tests for rheumatologic diseases (antinuclear antibody [ANA], antineutrophil cytoplasmic antibody [ANCA], etc.), amyloidosis (serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP]), or pheochromocytoma (catecholamines) should be considered (*Circulation 2013;62:e147*).

Electrocardiography

An ECG should be performed to look for evidence of ischemia (ST-T wave abnormalities), hypertrophy (increased voltage), infiltration (reduced voltage), previous myocardial infarction (MI) (Q waves), conduction block (PR interval), interventricular conduction delays (QRS), and arrhythmias (supraventricular and ventricular).

Imaging

- Chest radiography should be performed to evaluate the presence of pulmonary edema or cardiomegaly and rule out other etiologies of dyspnea (e.g., pneumonia, pneumothorax). Although chest radiograph findings of cephalization and interstitial edema are highly specific for identifying patients presenting with acute HF (specificity of 98% and 99%, respectively), they have limited sensitivity (41% and 27%, respectively) (*Am J Med 2004; 116(6):363*).
- An echocardiogram should be performed to assess right ventricular (RV) and LV systolic and diastolic function, valvular structure and function, and chamber size and to exclude cardiac tamponade.
- LV function may also be evaluated using radionuclide ventriculography (i.e., multigated acquisition [MUGA] scan) or cardiac catheterization with ventriculography and invasive hemodynamics.

- Cardiac MRI may also be useful in assessing ventricular function and evaluating the presence of intracardiac shunting, valvular heart disease, infiltrative cardiomyopathy, myocarditis, and previous MI.

Diagnostic Procedures

- Coronary angiography should be performed in patients with angina or evidence of ischemia by ECG or stress testing, unless the patient is not a candidate for revascularization (*J Am Coll Cardiol 2013;62:e147-e239*).
- Stress nuclear imaging or echocardiography may be an acceptable alternative for assessing ischemia in patients presenting with HF who have known CAD and no angina, unless they are ineligible for revascularization (*J Am Coll Cardiol 2013;62:e147-e239*).
- Right heart catheterization with placement of a pulmonary artery catheter may help guide therapy in patients with hypotension and evidence of shock.
- Cardiopulmonary exercise testing with measurement of peak oxygen consumption (VO_2) is useful in assessing functional capacity and in identifying candidates for heart transplantation (*J Heart Lung Transplant 2003;22:70*; *Circulation 2009;83:778*).
- Endomyocardial biopsy should be considered when seeking a specific diagnosis that would influence therapy, specifically in patients with rapidly progressive and unexplained cardiomyopathy, those in whom active myocarditis, especially giant cell myocarditis, is considered, and those with possible infiltrative processes such as cardiac amyloidosis and sarcoidosis (*Circulation 2007;116:2216-33*).

Treatment of Heart Failure

PHARMACOTHERAPY

- In general, pharmacologic therapy in chronic HF is aimed at blocking the neurohormonal pathways that contribute to cardiac remodeling and the progression of HF, while reducing symptoms, hospitalizations, and

mortality.

- The cornerstone of medical therapy for HF includes RAAS blockade, β-adrenergic blockade, vasodilators, and diuretic therapy for volume overload.
- Pharmacotherapy is determined by the presence of a preserved or reduced LVEF. Several pharmacotherapies for HFrEF have been demonstrated to reduce death and hospitalization and improve quality of life in HF. No pharmacotherapy has been demonstrated to improve mortality in patients with HFpEF.

Chronic Medical Therapy with Reduced Ejection Fraction (HFrEF)

- **β-Adrenergic receptor antagonists (β-blockers)** (Table 5-3). β-Blockers are a critical component of HF therapy and work by blocking the toxic effects of chronic adrenergic stimulation on the heart.
  - Large randomized trials have documented the beneficial effects of β-blockers on functional status, disease progression, and survival in patients with NYHA class II-IV symptoms.
  - Improvement in EF, exercise tolerance, and functional class are common after the institution of a β-blocker (*Circulation 1995;92(6):1499*).
  - Typically, 2-3 months of therapy is required to observe significant effects on LV function, but reduction of cardiac arrhythmia and incidence of sudden cardiac death (SCD) may occur much earlier (*JAMA 2003;289:712*).
  - β-Blockers should be instituted at a low dose and titrated with careful attention to blood pressure and heart rate. Some patients experience volume retention and worsening HF symptoms that typically respond to transient increases in diuretic therapy.

TABLE 5-3 Drugs Commonly Used for Treatment of Heart Failure

Drug	Initial Dose	Target
Angiotensin-Converting Enzyme Inhibitors		
Captopril	6.25-12.5 mg q6-8h	50 mg tid
Enalapril	2.5 mg bid	10 mg bid
Fosinopril	5-10 mg daily; can use bid	20 mg daily
Lisinopril	2.5-5.0 mg daily; can use bid	10-20 mg bid
Quinapril	2.5-5.0 mg bid	10 mg bid
Ramipril	1.25-2.5 mg bid	5 mg bid
Trandolapril	0.5-1.0 mg daily	4 mg daily

Angiotensin Receptor Blockers		
Valsartan[a]	40 mg bid	160 mg bid
Losartan	25 mg daily; can use bid	25-100 mg daily
Irbesartan	75-150 mg daily	75-300 mg daily
Candesartan[a]	2-16 mg daily	2-32 mg daily
Olmesartan	20 mg daily	20-40 mg daily
Thiazide Diuretics		
HCTZ	25-50 mg daily	25-50 mg daily
Metolazone	2.5-5.0 mg daily or bid	10-20 mg total daily
Loop Diuretics		
Bumetanide	0.5-1.0 mg daily or bid	10 mg total daily (maximum)
Furosemide	20-40 mg daily or bid	400 mg total daily (maximum)
Torsemide	10-20 mg daily or bid	200 mg total daily (maximum)
Aldosterone Antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5-25.0 mg daily	25 mg daily
β-Blockers		
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg q12h	25-50 mg q12h
Metoprolol succinate	12.5-25.0 mg daily	200 mg daily
Digoxin	0.125-0.25 mg daily	0.125-0.25 mg daily

HCTZ, hydrochlorothiazide.

[a]Valsartan and candesartan are the only U.S. Food and Drug Administration-approved angiotensin II receptor blockers in the treatment of heart failure.

- The survival benefit of β-blockers is proportional to the heart rate reduction achieved (*Ann Intern Med 2009;150(11):784-94*).
- Individual β-blockers have unique properties, and the beneficial effect of β-blockers may not be a class effect. Therefore, one of three β-blockers with proven benefit on mortality in large clinical trials should be used (*Circulation 2013;128:e240-e327*):
  - **Carvedilol** (*N Engl J Med 2001;344:1651*; *Lancet 2003;362:7*)
  - **Metoprolol succinate** (*JAMA 2000;283:1295*)
  - **Bisoprolol** (*Lancet 1999;353:9*)

- **Angiotensin-converting enzyme (ACE) inhibitors** (see Table 5-3) attenuate vasoconstriction, vital organ hypoperfusion, hyponatremia, hypokalemia, and fluid retention attributable to compensatory activation of the renin-angiotensin system. They are the first choice for antagonism of the RAAS.
  - Multiple large clinical trials have clearly demonstrated that ACE inhibitors improve symptoms and survival in patients with LV systolic dysfunction (*Circulation 2013;128:e240-e327*).
  - ACE inhibitors may also prevent the development of HF in patients with asymptomatic LV dysfunction and in those at high risk of developing structural heart disease or HF symptoms (e.g., patients with CAD, diabetes mellitus, hypertension).
  - Currently, no consensus has been reached regarding the optimal dosing of ACE inhibitors in HF, although higher doses have been shown to reduce morbidity without improving overall survival (*Circulation 1999;100:2312*).
  - Absence of an initial beneficial response to treatment with an ACE inhibitor does not preclude long-term benefit.
  - Most ACE inhibitors are excreted by the kidneys, necessitating careful dose titration in patients with renal insufficiency. ACE inhibitors should not be administered if creatinine >3 mg/dL, if potassium >5 mEq/L, or in patients with bilateral renal artery stenosis. Renal function and potassium levels should be monitored with dose adjustment and periodically with chronic use.
  - A rise in serum creatinine up to 30% above baseline may be seen when initiating an ACE inhibitor and should not result in reflexive discontinuation of therapy (*N Engl J Med 2002;347:1256-61*).
  - Additional adverse effects may include cough, rash, angioedema, dysgeusia, increase in serum creatinine, proteinuria, hyperkalemia, and leukopenia.
  - Oral potassium supplements, potassium salt substitutes, and potassium-sparing diuretics should be used with caution during treatment with an ACE inhibitor.
  - Agranulocytosis and angioedema are more common with captopril than with other ACE inhibitors, particularly in patients with associated collagen vascular disease or serum creatinine >1.5 mg/dL.
  - **ACE inhibitors are contraindicated in pregnancy. Enalapril and captopril may be safely used by breastfeeding mothers.**
- **Angiotensin II receptor blockers (ARBs)** (see Table 5-3) inhibit the renin-angiotensin system via specific

blockade of the angiotensin II receptor.

- ARBs reduce morbidity and mortality associated with HF in patients who are not receiving an ACE inhibitor (*Lancet 2000;355:1582*; *N Engl J Med 2001;345:1667*; *Lancet 2003;362:777*) and therefore should be instituted when ACE inhibitors are not tolerated (*Circulation 2013;128:e240-e327*).
- In contrast to ACE inhibitors, ARBs do not increase bradykinin levels and therefore are not associated with cough.
- Renal precautions and monitoring for ARB use are similar to ACE inhibitor use.
- Use of ARBs is contraindicated in patients taking ACE inhibitors and aldosterone antagonists due to a high risk for hyperkalemia.
- **ARBs are contraindicated in pregnancy and breastfeeding.**

- **Aldosterone receptor antagonists** attenuate aldosterone-mediated sodium retention, vascular reactivity, oxidant stress, inflammation, and fibrosis.
  - **Spironolactone** is a nonselective aldosterone receptor antagonist that has been shown to improve survival and decrease hospitalizations in NYHA class III-IV patients with low EF (*N Engl J Med 1999;341:709*) and is therefore indicated in such patients if the creatinine is <2.5 mg/dL and potassium is <5.0 mEq/L (see Table 5-3) (*Circulation 2013;128:e240-e327*).
  - **Eplerenone** is a selective aldosterone receptor antagonist without the estrogenic side effects of spironolactone. It has proven beneficial in patients with HF following MI (*N Engl J Med 2003;348:1309*) and in less symptomatic HF patients (NYHA Class II) with reduced EF (*N Engl J Med 2011;364:11*).
  - The potential for development of life-threatening hyperkalemia exists with the use of these agents. Serum potassium must be monitored closely after initiation; concomitant use of ACE inhibitors and NSAIDs and the presence of renal insufficiency increase the risk of hyperkalemia.
  - Gynecomastia may develop in 10-20% of men treated with spironolactone; eplerenone should be used in this case.
- **Vasodilator therapy** alters preload and afterload conditions to improve cardiac output.
  - **Hydralazine** acts directly on arterial smooth muscle to produce vasodilation and to reduce afterload.
  - **Nitrates** are predominantly venodilators and help relieve symptoms of venous and pulmonary congestion. They also reduce myocardial ischemia by decreasing ventricular filling pressures and by directly dilating coronary arteries.
  - A **combination of hydralazine and isosorbide dinitrate** (starting dose: 37.5/20 mg three times daily), when added to standard therapy with β-blockers and ACE inhibitors, has been shown to reduce mortality in African American patients (*N Engl J Med 2004;351:2049*).
  - In the absence of ACE inhibitors, ARBs, aldosterone receptor antagonists, and β-blockers, the combination of nitrates and hydralazine improves survival in patients with HFrEF (*N Engl J Med 1986;314:1547*) and should therefore be considered for use in all HFrEF patients unable to tolerate RAAS blockade.
  - Reflex tachycardia and increased myocardial oxygen consumption may occur in the setting of hydralazine use, requiring cautious use in patients with ischemic heart disease.
  - Nitrate therapy may precipitate hypotension in patients with reduced preload.

- **Digitalis glycosides** increase myocardial contractility and may attenuate the neurohormonal activation associated with HF.
  - Digoxin has been show to decrease rates of HF hospitalizations without improving overall mortality (*N Engl J Med 1997;336:525*).
  - Digoxin has a **narrow therapeutic index**, and serum levels should be followed closely, particularly in patients with unstable renal function.
  - The usual daily dose is 0.125-0.25 mg and should be decreased in patients with renal insufficiency.
  - Clinical benefits may not be related to the serum levels. Although serum digoxin levels of 0.8-2.0 ng/mL are considered therapeutic, toxicity can occur in this range.
  - Women and patients with higher serum digoxin levels (1.2-2.0 ng/mL) have an increased mortality risk (*N Engl J Med 2002;347:1403*; *JAMA 2003;289:871*).
  - Discontinuation of digoxin in patients who are stable on a regimen of digoxin, diuretics, and an ACE inhibitor may result in clinical deterioration (*N Engl J Med 1993;329:1*).
  - Drug interactions with digoxin are common and may lead to toxicity. Agents that may increase levels include erythromycin, tetracycline, quinidine, verapamil, flecainide, and

    amiodarone. Electrolyte abnormalities (particularly hypokalemia), hypoxemia, hypothyroidism, renal insufficiency, and volume depletion may also exacerbate toxicity.
  - Digoxin is not dialyzable, and toxicity is only treatable by the administration of digoxin immune Fab.
- **α-Adrenergic receptor antagonists** have not been shown to improve survival in HF, and hypertensive patients treated with doxazosin as first-line therapy are at increased risk of developing HF (*JAMA 2000;283:1967*).
- **Calcium channel blockers** have no favorable effects on mortality in HFrEF.
  - Dihydropyridine calcium channel blockers such as amlodipine may be used in hypertensive HF patients already on maximal guideline-directed medical therapy (GDMT); however, these agents do not improve mortality (*N Engl J Med 1996;335:1107-14*; *JACC Heart Failure 2013;1(4):308-14*).
  - Nondihydropyridine calcium channel blockers should be avoided in HFrEF because their negative inotropic effects may potentiate worsening HF.
- **Diuretic therapy** (see Table 5-3), in conjunction with restriction of dietary sodium and fluids, often leads to clinical improvement in patients with symptomatic HF. Frequent assessment of the patient's weight and careful observation of fluid intake and output are essential during initiation and maintenance of therapy. Frequent complications of therapy include hypokalemia, hyponatremia, hypomagnesemia, volume contraction alkalosis, intravascular volume depletion, and hypotension. Serum electrolytes, BUN, and creatinine levels should be followed after institution of diuretic therapy. Hypokalemia may be life threatening in patients who are receiving digoxin or in those who have severe LV dysfunction that predisposes them to ventricular arrhythmias. Potassium supplementation or a potassium-sparing diuretic should be considered in addition to careful monitoring of serum potassium levels.
  - **Potassium-sparing diuretics (amiloride)** do not exert a potent diuretic effect when used alone.
  - **Thiazide diuretics (hydrochlorothiazide, chlorthalidone)** can be used as initial agents in patients with normal renal function in whom only a mild diuresis is desired. **Metolazone**, unlike other oral thiazides,

exerts its action at the proximal and distal tubule and may be useful in combination with a loop diuretic in patients with a low glomerular filtration rate.

- **Loop diuretics (furosemide, torsemide, bumetanide, ethacrynic acid)** should be used in patients who require significant diuresis and in those with markedly decreased renal function.
  - Furosemide reduces preload acutely by causing direct venodilation when administered intravenously, making it useful for managing severe HF or acute pulmonary edema (*Circulation 1997;96(6):1847*).
  - Use of loop diuretics may be complicated by hyperuricemia, hypocalcemia, ototoxicity, rash, and vasculitis. Furosemide, torsemide, and bumetanide are sulfa derivatives and may rarely cause drug reactions in sulfa-sensitive patients; ethacrynic acid can be used in such patients.
  - Dose equivalence of oral loop diuretics is approximately 50 mg ethacrynic acid = 40 mg furosemide = 20 mg torsemide = 1 mg bumetanide.

- **New and emerging agents**
  - **LCZ-696 (Entresto™)** is a combination of the ARB valsartan and neprilysin inhibitor sacubitril recently approved for use in patients with HFrEF and NYHA Class II-IV symptoms. Neprilysin is a neutral endopeptidase involved in the degradation of vasoactive peptides including the natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increased the availability of these peptides, which exert favorable effects in HF. In a large trial, this agent was shown to be superior to enalapril in reducing death and rehospitalization among NYHA class II-IV patients with HFrEF.

  - **Ivabradine** is an inhibitor of the I_{Kf} channel involved in generating "pacemaker" currents in cardiac tissue. Use of ivabradine in outpatients with HFrEF was shown to reduce HF hospitalization and HF death (*Lancet 2010;9744:875-85*), and it is indicated for the reduction of HF hospitalization in patients with EF <35%, stable HF symptoms, and sinus rhythm with a resting heart rate ≥70 bpm who are already taking β-blockers at the highest tolerated dose.

Chronic Medical Therapy with Preserved Ejection Fraction (HFpEF)

- No pharmacotherapy has been demonstrated to improve mortality in HFpEF.
- Control of blood pressure is recommended. The use of ACE inhibitors, ARBs, spironolactone, and β-blockers is reasonable. Use of these particular agents may be associated with a small reduction in HF hospitalization rates.
- Treatment of atrial fibrillation through rate or rhythm control in accordance with practice guidelines is recommended.
- Treatment of coronary disease and angina through pharmacotherapy and/or revascularization in accordance with practice guidelines is recommended.

Parenteral Agents

- **Parenteral vasodilators** should be reserved for patients with severe HF not responding to oral medications. Intravenous (IV) vasodilator therapy may be guided by central hemodynamic monitoring (pulmonary artery catheterization) to assess efficacy and avoid hemodynamic instability. Parenteral agents should be started at low doses, titrated to the desired hemodynamic effect, and discontinued slowly to avoid rebound vasoconstriction.

- **Nitroglycerin** is a potent vasodilator with effects on venous and, to a lesser extent, arterial vascular beds. It relieves pulmonary and systemic venous congestion and is an effective coronary vasodilator. Nitroglycerin is the preferred vasodilator for treatment of HF in the setting of acute MI or unstable angina.
- **Sodium nitroprusside** is a direct arterial vasodilator with less potent venodilatory properties. Its predominant effect is to reduce afterload, and it is particularly effective in patients with HF who are hypertensive or who have severe aortic or mitral valvular regurgitation. Nitroprusside should be used cautiously in patients with myocardial ischemia because of a potential reduction in regional myocardial blood flow (**coronary steal**).
  - The initial dose of **0.25 µg/kg/min** can be titrated **(maximum dose of 10 µg/kg/min)** to the desired hemodynamic effect or until hypotension develops.
  - The half-life of nitroprusside is 1-3 minutes, and its metabolism results in the release of cyanide, which is metabolized by the liver to thiocyanate and is then excreted via the kidney.
  - Toxic levels of thiocyanate (>10 mg/dL) may develop in patients with renal insufficiency. Thiocyanate toxicity may manifest as nausea, paresthesias, mental status changes, abdominal pain, and seizures.
  - **Methemoglobinemia** is a rare complication of treatment with nitroprusside.
- **Recombinant BNP (nesiritide)** is an arterial and venous vasodilator.
  - IV infusion of nesiritide reduces right atrial and LV end-diastolic pressures and systemic vascular resistance and results in an increase in cardiac output.
  - It is administered as a 2-µg/kg IV bolus, followed by a continuous IV infusion starting at 0.01 µg/kg/min.
  - Nesiritide is approved for use in acute HF exacerbations and relieves HF symptoms early after its administration (*JAMA 2002;287:1531*). It does not have an effect on survival or rehospitalization in patients with HF (*N Engl J Med 2011;365:32*).
  - *Hypotension* is the most common side effect of nesiritide, and its use should be avoided in patients with systemic hypotension (systolic blood pressure <90 mm Hg) or evidence of cardiogenic shock. Episodes of hypotension should be managed with discontinuation of nesiritide and cautious volume expansion or vasopressor support if necessary.

- **Inotropic agents**
  - **Sympathomimetic agents** are potent drugs reserved for the treatment of severe HF. Beneficial and adverse effects are mediated by stimulation of myocardial β-adrenergic receptors. The most important adverse effects are related to the arrhythmogenic nature of these agents and the potential for exacerbation of myocardial ischemia. Treatment should be guided by careful hemodynamic and ECG monitoring. Patients with refractory chronic HF may benefit symptomatically from continuous ambulatory administration of IV inotropes as palliative therapy or as a bridge to mechanical ventricular support or cardiac transplantation. However, this strategy may increase the risk of life-threatening arrhythmias or indwelling catheter-related infections (*Circulation 2013;128:e240-e327*).
  - **Norepinephrine**, rather than **dopamine** (Table 5-4), should be used for stabilization of the hypotensive HF patient. Although a large randomized trial found no mortality difference between dopamine and norepinephrine in a cohort of undifferentiated shock patients, there were more adverse events (primarily arrhythmic) in the dopamine group, and subgroup analysis of those with cardiogenic shock (n = 280) showed an increased rate of death at 28 days in the dopamine group (*N Engl J Med 2010; 362:779-89*).
  - **Dobutamine** (see Table 5-4) is a synthetic analog of dopamine with predominantly β_1-adrenoreceptor

activity. It increases cardiac output, lowers cardiac filling pressures, and generally has a neutral effect on systemic blood pressure. Dobutamine tolerance has been described, and several studies have demonstrated increased mortality in patients

treated with continuous dobutamine. Dobutamine has no significant role in the treatment of HF resulting from diastolic dysfunction or a high-output state.

TABLE 5-4 Inotropic Agents[a]

Drug	Dose	Mechanism	Effects/Side Effects
Dopamine	1-3 μg/kg/min	Dopaminergic receptors	Splanchnic vasodilation
	2-8 μg/kg/min	β_1-receptor agonist	+ Inotropic
	7-10 μg/kg/min	α-receptor agonist	↑ SVR
Dobutamine	2.5-15.0 μg/kg/min	β_1- > β_2- > α-receptor agonist	+ Inotropic, ↓ SVR, tachycardia
Epinephrine	0.05-1 μg/kg/min; titrate to desired mean arterial pressure. May adjust dose every 10-15 min by 0.05-0.2 μg/kg/min to achieve desired blood pressure goal	β_1 > α_1 Low doses = β High doses = α	+ Inotropic, ↑ SVR
Milrinone[b]	50-μg/kg bolus IV over 10 min, 0.375-0.75 μg/kg/min	↑ cAMP	+ Inotropic, ↓ SVR

cAMP, cyclic adenosine monophosphate; SVR, systemic vascular resistance; ↑, increased; ↓, decreased.

[a]Increased risk of atrial and ventricular tachyarrhythmias.

[b]Needs dose adjustment for creatinine clearance.

- **Phosphodiesterase inhibitors** increase myocardial contractility and produce vasodilation by increasing intracellular cyclic adenosine monophosphate (cAMP). **Milrinone** is currently available for clinical use and is indicated for treatment of refractory HF. Hypotension may develop in patients who receive vasodilator

therapy or have intravascular volume contraction, or both. Milrinone may improve hemodynamics in patients who are treated concurrently with dobutamine or dopamine. Data suggest that in-hospital short-term milrinone administration in addition to standard medical therapy does not reduce the length of hospitalization or the 60-day mortality or rehospitalization rate when compared with placebo (*JAMA 2002;287:1541*).

Antiarrhythmic Therapy

- Suppression of asymptomatic ventricular premature beats or nonsustained ventricular tachycardia (NSVT) using antiarrhythmic drugs in patients with HF does not improve survival and may increase mortality as a result of the pro-arrhythmic effects of the drugs (*N Engl J Med 1989;321:406*; *N Engl J Med 1995;333:77*; *N Engl J Med 2005;352:225*).
- For patients with atrial fibrillation (AF) as a suspected cause of new-onset HF, a rhythm control strategy should be pursued. For patients with preexisting HF who develop AF, despite evidence suggesting improved symptom status in patients treated with rhythm control, the use of antiarrhythmic drug therapy for the maintenance of sinus rhythm has not been shown to improve mortality (*N Engl J Med 2008;358:2667-77*).
- Agents recommended for the maintenance of sinus rhythm in HF with reduced LVEF include dofetilide and amiodarone. Sotalol may also be considered in patients with mildly depressed LVEF. These agents require close monitoring of the QT interval.
- In patients with severe LV systolic dysfunction and HF, dronedarone should not be used (*N Engl J Med 2008;358:2678-87*).

Anticoagulant and Antiplatelet Therapy

- Although patients with HF are at relatively greater risk for thromboembolic events, the absolute risk is modest, and routine anticoagulation is not recommended in HF patients in the absence of AF, prior thromboembolism, or a prior cardioembolic source.
- In patients with AF, use of the CHADS2 or CHADS2-VASc risk score is recommended for determining when to use anticoagulant therapies.
- The novel anticoagulants dabigatran, rivaroxaban, and apixaban have been shown to be effective in HF patients with nonvalvular AF.
- There are insufficient data to support the routine use of aspirin in patients with HF who do not have coronary disease or atherosclerosis. Furthermore, certain data suggest that aspirin use may reduce the beneficial effects of ACE inhibitors (*Arch Intern Med 2003;163(13):1574*).

NONPHARMACOLOGIC THERAPIES FOR HEART FAILURE

- **Coronary revascularization** reduces ischemia and may improve systolic function in some patients with CAD.
  - Guidelines state that surgical or percutaneous revascularization is recommended in HF patients with angina and suitable anatomy (Class I recommendation) and may be considered in patients without angina who have suitable anatomy, whether in the presence of viable myocardium (Class IIa recommendation) or nonviable myocardium (Class IIb recommendation) (*Circulation 2013;128:e240-e327*).
  - In a large randomized trial of HF patients with CAD and LVEF <35% comparing medical therapy to medical therapy plus coronary artery bypass graft surgery (CABG),

there was no difference in the primary outcome of death from any cause (hazard ratio [HR] with CABG,

0.86; 95% confidence interval [CI], 0.72-1.04; *P* = 0.12). A prespecified secondary analysis of death from cardiovascular causes favored CABG over medical therapy alone (HR with CABG, 0.81; 95% CI, 0.66-1.00; *P* = 0.05) (*N Engl J Med 2011;364:1607-16*).

- **Cardiac resynchronization therapy (CRT)** or **biventricular pacing** (see Chapter 7, Cardiac Arrhythmias) can improve quality of life and reduce the risk of death in certain patients with an EF of ≤35%, NYHA class II-IV HF, and conduction abnormalities (left bundle branch block [LBBB] and atrioventricular delay) (*N Engl J Med 2005;352:1539*; *N Engl J Med 2010;363:2385-95*).
  - CRT can also be useful (Class IIA recommendation) in the following situations (*Circulation 2013;128:1810-52*):
    - LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS ≥150 milliseconds, and NYHA class III/ambulatory class IV symptoms on GDMT
    - LVEF ≤35%, sinus rhythm, LBBB with a QRS 120-149 milliseconds, and NYHA class II, III, or ambulatory IV symptoms on GDMT
    - AF and LVEF ≤35% on GDMT if the patient requires ventricular pacing and atrioventricular nodal ablation or rate control allows near 100% ventricular pacing with CRT
    - Patients on GDMT who have LVEF ≤35% and are undergoing new or replacement device implantation with anticipated frequent ventricular pacing (>40% of the time)
  - Factors most strongly favoring response to CRT include female sex, QRS duration ≥150 milliseconds, LBBB, body mass index <30 kg/m^2, nonischemic cardiomyopathy, and a small left atrium (*J Am Coll Cardiol 2012;59(25):2366-73*).
- **Implantable cardioverter-defibrillator (ICD)** placement is recommended for selected HF patients with a persistently reduced LVEF ≤35% for primary prevention of SCD. SCD occurs six to nine times more often in patients with HF compared to the general population and is the leading cause of death in ambulatory HF patients.
  - Multiple large randomized trials have demonstrated a survival benefit of 1-1.5% per year in patients with both ischemic and nonischemic cardiomyopathy (*N Engl J Med 2005;352:1539*; *Circulation 2013;128:e240-e327*).
  - Patients should receive at least 3-6 months of optimal GDMT prior to reassessment of EF and implantation of an ICD.
  - Following an acute MI or revascularization, EF should be assessed after 40 days of GDMT prior to ICD implantation.
  - ICD therapy should be reserved for patients expected to otherwise live >1 year with good functional capacity. ICD therapy should not be used in end-stage HF patients who are not candidates for transplantation or durable mechanical circulatory support.
- An **intra-aortic balloon pump (IABP)** can be considered for temporary hemodynamic support in patients who have failed pharmacologic therapies and have transient myocardial dysfunction or are awaiting a definitive procedure such as a LV assist device (LVAD) or transplantation. Severe aortoiliac atherosclerosis and moderate to severe aortic valve insufficiency are contraindications to IABP placement.
- **Percutaneous LVADs** are now available to provide short-term hemodynamic support for patients in cardiogenic shock. These devices have been shown to provide superior hemodynamic effects compared to

IABP. However, use of percutaneous LVADs compared to IABP did not improve 30-day survival in critically ill patients (*Eur Heart J 2009;30:2102*).

SURGICAL MANAGEMENT

- **Surgical or nonsurgical replacement or repair** of the mitral valve in the setting of a reduced LVEF and severe MR is discussed elsewhere (see Chapter 6, Pericardial and Valvular Heart Disease).

- **Ventricular assist devices (VADs)** are surgically implanted devices that draw blood from the left ventricle, energize flow through a motor unit, and deliver the energized blood to the aorta, resulting in augmented cardiac output and lower intracardiac filling pressures. These devices may be temporary (CentriMag, percutaneous LVADs) or durable (Heartmate II, HeartWare).
  - Temporary support is indicated for patients with severe HF after cardiac surgery or individuals with intractable cardiogenic shock after acute MI.
  - Durable support is indicated as a "bridge to transplantation" for patients awaiting heart transplantation or as "destination" therapy for select patients ineligible for transplant with refractory end-stage HF and HF-related life expectancy with therapy of <2 years (*Circulation 2013;128:e240-e327*).
  - Currently available devices vary with regard to degree of mechanical hemolysis, intensity of anticoagulation required, and difficulty of implantation.
  - The decision to institute mechanical circulatory support must be made in consultation with an HF cardiologist and a cardiac surgeon who have experience with this technology.
- **Cardiac transplantation** is an option for selected patients with severe end-stage HF that has become refractory to aggressive medical therapy and for whom no other conventional treatment options are available.
  - Only approximately 2200 heart transplants are performed each year in the United States.
  - Candidates considered for transplantation should generally be <65 years old (although selected older patients may also benefit), have advanced HF (NYHA class III-IV), have a strong psychosocial support system, have exhausted all other therapeutic options, and be free of irreversible extracardiac organ dysfunction that would limit functional recovery or predispose them to posttransplant complications (*J Heart Lung Transplant 2006;25:1024-42*).
  - Survival rates after heart transplant are approximately 90%, 70%, and 50% at 1, 5, and 10 years, respectively. Annual statistics can be found on the United Network for Organ Sharing website (*www.unos.org*).
  - In general, functional capacity and quality of life improve significantly after transplantation, although VO_2 does not reach levels of age- and gender-matched controls, improving by approximately 40% at 2 years (*Eur J Heart Fail 2007;9(3):310-6*).
  - **Posttransplant complications** may include acute or chronic rejection, typical and atypical infections, and adverse effects of immunosuppressive agents. Surgical complications and acute rejection are the major causes of death in the first posttransplant year. Cardiac allograft vasculopathy (CAD/chronic rejection) and malignancy are the leading causes of death after the first posttransplant year.

LIFESTYLE/RISK MODIFICATION

- Dietary counseling for sodium and fluid restriction should be provided. Daily intake of approximately 2 g of sodium per day is reasonable. Excessive restriction (<1.5 g/d of sodium) may be harmful.

- Smoking cessation should be strongly encouraged.
- Abstinence from alcohol is recommended in symptomatic HF patients with low EF.
- Exercise training is recommended in stable HF patients as an adjunct to pharmacologic treatment. Exercise training in patients with HF has been shown to improve exercise capacity (peak VO_2 max as well as 6-minute walk time), improve quality of life, and decrease neurohormonal activation (*JAMA 2009;301:1439*; *JAMA 2009;301:1451*). Treatment programs should be individualized and include a warm-up period, 20-30 minutes of exercise at the desired intensity, and a cool-down period (*Circulation 2003;107:1210*).
- Weight loss should be recommended in obese HF patients.

Special Considerations

- **Fluid and free water restriction** (<1.5 L/d) is especially important in the setting of hyponatremia (serum sodium <130 mEq/L) and volume overload.
- **Minimization of medications** with deleterious effects in HF should be attempted.
  - **Negative inotropes** (e.g., verapamil, diltiazem) should be avoided in patients with impaired ventricular contractility, as should over-the-counter β stimulants (e.g., compounds containing ephedra, pseudoephedrine hydrochloride).
  - **NSAIDs**, which antagonize the effect of ACE inhibitors and diuretic therapy, should be avoided if possible.
- **Administration of supplemental oxygen** may relieve dyspnea, improve oxygen delivery, reduce the work of breathing, and limit pulmonary vasoconstriction in patients with hypoxemia but is not routinely recommended in patients without hypoxemia.
- **Sleep apnea** has a prevalence as high as 37% in the HF population. Treatment with nocturnal positive airway pressure improves symptoms and EF (*Am J Respir Crit Care Med 2001;164:2147*; *N Engl J Med 2003;348:1233*).
- **Dialysis** or **ultrafiltration** may be beneficial in patients with severe HF and renal dysfunction who cannot respond adequately to fluid and sodium restriction and diuretics (*J Am Coll Cardiol 2007;49:675*) but is not superior to a scaled diuretic regimen in patients with acute HF and cardiorenal syndrome (*N Engl J Med 2012;367:2296-304*). Other mechanical methods of fluid removal such as therapeutic thoracentesis and paracentesis may provide temporary symptomatic relief of dyspnea. Care must be taken to avoid rapid fluid removal and hypotension.
- **End-of-life considerations** may be necessary in patients with advanced HF who are refractory to therapy. Discussions regarding the disease course, treatment options, survival, functional status, and advance directives should be addressed early in the treatment of the patient with HF. For those with end-stage disease (stage D, NYHA class IV) with multiple hospitalizations and severe decline in their functional status and quality of life, hospice and palliative care should be considered (*J Card Fail 2014;20(2):121-34*).

Acute Heart Failure and Cardiogenic Pulmonary Edema

GENERAL PRINCIPLES

Cardiogenic pulmonary edema (CPE) occurs when the pulmonary capillary pressure exceeds the forces that

maintain fluid within the vascular space (serum oncotic pressure and interstitial hydrostatic pressure).

- Increased pulmonary capillary pressure may be caused by LV failure of any cause, obstruction to transmitral flow (e.g., mitral stenosis [MS], atrial myxoma), or rarely, pulmonary veno-occlusive disease.
- Alveolar flooding and impairment of gas exchange follow accumulation of fluid in the pulmonary interstitium.

DIAGNOSIS

Clinical Presentation

- Clinical manifestations of CPE may occur rapidly and include dyspnea, anxiety, cough, and restlessness.
- The patient may expectorate pink frothy fluid.
- Physical signs of decreased peripheral perfusion, pulmonary congestion, hypoxemia, use of accessory respiratory muscles, and wheezing are often present.

Diagnostic Testing

- Radiographic abnormalities include cardiomegaly, interstitial and perihilar vascular engorgement, Kerley B lines, and pleural effusions.
- The radiographic abnormalities may follow the development of symptoms by several hours, and their resolution may be out of phase with clinical improvement.

TREATMENT

- Placing the patient in a sitting position improves pulmonary function.
- Bed rest, pain control, and relief of anxiety can decrease cardiac workload.
- **Supplemental oxygen** should be administered initially to raise the arterial oxygen tension to **>60 mm Hg**.
- **Mechanical ventilation** is indicated if oxygenation is inadequate or hypercapnia occurs. Noninvasive positive-pressure ventilation is preferred and may have particularly favorable effects in the setting of pulmonary edema (*JAMA 2005;294(24):3124-30*).
- **Precipitating factors** should be identified and corrected, because resolution of pulmonary edema can often be accomplished with correction of the underlying process. The most common precipitants are:
  - Severe hypertension
  - MI or myocardial ischemia (particularly if associated with MR)
  - Acute valvular regurgitation
  - New-onset tachyarrhythmias or bradyarrhythmias
  - Volume overload in the setting of severe LV dysfunction

Medications

- **Morphine sulfate** reduces anxiety and dilates pulmonary and systemic veins; 2-4 mg can be given intravenously over several minutes and can be repeated every 10-25 minutes until an effect is seen.
- **Furosemide** is a venodilator that decreases pulmonary congestion within minutes of IV administration, well before its diuretic action begins. An initial dose of 20-80 mg IV should be given over several minutes and can be increased based on response to a maximum of 200 mg in subsequent doses.

- **Nitroglycerin** is a venodilator that can potentiate the effect of furosemide. IV administration is preferable to oral and transdermal forms because it can be rapidly titrated.
- **Nitroprusside** is an effective adjunct in the treatment of acute CPE and is useful when CPE is brought on by acute valvular regurgitation or hypertension (see Chapter 6, Pericardial and Valvular Heart Disease). Pulmonary and systemic arterial catheterization should be considered to guide titration of nitroprusside therapy.
- **Inotropic agents**, such as dobutamine or milrinone, may be helpful after initial treatment of CPE in patients with concomitant hypotension or shock.
- **Recombinant BNP (nesiritide**) is administered as an IV bolus followed by an IV infusion. Nesiritide reduces intracardiac filling pressures by producing vasodilation and indirectly increases the cardiac output. In conjunction with furosemide, nesiritide produces natriuresis and diuresis.

SPECIAL CONSIDERATIONS

- **Right heart catheterization** (e.g., Swan-Ganz catheter) may be helpful in cases where a prompt response to therapy does not occur by allowing differentiation between cardiogenic and noncardiogenic causes of pulmonary edema via measurement of central hemodynamics and cardiac output. It may then be used to guide subsequent therapy. The routine use of right heart catheterization in acute HF patients is not beneficial (*JAMA 2005;294(13):1625-33*).

- **Acute hemodialysis and ultrafiltration** may be required in the patient with significant renal dysfunction and diuretic resistance (*J Am Coll Cardiol 2007;49:675*; *Congest Heart Fail 2008;14:19*) but is not a first-line therapy.

CARDIOMYOPATHY

Dilated Cardiomyopathy

GENERAL PRINCIPLES

Definition

Dilated cardiomyopathy (DCM) is a disease of heart muscle characterized by dilation of the cardiac chambers and reduction in ventricular contractile function.

Epidemiology

DCM is the most common form of cardiomyopathy and is responsible for approximately 10,000 deaths and 46,000 hospitalizations each year. The lifetime incidence of DCM is about 30 cases per 100,000 persons.

Pathophysiology

- DCM may be secondary to progression of any process that affects the myocardium, and dilation is directly related to neurohormonal activation. The majority of cases are idiopathic (*Am J Cardiol 1992;69:1458*), although genetic causes are increasingly recognized (*J Am Coll Cardiol 2005;45(7):969*).
- Dilation of the cardiac chambers and varying degrees of hypertrophy are anatomic hallmarks. Tricuspid

and mitral regurgitation are common due to the effect of chamber dilation on the valvular apparatus.

- **Atrial and ventricular arrhythmias** are present in as many as one-half of these patients and contribute to the high incidence of sudden death in this population.

DIAGNOSIS

Clinical Presentation

- Symptomatic HF (dyspnea, volume overload) is often present.
- A portion of patients with clinical disease may be asymptomatic.
- The ECG is usually abnormal, but changes are typically nonspecific.

Diagnostic Testing

Imaging

- Diagnosis of DCM can be confirmed with echocardiography or radionuclide ventriculography.
- Two-dimensional and Doppler echocardiography are helpful in differentiating this condition from HCM or restrictive cardiomyopathy (RCM), pericardial disease, and valvular disorders.

Diagnostic Procedures

Endomyocardial biopsy provides little information that affects treatment of patients with DCMs and is not routinely recommended (*Eur Heart J 2007;28:3076*; *Circulation 2013;128:e240-e327*). Settings where endomyocardial biopsy for DCM is recommended include:

- New-onset HF of <2 weeks in duration with normal-sized or dilated left ventricle and hemodynamic compromise.

- New-onset HF of 2 weeks to 3 months in duration associated with a dilated left ventricle and new ventricular arrhythmias, high-grade atrioventricular block (type II second-degree or third-degree), and failure to respond to usual care.
- Clinical scenarios that may result in the diagnosis of a treatable form of acute myocarditis, such as giant cell myocarditis or eosinophilic myocarditis.

TREATMENT

Medications

- The medical management of symptomatic patients is identical to that for HFrEF from other causes. This consists of controlling total body sodium and volume and pharmacotherapy including β-blockers, ACE inhibitors or ARBs, aldosterone antagonists, and vasodilator therapy.
- Immunizations against influenza and pneumococcal pneumonia are recommended.
- Immunosuppressive therapy with agents such as prednisone, azathioprine, and cyclosporine for biopsy-proven myocarditis has been advocated by some, but efficacy has not been established, with the possible exception of the very rare patient with giant cell myocarditis (*N Engl J Med 1995;333:269*; *Circulation 2013;128:e240-e327*).

Other Nonpharmacologic Therapies

Nonpharmacologic therapies for DCM are identical to those for HFrEF in general and, when indicated by practice guidelines, include ICD implantation, CRT, and temporary mechanical circulatory support.

Surgical Management

- Cardiac transplantation should be considered for selected patients with HF due to DCM that is refractory to medical therapy.
- LVAD placement may be necessary for stabilization of patients in whom cardiac transplantation is an option or in select patients who are not eligible for transplantation.

Heart Failure with Preserved Ejection Fraction

GENERAL PRINCIPLES

Definition

- HFpEF, also called diastolic HF, refers to the clinical syndrome of HF in the presence of preserved systolic function (LVEF >50%).
- Diastolic dysfunction refers to an abnormality in the mechanical function of the heart during the relaxation phase of the cardiac cycle, resulting in elevated filling pressures and impairment of ventricular filling.

Epidemiology

- Almost half of patients admitted to the hospital with HF have a normal or nearnormal EF.
- HFpEF is most prevalent in older women, most of whom have hypertension and/or diabetes mellitus. Many of these patients also have CAD and/or AF.

Etiology

- The vast majority of patients with HFpEF have hypertension and LV hypertrophy.
- Myocardial disorders associated with HFpEF include RCM, obstructive and nonobstructive HCM, infiltrative cardiomyopathies, and constrictive pericarditis.

Pathophysiology

- Reduced ventricular compliance and elastance play a major role in the pathophysiology of HFpEF.
- Factors contributing to the clinical HFpEF syndrome include abnormal sodium handling by the kidneys, atrial dysfunction, autonomic dysfunction, increased arterial stiffness, pulmonary hypertension, sarcopenia, obesity, deconditioning, and other comorbidities.

DIAGNOSIS

- Differentiating between HFpEF and HFrEF cannot be reliably accomplished without assessment of LVEF, preferably with two-dimensional echocardiography.
- Diagnosis is based on echocardiographic criteria and Doppler findings of normal LVEF and impaired diastolic relaxation and elevated filling pressures. More sensitive echocardiographic parameters of

systolic function, such as LV strain, may be abnormal in patients with HFpEF.

TREATMENT

No pharmacologic therapy has been shown in a randomized controlled trial to reduce mortality in HFpEF patients. Subgroup analysis indicates a possible modest benefit with respect to morbidity from the use of aldosterone receptor antagonists, ACE inhibitors/ARBs, and β-blockers. Practice guidelines for HFpEF emphasize blood pressure control, heart rate control or restoration of sinus rhythm in symptomatic patients, judicious diuretic use, and treatment of ischemic heart disease.

Hypertrophic Cardiomyopathy

GENERAL PRINCIPLES

Definition

HCM can be defined broadly as the presence of increased LV wall thickness that is not solely explained by abnormal loading conditions (*Eur Heart J 2014;35(39):2733-79*). More specifically, HCM is a genetically determined disease wherein sarcomere mutations lead to LV hypertrophy associated with nondilated ventricular chambers in the absence of another disease that would be capable of causing the magnitude of hypertrophy present in a given individual (*J Am Coll Cardiol 2011;58(25):e212-60*).

Epidemiology

- HCM is the most commonly inherited heart defect, occurring in 1 out of 500 individuals.
- Approximately 500,000 people have HCM in the United States, although many are unaware. An estimated 36% of young athletes who die suddenly have probable or definite HCM, making it the leading cause of SCD in young people in the United States, including trained athletes (*Circulation 2013;128:e240-e327*).

Pathophysiology

- HCM results from a mutation in a gene encoding one of the proteins involved in essential myocardial sarcomere functions, such as structural or contractile proteins, calcium handling proteins, or mitochondrial proteins.
  - There are currently at least 27 putative HCM susceptibility genes that lead to autosomal dominant transmission with variable phenotypic expression and penetrance.

  - The most common mutations involve myosin binding protein C (*MYBPC3*) and myosin heavy chain 7 (*MYH7*).
  - Over 50% of clinically affected patients have an identified mutation (*J Am Coll Cardiol 2009;54(3):201-11*).
- The histopathologic change in HCM consists of hypertrophied myocytes arranged in a disorganized manner with interstitial fibrosis.
- These changes lead grossly to myocardial hypertrophy that is typically predominant in the ventricular septum (asymmetric septal hypertrophy) but may involve any and all ventricular segments. HCM can be classified clinically according to the presence or absence of LV outflow tract (LVOT) obstruction. When

present, it is termed **hypertrophic obstructive cardiomyopathy (HOCM)**.

- LVOT obstruction may occur at rest but is enhanced by factors that increase LV contractility (exercise), decrease ventricular volume (e.g., Valsalva maneuver, volume depletion, large meal), or decrease afterload (vasodilators).
- Delayed ventricular diastolic relaxation and decreased compliance are common and, along with MR, may lead to pulmonary congestion.
- Myocardial ischemia is common, secondary to a myocardial oxygen supply-demand mismatch.
- Systolic anterior motion (SAM) of the anterior leaflet of the mitral valve is often associated with MR and likely determines the severity of LVOT obstruction.

DIAGNOSIS

HCM is usually diagnosed by maximal LV wall thickness ≥15 mm in the absence of another disease that could account for the degree of hypertrophy, often accompanied by supporting information (family history of HCM or sudden death, SAM, genetic testing).

Clinical Presentation

- Presentation varies but may include exertional dyspnea, angina, fatigue, dizziness, syncope, palpitations, or sudden death.
- Sudden death is most common in children and young adults between the ages of 10 and 35 years and often occurs during or immediately after periods of strenuous exertion.

Physical Examination

- Coarse **systolic outflow murmur** localized along the left sternal border that is **accentuated by maneuvers that decrease preload** (e.g., standing, Valsalva maneuver) and may be associated with a forceful double or triple apical impulse.
- Bisferiens (double peak per cardiac cycle) carotid pulse (in the presence of obstruction).

Diagnostic Testing

Electrocardiography

The ECG of HCM is usually abnormal and invariably so in symptomatic patients with LVOT obstruction. The most common abnormalities are ST-segment and T-wave abnormalities, followed by evidence of LV hypertrophy (*Am J Cardiol 2002;90:1020*). The ECG in apical-variant HCM is characterized by large, inverted T waves across the precordial leads.

Imaging

- Two-dimensional echocardiography and Doppler flow studies can establish the presence of a significant LV outflow gradient at rest or with provocation.
- Additional risk stratification should be pursued with 24- to 48-hour Holter monitoring and exercise testing.
- Cardiac MRI is indicated in patients with suspected HCM in whom the diagnosis cannot be confirmed with echocardiography.

Genetic Testing

Genetic testing for HCM is commercially available. Roughly 50% of patients with HCM have a known pathogenic mutation. Genetic testing can be used to aid in diagnosis of HCM when the clinical presentation is unclear. Genetic testing is reasonable in an index patient to facilitate family screening to determine at-risk

first-degree relatives (*J Am Coll Cardiol 2011;58(25):e212-60*).

TREATMENT

- Management is directed toward relief of symptoms and prevention of sudden death.
- Infective endocarditis prophylaxis remains controversial, and prophylactic antibiotics are no longer recommended by guidelines.
- Treatment in asymptomatic individuals is controversial, and no conclusive evidence has been found that medical therapy is beneficial.
- All individuals with HCM should avoid strenuous physical activity, including most competitive sports. Activity-specific recommendations are available (*Circulation 2004; 109:2807-16*).

Medications

- β-Blockers are generally the first-line agent to reduce symptoms of HCM by reducing myocardial contractility and heart rate.
- Nondihydropyridine calcium channel antagonists (verapamil and diltiazem) may improve the symptoms of HCM by reducing myocardial contractility and heart rate. Therapy should be initiated at low doses, with careful titration in patients with outflow obstruction. The dose should be increased gradually over several days to weeks if symptoms persist. Dihydropyridines should be avoided in patients with LVOT obstruction as a result of their vasodilatory properties.
- Disopyramide, a negative inotropic agent that results in lowering of the LVOT gradient, may be added for HCM patients who remain symptomatic despite the use of β-blockers and calcium channel blockers (alone or in combination). Use requires monitoring of the QT interval, and concomitant use of other antiarrhythmic drugs should be avoided.
- Diuretics may improve pulmonary congestive symptoms in patients with elevated pulmonary venous pressures. These agents should be used cautiously in patients with LVOT obstruction because excessive preload reduction worsens the obstruction.
- Nitrates and vasodilators should be avoided because of the risk of increasing the LVOT gradient.
- **Atrial and ventricular arrhythmias** occur commonly in patients with HCM. Supraventricular tachyarrhythmias are tolerated poorly and should be treated aggressively. Cardioversion is indicated if hemodynamic compromise develops.
  - **Digoxin is relatively contraindicated** because of its positive inotropic properties and potential for exacerbating ventricular outflow obstruction.
  - AF should be converted to sinus rhythm when possible, and anticoagulation is recommended if paroxysmal or chronic AF develops.
  - **Diltiazem, verapamil, or β-blockers** can be used to control the ventricular response before cardioversion. Procainamide, disopyramide, or amiodarone (see Chapter 7, Cardiac Arrhythmias) may be effective in the chronic suppression of AF.
  - ICD implantation is recommended for patients with HCM and prior cardiac arrest, ventricular fibrillation, or hemodynamically significant ventricular tachycardia.
  - ICD placement is reasonable in high-risk patients such as those with:
    - Recent unexplained syncope
    - LV hypertrophy with a maximal wall thickness >30 mm

- History of sudden death presumably caused by HCM in one or more first-degree relatives
- Multiple episodes of NSVT on Holter recordings (especially in patients <30 years old)
- Hypotensive response to exercise

- Symptomatic ventricular arrhythmias should be treated as outlined in Chapter 7, Cardiac Arrhythmias.

Nonpharmacologic Therapies for HCM

Dual-chamber pacing (see Chapter 7, Cardiac Arrhythmias) improves symptoms in some patients with HCM. Alteration of the ventricular activation sequence via RV pacing may minimize LVOT obstruction secondary to asymmetric septal hypertrophy. Only 10% of patients with HCM meet the criteria for pacemaker implantation, and the effect on decreasing the LVOT gradient is only 25%. A subset of patients with HCM may derive symptomatic benefit from dual-chamber pacing without an effect on survival (*Heart 2010;96(5):352*).

Surgical Management

- Septal reduction therapy (surgical myectomy or catheter-based alcohol septal ablation) provides symptom relief without proven survival benefit in the treatment of medicationrefractory HCM symptoms.
- Septal myectomy is the most commonly performed surgical intervention in HCM. In experienced centers, it is associated with symptom improvement in 95% of patients with <1% operative mortality (*J Am Coll Cardiol 2005;46:470-6*). Concomitant mitral valve intervention (mitral valve repair or replacement) is rarely required in experienced centers because MR generally responds well to septal reduction.
- Alcohol septal ablation, a catheter-based alternative to surgical myectomy, also provides relief of obstruction and symptomatic benefit with low procedural mortality, although it can be associated with heart block, requiring pacemaker placement in up to 20% of patients (*Circulation 2008;118:131-9*).
- Cardiac transplantation should be considered for patients with refractory end-stage HCM with symptomatic HF.

PATIENT EDUCATION

Genetic counseling and family screening are recommended for first-degree relatives of patients with HCM because it is transmitted as an autosomal dominant trait.

Restrictive Cardiomyopathy

GENERAL PRINCIPLES

Definition

- RCM is characterized by a rigid heart with poor ventricular filling but generally a nondilated LV and normal LVEF. Right heart failure symptoms often predominate.
- RCM may be primary, including conditions such as idiopathic RCM, endomyocardial fibrosis, and Löffler endocarditis, or secondary to either infiltrative conditions (amyloidosis, sarcoidosis, hypereosinophilic syndrome) or storage diseases (Fabry disease, hemochromatosis, and the glycogen storage diseases).
- Constrictive pericarditis may present similarly to RCM but is a disease wherein the pericardium limits diastolic filling. Constriction carries a different prognosis and therapy, and the distinction between constriction and RCM is essential.

Pathophysiology

- In amyloidosis, misfolded protein (amyloid) deposits in the cardiac interstitium, interrupting the normal myocardial contractile units and causing restriction.
- In sarcoidosis, granulomatous infiltration of the myocardium is often subclinical and more commonly presents with arrhythmias or conduction system disease; however, in up to 5% of sarcoidosis cases, restriction is manifested.
- In hemochromatosis, excess iron is deposited in the cardiomyocyte sarcoplasm, ultimately overcoming antioxidant capacity and resulting in lipid peroxidation and membrane permeability. Injury occurs initially in the epicardium and then later in the myocardium and endocardium, with systolic function initially preserved.
- Fabry disease, an X-linked genetic disorder, is characterized by deficient activity of the lysosomal enzyme α-galactosidase A, resulting in lysosomal accumulation of globotriaosylceramide in tissues, with more than half of patients manifesting cardiomyopathy, typically with LV hypertrophy and RCM.

DIAGNOSIS

Diagnostic Testing

Electrocardiography

The classic ECG finding in amyloidosis is low voltage (despite echocardiographically evident ventricular thickening) with poor R-wave progression. In sarcoidosis, conduction disease is often present.

Imaging

- In RCM, echocardiography with Doppler analysis often demonstrates thickened myocardium with normal or abnormal systolic function, abnormal diastolic filling patterns, and evidence of elevated intracardiac pressure. Compared with constrictive pericarditis, respiratory variation is less marked and tissue Doppler velocities are reduced.
- Cardiac MRI, position emission tomography (PET), and CT are emerging as useful diagnostic tools for patients with cardiac sarcoidosis because granulomas, inflammation, and edema may be seen, which appear to improve with therapy (*Am Heart J 2009;157:746*).

Diagnostic Procedures

- On cardiac catheterization, elevated and equalized RV and LV filling pressures are seen with a classic “dip-and-plateau” pattern in the RV and LV pressure tracing. Although pericardial constriction may produce similar findings, absence of ventricular interdependence identifies RCM as opposed to constriction (*J Am Coll Cardiol 2008;51(3):315-9*).
- RV endomyocardial biopsy may be diagnostic and should be considered in patients in whom a diagnosis is not established.

TREATMENT

- Specific therapy aimed at amelioration of the underlying cause should be initiated.

- Cardiac hemochromatosis may respond to reduction of total body iron stores via phlebotomy or chelation therapy with desferoxamine.
- Cardiac sarcoidosis may respond to glucocorticoid therapy, but prolongation of survival with this approach has not been established.
- Fabry disease may be treated with recombinant α-galactosidase A enzyme replacement therapy.
- In those with syncope and/or ventricular arrhythmias, placement of an ICD is indicated. Patients with high-grade conduction disease warrant pacemaker placement.
- No pharmacotherapy is known to be effective at reversing the progression of cardiac amyloidosis.

- Digoxin should be avoided in patients with cardiac amyloidosis because digoxin is bound extracellularly by amyloid fibrils and may cause hypersensitivity and toxicity (*Circulation 1981;63:1285*).

Peripartum Cardiomyopathy

GENERAL PRINCIPLES

Definition

- PPCM is defined as LV systolic dysfunction diagnosed in the last month of pregnancy up to 5 months postpartum.
- The incidence of PPCM is 1 in 3000 to 4000 pregnancies in the United States.

Etiology

- The etiology of PPCM remains unclear. There is evidence to support **viral triggers**, including coxsackievirus, parvovirus B19, adenovirus, and herpesvirus, which may replicate unchecked in the reduced immunologic state brought on by pregnancy.
- **Fetal microchimerism**, wherein fetal cells escape into the maternal circulation and induce an autoimmune myocarditis, has also been suggested as a cause (*Lancet 2006;368:687*).
- A cleavage product of **prolactin** has also been implicated in the development of PPCM (*Cell 2007;128:589*).

Risk Factors

Risk factors that predispose a woman to PPCM include advanced maternal age, multiparity, multiple pregnancies, preeclampsia, and gestational hypertension. There is a higher risk in African American women, but this may be confounded by the higher prevalence of hypertension in this population.

DIAGNOSIS

Clinical Presentation

- Clinically, women with PPCM present with the signs and symptoms of HF.
- Because dyspnea on exertion and lower extremity edema are common in late pregnancy, PPCM may be difficult to recognize. Cough, orthopnea, and paroxysmal nocturnal dyspnea are warning signs that PPCM may be present, as is the presence of a displaced apical impulse and a new MR murmur on exam.
- Most commonly, patients present with NYHA class III and IV HF, although mild cases and sudden cardiac arrest also occur.

Diagnostic Testing

Electrocardiography

On ECG, LV hypertrophy is often present, as are ST-T-wave abnormalities.

Imaging

Diagnosis requires an echocardiogram with a newly depressed EF and/or LV dilatation.

TREATMENT

Medications

- The mainstay of treatment is afterload and preload reduction.
- **ACE inhibitors** are used in the postpartum patient, whereas hydralazine is used in the patient who is still pregnant.

- **β-Blockers** are used to reduce tachycardia, arrhythmia, and risk of SCD and are relatively safe, although β_1-selective blockers are preferred because they avoid peripheral vasodilation and uterine relaxation.
- **Digoxin** is also safe during pregnancy and may be used to augment contractility and for rate control, although levels need to be closely monitored.
- **Diuretics** are used for preload reduction and symptom relief and are also safe.
- In those with thromboembolism, **heparin** is required, followed by **warfarin** after delivery.

OUTCOME/PROGNOSIS

- The prognosis in PPCM is better than that seen in other forms of nonischemic cardiomyopathy.
- The extent of ventricular recovery at 6 months after delivery can predict overall recovery, although continued improvement has been seen up to 2-3 years after diagnosis.
- Subsequent pregnancies in patients with PPCM may be associated with significant deterioration in LV function and can even result in death. Family planning counseling is essential after the diagnosis of PPCM is made, and women who do not recover their LV function should be encouraged to consider foregoing future pregnancy.

6
Pericardial and Valvular Heart Disease

Jacob S. Goldstein

Brian R. Lindman

PERICARDIAL DISEASE

Acute Pericarditis

GENERAL PRINCIPLES

Etiology

- The yield of standard diagnostic testing is relatively low.
- **Common:** neoplastic, autoimmune, viral, tuberculosis, bacterial (nontuberculous), uremia, post-cardiac surgery, idiopathic.
- **Less common:** trauma, post-myocardial infarction, drugs, dissecting aortic aneurysm.

Pathophysiology

The pericardium is a fibrous sac surrounding the heart consisting of two layers: a thin visceral layer attached to the pericardium and a thicker parietal layer. The pericardial space is normally filled with 15-50 mL of fluid, and the two layers slide smoothly against each other, allowing for normal expansion and contraction of the heart. Pericarditis occurs when these layers are inflamed.

DIAGNOSIS

Clinical Presentation

History

- The clinical presentation of acute pericarditis can vary depending on the underlying etiology. Patients with a known autoimmune diagnosis or malignancy can present with signs or symptoms specific to the underlying disorder. An infectious etiology can be preceded by, for example, a viral prodrome.
- Chest pain: typically sudden onset, anterior chest, sharp and pleuritic, improved by sitting up and leaning forward, made worse by inspiration, lying flat.

Physical Exam

Pericardial friction rub: highly specific for acute pericarditis. A scratchy or squeaking sound heard best over the left sternal border with the diaphragm of the stethoscope.

Differential Diagnosis

Must differentiate from other causes of acute chest pain: myocardial ischemia, aortic dissection, pulmonary embolism, musculoskeletal pain, gastroesophageal reflux disease.

Diagnostic Testing

- **ECG:** Diffuse ST-segment elevation and PR depression

- CXR: typically normal

- Echocardiogram: often normal, but may observe an associated pericardial effusion
- Other tests: complete blood count, troponin level, C-reactive protein, erythrocyte sedimentation rate, blood cultures (if febrile)

TREATMENT

- Tailor therapy to the etiology, as appropriate.
- NSAIDs: ibuprofen, aspirin, ketorolac.
- Colchicine: when added to conventional anti-inflammatory therapy, significantly reduces symptoms, recurrence rates, and hospitalizations.
- Glucocorticoids: reserved for cases refractory to standard therapy or in the setting of uremia, connective tissue disease, or immune-mediated pericarditis.

Constrictive Pericarditis

GENERAL PRINCIPLES

Constrictive pericarditis, as a cause of right-sided heart failure (HF), often goes undiagnosed. It is often difficult to distinguish from restrictive cardiomyopathies (RCMs). Multiple imaging modalities and invasive hemodynamics are often needed to confirm the diagnosis.

Etiology

- **Common**

  Idiopathic, viral pericarditis (chronic or recurrent), postcardiotomy, chest irradiation

- **Less common**

  Autoimmune connective tissue disorders, end-stage renal disease, uremia, malignancy (e.g., breast, lung, lymphoma), tuberculosis (most common cause in developing countries)

Pathophysiology

In the setting of chronic inflammation, the pericardial layers become thickened, scarred, and calcified; the pericardial space is obliterated, and the pericardium becomes noncompliant, which impairs ventricular filling and leads to an equalization of pressures in all four chambers and subsequent HF symptoms.

DIAGNOSIS

Clinical Presentation

History

The clinical presentation of constrictive pericarditis is insidious, with gradual development of fatigue, exercise intolerance, and venous congestion.

Physical Examination

- Features of right-sided HF

Lower extremity edema, hepatomegaly, ascites, elevated jugular venous pressure (JVP)

- Features more specific for constriction
  - Increased JVP with prominent y descent
  - Kussmaul sign: lack of expected decrease or obvious increase of JVP on inspiration
  - Pericardial knock: early, loud, high-pitched S_3

Differential Diagnosis

- **Pericardial constriction**
  - Ventricular interdependence **present**
  - Abnormal pericardial features (thickened, adherent, and/or calcified)
  - Preserved (or increased) tissue Doppler velocities on echocardiography
  - Pulmonary hypertension (PH) mild or absent
  - Septal bounce seen on noninvasive imaging
  - Equalization of pressures in all cardiac chambers
  - B-type natriuretic peptide (BNP) usually low or mildly elevated
- **RCM**
  - Ventricular interdependence **absent**
  - Abnormal myocardial features (infiltration, thickened, fibrotic, conduction system disease)
  - Decreased tissue Doppler velocities on echocardiography
  - PH present
  - Normal septal motion
  - Left ventricular end-diastolic pressure (LVEDP) - right ventricular end-diastolic pressure (RVEDP) >5 mm Hg, RVEDP/right ventricular systolic pressure <1/3
  - BNP elevated

Diagnostic Testing

- **Echocardiogram**
  - First-line diagnostic test.
  - Helpful for distinguishing constriction from restriction (see earlier).
  - Ventricular systolic function is often normal and can lead to the false assessment that the heart function is “normal” and not a cause of the patient's symptoms.
  - Features suggestive of constriction include:
    - Thickened, echogenic pericardium
    - Tethering of the pericardium to the myocardium
    - Dilated, incompressible inferior vena cava (IVC)
    - Septal bounce
    - Inspiratory variation in mitral flow velocity curves
    - Expiratory reversal of hepatic vein flow

- Preserved (or increased) tissue Doppler velocities of the mitral annulus

- **Cardiac catheterization**

  Often required to make the diagnosis of constriction and is the method of choice for an accurate hemodynamic assessment. Allows simultaneous measurement of RVEDP and LVEDP. Right atrial pressure will be very high, whereas pulmonary artery pressures will be near normal.

- **Cardiac CT and MRI**
  - Provide excellent anatomy of the pericardium (thickness and calcification).
  - An MRI and gated CT can show evidence of ventricular interdependence (septal bounce).
  - Can provide other anatomic information that may be helpful in making the diagnosis of constriction (i.e., engorgement of IVC and hepatic veins) and its etiology (i.e., lymph nodes, tumors).

TREATMENT

- Limited role for medical therapy: diuretics and low-salt diet to alleviate edema.
- Patients with constriction often have a resting sinus tachycardia. Due to limited stroke volume (SV), they are more dependent on heart rate for adequate cardiac output (CO). Avoid efforts to slow the heart rate.

Surgical Management

Surgical pericardiectomy is the only definitive treatment and should be pursued once the diagnosis is made. Operative mortality is 5-15%; more advanced congestive heart failure (CHF) symptoms confer higher operative risk. A significant majority experience a symptomatic benefit from surgery.

Cardiac Tamponade

GENERAL PRINCIPLES

Cardiac tamponade is a **clinical diagnosis** and is considered a medical emergency.

Etiology

- More likely to cause tamponade: procedural complications, infection, neoplasms, or idiopathic pericarditis
- Others: postcardiotomy, autoimmune connective tissue disorders, uremia, trauma, radiation, myocardial infarction (subacute), drugs (hydralazine, procainamide, isoniazid, phenytoin, minoxidil), hypothyroidism

Pathophysiology

Fluid accumulation in the pericardial space increases the pericardial pressure. The pressure depends on the amount of fluid, the rate of accumulation, and the compliance of the pericardium. Tamponade develops when the pressure in the pericardial space is sufficiently high to interfere with adequate cardiac filling, resulting in a decrease in CO.

DIAGNOSIS

Clinical Presentation

History

- The diagnosis of cardiac tamponade should be suspected in patients with elevated JVP, hypotension, and distant heart sounds (**Beck triad**).
- Symptoms can include dyspnea, fatigue, anxiety, presyncope, chest discomfort, abdominal fullness, lethargy, and a vague sense of being “uncomfortable”; patients often feel more comfortable sitting forward.

Physical Examination

- Pulsus paradoxus >10 mm Hg, jugular venous distention, and diminished heart sounds
- Tachycardia, hypotension, and signs of shock

Diagnostic Testing

- **ECG**

  Low voltage (more likely with larger effusions), tachycardia, electrical alternans (specific but not sensitive)
- **Transthoracic echocardiogram (TTE)**
  - First-line diagnostic test to diagnose an effusion and evaluate its hemodynamic significance.
  - Features suggestive of a hemodynamically significant effusion:
    - Dilated, incompressible IVC.
    - Significant respiratory variation of tricuspid and mitral inflow velocities.
    - Early diastolic collapse of the right ventricle and systolic collapse of the right atrium.
    - Usually the effusion is circumferential.

- **Transesophageal echocardiogram (TEE)**

  Helpful when TTE images are poor or when there is a suspicion for a loculated effusion (particularly those that might develop posteriorly, adjacent to the atria, after cardiac surgery).
- **CT and MRI**

  Can be helpful in assessing the anatomic location of the effusion (particularly if loculated). May be helpful in determining the etiology of the effusion and the content of the pericardial fluid. Should be avoided in an unstable patient.

TREATMENT

- Limited role for medical therapy. Goal is to maintain adequate filling pressures with IV fluids. Avoid diuretics, nitrates, and any other preload-reducing medications. Avoid efforts to slow sinus tachycardia; it compensates for a reduced SV to try to maintain adequate CO.
- If intubation is to be performed for respiratory distress before the fluid is drained, make sure volume status is replete and a pericardiocentesis needle is immediately available before any sedatives are given (a patient can arrest with the preload reduction from sedation).

Other Nonoperative Therapies

Percutaneous pericardiocentesis with echocardiographic guidance can be a relatively safe and effective way to drain the pericardial fluid; the approach should be guided by location of the fluid and is usually easiest when the effusion is anterior.

Surgical Management

- Open pericardiocentesis with the creation of a window is a minimally invasive procedure and is preferred for recurring effusions, loculated effusions, or those not safely accessible percutaneously.
- Allows pericardial biopsies to be taken, which may be helpful in making a diagnosis.

VALVULAR HEART DISEASE

The 2014 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines describe different stages in the progression of valvular heart disease (VHD).

- Stage A (at risk): patients with risk factors for development of VHD
- Stage B (progressive): patients with progressive VHD (mild to moderate severity and asymptomatic)
- Stage C (asymptomatic severe): asymptomatic patients who meet criteria for severe VHD
  - C1: asymptomatic patients with a compensated left and right ventricle
  - C2: asymptomatic patients with decompensation of the left or right ventricle
- Stage D (symptomatic severe): patients who have developed symptoms as a result of VHD

Mitral Stenosis

GENERAL PRINCIPLES

- Mitral stenosis (MS) is characterized by incomplete opening of the mitral valve during diastole, which limits antegrade flow and yields a sustained diastolic pressure gradient between the left atrium (LA) and the left ventricle (LV).
- Due to the widespread use of antibiotics, the incidence of rheumatic heart disease (and MS) has decreased in the developed world.

Etiology

- **Rheumatic**
  - Predominant cause of MS; two-thirds of patients are females; may be associated with mitral regurgitation (MR).
  - Rheumatic fever can cause fibrosis, thickening, and calcification, leading to fusion of the commissures, leaflets, chordae, and/or papillary muscles.
- **Other causes:** systemic lupus erythematosus (SLE), rheumatoid arthritis, congenital, substantial mitral annular calcification, oversewn or small mitral annuloplasty ring; “functional MS” may occur with obstruction of the LA outflow due to tumor (particularly myxoma), LA thrombus, or endocarditis with a large vegetation.

Pathophysiology

Physiologic states that either increase the transvalvular flow (enhance CO) or decrease diastolic filling time (via tachycardia) can increase symptoms at any given valve area. Pregnancy, exercise, hyperthyroidism, atrial fibrillation (AF) with rapid ventricular response, and fever are examples in which either or both of these conditions occur. Symptoms are often first noticed at these times. MS causes increased pressure in the LA,

which then dilates as a compensatory mechanism to minimize the increase in pressure. A dilated and fibrosed atrium develops, predisposing to atrial arrhythmias and clot formation. A sustained increase in pulmonary venous pressures is transmitted backward to cause PH and, with time, increased pulmonary vascular resistance and right ventricular pressure overload and dysfunction.

DIAGNOSIS

Clinical Presentation

History

After a prolonged asymptomatic period, patients may report any of the following: dyspnea, decreased functional capacity, orthopnea and/or paroxysmal nocturnal dyspnea, fatigue, palpitations (often due to AF), systemic embolism, hemoptysis, chest pain, and/or signs and symptoms of infective endocarditis.

Physical Examination

Findings on physical exam will depend on the severity of valve obstruction and the associated adaptations that developed; they may include:

- Opening snap (OS) caused by sudden tensing of the valve leaflets; the A_2-OS interval varies inversely with the severity of stenosis (shorter interval = more severe stenosis).
- Mid-diastolic rumble: low-pitched murmur heard best at the apex with the bell of the stethoscope; the severity of stenosis is related to the duration of the murmur, not intensity.
- Signs of right-sided HF and PH.

Diagnostic Testing

- **ECG**

  P mitrale (P-wave duration in lead II ≥0.12 seconds indicating LA enlargement [LAE]), AF, right ventricular hypertrophy
- **CXR**
  - LAE, enlarged right atrium/right ventricle and/or enlarged pulmonary arteries
  - Calcification of the mitral valve (MV) and/or annulus
- **TTE**
  - Assess etiology of MS.
  - Assess leaflets and subvalvular apparatus to determine candidacy for percutaneous mitral balloon commissurotomy (PMBC).

  - Determine MV area and mean transmitral gradient.
  - Estimate pulmonary artery systolic pressure and evaluate right ventricular size and function.
- **TEE**
  - Assess presence or absence of clot and severity of MR in patients being considered for percutaneous mitral balloon valvuloplasty.
  - Evaluate MV morphology and hemodynamics in patients with MS for whom TTE was suboptimal.
- **Cardiac catheterization**
  - Indicated to determine severity of MS when clinical and echocardiography assessment are discordant

- Reasonable in patients with MS to assess the cause of severe PH when out of proportion to the severity of MS as determined by noninvasive testing; can also assess the reversibility of PH

- **Severe MS**
  - Valve area ≤1.5 cm^2 (very severe MS ≤1.0 cm^2)
  - Usually accompanied by LAE and often PH

TREATMENT

Medical Management

- Diuretics and low-salt diet for HF symptoms.
- Secondary prevention of rheumatic fever is indicated for rheumatic MS.
- **AF** (occurs in 30-40% of patients with severe MS).
  - Therapy is mostly aimed at rate control (negative dromotropic agents) and prevention of thromboembolism; rhythm control is rarely successful.
  - **AHA/ACC Guidelines—class I indications for anticoagulation** for prevention of systemic embolization in patients with MS:
    - MS and AF (paroxysmal, persistent, or permanent)
    - MS and a prior embolic event, even in sinus rhythm
    - MS with LA thrombus

Other Nonoperative Therapies

PMBC

- **AHA/ACC recommendations for intervention:**
  - Symptomatic patients with severe MS (valve area ≤1.5 cm^2) (stage D) and favorable valve anatomy in the absence of an LA clot or moderate to severe MR (class I)
  - Asymptomatic patients with very severe MS (valve area ≤1.0 cm^2) (stage C) and favorable valve anatomy in the absence of a LA clot or moderate to severe MR (class IIa)
  - Asymptomatic patients with severe MS (stage C) and favorable valve anatomy in the absence of a LA clot or moderate to severe MR who have new-onset AF (class IIb)
- Balloon inflation separates the commissures and fractures some of the nodular calcium in the leaflets, yielding an increased valve area.
- It compares favorably with surgical mitral commissurotomy (open or closed) and is the procedure of choice in experienced centers in patients without contraindications.

Surgical Management

AHA/ACC recommendations for intervention (repair, commissurotomy, or replacement)

- Severely symptomatic patients (NYHA class III/IV) with severe MS (valve area <1.5 cm^2; stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC (class I).
- Concomitant MV surgery is indicated for patients with severe MS (valve area <1.5 cm^2; stage C or D) undergoing other cardiac surgery.

Aortic Stenosis

GENERAL PRINCIPLES

- **Aortic stenosis** (AS) is the most common cause of LV outflow tract obstruction.
- Other causes of obstruction occur above the valve (supravalvular) and below the valve (subvalvular), both fixed (i.e., subaortic membrane) and dynamic (i.e., hypertrophic cardiomyopathy with obstruction).
- **Aortic sclerosis** is thickening of the aortic valve leaflets that causes turbulent flow through the valve and a murmur but no significant gradient; over time, it can develop into AS.

Epidemiology

- **Calcific/degenerative**
  - Most common cause in United States.
  - Trileaflet calcific AS usually presents in the seventh to ninth decades (mean age, mid-70s).
  - Risk factors similar to coronary artery disease (CAD).
- **Bicuspid**
  - Occurs in 1-2% of population (congenital lesion).
  - Usually presents in the sixth to eighth decades (mean age, mid-late 60s).
  - Approximately 50% of patients needing aortic valve replacement (AVR) for AS have a bicuspid valve.
  - More prone to endocarditis than trileaflet valves.
  - Associated with aortopathies (i.e., dissection, aneurysm) in a significant proportion of patients.
- **Rheumatic**
  - More common cause worldwide; much less common in the United States.
  - Usually presents in the third to fifth decades.
  - Almost always accompanied by MV disease.

Pathophysiology

The pathophysiology for calcific AS involves both the valve and the ventricular adaptation to the stenosis. Within the valve (trileaflet and bicuspid), there is growing evidence for an active biologic process that begins much like the formation of an atherosclerotic plaque and eventually leads to calcified bone formation (Figure 6-1).

DIAGNOSIS

Clinical Presentation

History

- The classic triad of symptoms includes **angina, syncope, and HF**.
- Frequently, patients will gradually limit themselves in ways that mask the presence of symptoms but indicate a progressive and premature decline in functional capacity. In the setting of severe AS, these

patients should be viewed as symptomatic.

Physical Examination

- Harsh systolic crescendo-decrescendo murmur heard best at the right upper sternal border and radiating to both carotids; time to peak intensity correlates with severity (later peak = more severe).
- Diminished or absent A_2 (soft S_2) suggests severe AS.
- An ejection click suggests bicuspid AS.
- Pulsus parvus et tardus: late-peaking and diminished carotid upstroke in severe AS.
- Gallavardin phenomenon is an AS murmur heard best at the apex (could be confused with MR).

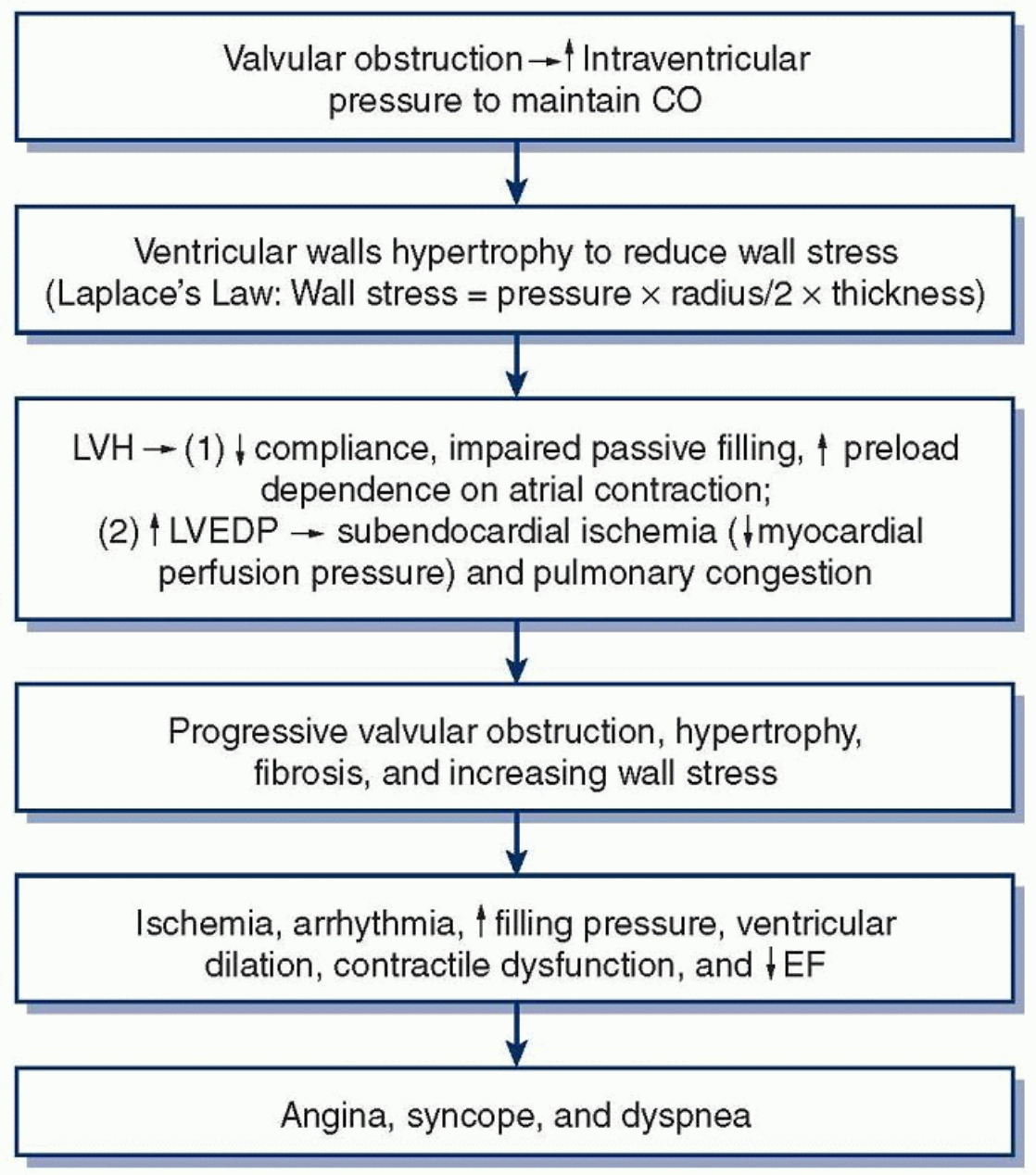


Figure 6-1. Pathophysiology of aortic stenosis. CO, cardiac output; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; LVH, left ventricular hypertrophy.

Diagnostic Testing

- **ECG:** LAE and LV hypertrophy (LVH)
- **CXR:** LVH, cardiomegaly, and calcification of the aorta, aortic valve, and/or coronaries

- **TTE**
  - Leaflet number, morphology, and calcification
  - Calculate valve area using continuity equation and measure transvalvular mean and peak gradients
  - **Severe AS**

    Peak jet velocity >4.0 m/s, mean gradient >40 mm Hg, valve area <1.0 cm^2
- **Further evaluation in selected patients**
  - **TEE**
    - Clarify whether there is a bicuspid valve if unclear on TTE.
    - Occasionally needed to evaluate for other or additional causes of LV outflow tract obstruction.
  - **Exercise testing:** Performed in the patient presumed to be asymptomatic or in whom symptoms are unclear; evaluate for exercise capacity, abnormal blood pressure response (<20 mm Hg increase with exercise), or exercise-induced symptoms.
  - **Dobutamine stress echocardiography**
    - Useful to assess the patient with a reduced SV (which may occur with a reduced or preserved ejection fraction [EF]) with a small calculated valve area (suggesting severe AS) but a low (<30-40 mm Hg) mean transvalvular gradient (suggesting less severe AS)

    - Can help distinguish truly severe AS from pseudo-severe AS
    - Assess for the presence of contractile reserve
  - **Cardiac catheterization**
    - Evaluate for CAD in patients with AS and symptoms of angina.
    - Hemodynamic assessment of severity of AS in patients for whom noninvasive tests are inconclusive or when there is discrepancy between noninvasive tests and clinical findings regarding AS severity (utilizes the Gorlin formula).
  - **CT**

    When the severity of AS is unclear, the extent of valve calcification can clarify the diagnosis.
  - **BNP or N-terminal prohormone BNP (NT-proBNP)**

    May be useful in predicting symptom-free survival in a patient with severe asymptomatic AS or clarifying whether symptoms of shortness of breath are more related to the lungs or the valve in a patient with concomitant severe lung disease.

TREATMENT

- **Severe symptomatic AS is a surgical disease;** currently, there are no medical treatments proven to decrease mortality or to delay surgery.
- **Hypertension** should be treated in patients with AS because inadequately treated hypertension imposes an additional load on the LV.
- **Diuretics** may alleviate shortness of breath in patients with symptomatic AS and evidence of volume overload prior to definitive therapy with valve replacement.
- **Severe AS with decompensated HF**

- Patients with severe AS and LV dysfunction may experience decompensated HF; depending on the clinical scenario, several options may help bridge the patient to definitive surgical management (e.g., AVR): Intra-aortic balloon pump (IABP) (contraindicated in patients with moderate to severe AR), sodium nitroprusside, balloon aortic valvuloplasty
- Each of the above measures provides some degree of afterload reduction, either at the level of the valve (valvuloplasty) or systemic vascular resistance (IABP, sodium nitroprusside [Nipride]), which can facilitate forward flow.

Other Nonoperative Therapies

Percutaneous

- Balloon aortic valvuloplasty has a limited role in the treatment of patients with severe AS; the improvement in valve area is modest, and the clinical improvement that it provides usually lasts weeks to months.
- **Transcatheter aortic valve replacement (TAVR)**
  - Requires a team of cardiologists and cardiac surgeons using fluoroscopic and echocardiographic guidance to place a stented bioprosthetic valve within the stenotic valve. This can be performed via a transfemoral, transaortic, or transapical approach.
  - To date, clinical trials have demonstrated that in patients at prohibitive risk for surgery, TAVR reduces mortality compared to medical therapy; for high-risk patients, TAVR and surgical valve replacement have similar outcomes.
  - These less-invasive, catheter-based techniques for valve replacement are rapidly evolving and are being investigated in ongoing clinical trials and clinical registries.

Surgical Management

- Symptomatic severe AS is a deadly disease; AVR is the only currently effective treatment.
- **AHA/ACC recommendations for intervention**
  - Symptomatic with severe high-gradient AS (stage D1; class I)
  - Asymptomatic with severe AS and LVEF <50% (stage C2; class I)

  - Patients with severe AS (stage C or D) undergoing other cardiac surgery (class I)
  - Asymptomatic patients with very severe AS (stage C1) and low surgical risk (class IIa)
  - Asymptomatic patients with severe AS (stage C1) and decreased exercise tolerance or fall in blood pressure on exercise testing (class IIa)

OUTCOME/PROGNOSIS

AS is a progressive disease typically characterized by an asymptomatic phase until the valve area reaches a minimum threshold, generally <1 cm^2. In the absence of symptoms, patients with AS have a good prognosis with a risk of sudden death estimated to be approximately 1% per year. Once patients experience symptoms, their average survival is 2-3 years with a high risk of sudden death.

Mitral Regurgitation

GENERAL PRINCIPLES

- Prevention of MR is dependent on the integrated and proper function of the MV (annulus and leaflets), subvalvular apparatus (chordae tendineae and papillary muscles), and LA and LV; abnormal function or size of any one of these components can lead to MR.
- **Primary MR**, or organic MR, refers to MR caused primarily by lesions to the valve leaflets and/or chordae tendineae (i.e., myxomatous degeneration, endocarditis, rheumatic).
- **Secondary MR**, or functional MR, refers to MR caused primarily by ventricular dysfunction usually with accompanying annular dilatation (i.e., dilated cardiomyopathy and ischemic MR).
- It is critical to define the mechanism of MR and the time course (acute vs. chronic) because these significantly impact clinical management.

Etiology

- **Primary MR**
  - **Degenerative** (overlap with MV prolapse syndrome)
    - Usually occurs as a primary condition (Barlow disease or fibroelastic deficiency) but has also been associated with heritable diseases affecting the connective tissue including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, etc.
    - May be familial or nonfamilial. Occurs in 1.0-2.5% of the population (based on stricter echocardiography criteria) in a female-to-male ratio of 2:1.
    - Most common reason for MV surgery.
    - Myxomatous proliferation and cartilage formation can occur in the leaflets, chordae tendineae, and/or annulus.
  - **Rheumatic**
    - May be pure MR or combined MR/MS.
    - Caused by thickening and/or calcification of the leaflets and chords.
  - **Infective endocarditis:** Usually caused by destruction of the leaflet tissue (i.e., perforation).
- **Secondary MR**
  - **Dilated cardiomyopathy**

    Mechanism of MR is due to both of the following:
    - Annular dilatation from ventricular enlargement.
    - Papillary muscle displacement due to ventricular enlargement and remodeling prevents adequate leaflet coaptation.
  - **Ischemic**
    - **Ischemic MR is mostly a misnomer**, because this is primarily postinfarction MR, not MR caused by active ischemia.

    - Mechanism of MR usually involves one or both of the following:

      Annular dilatation from ventricular enlargement.

Local LV remodeling with papillary muscle displacement (both the dilatation of the ventricle and the akinesis/dyskinesis of the wall to which the papillary muscle is attached can prevent adequate leaflet coaptation).

  - Rarely, MR may develop acutely from papillary muscle rupture (more commonly of the posteromedial papillary muscle).

- **Other causes**

  Congenital, infiltrative diseases (i.e., amyloid), SLE (Libman-Sacks lesion), hypertrophic cardiomyopathy with obstruction, mitral annular calcification, paravalvular prosthetic leak, drug toxicity (e.g., Fen-phen)

- **Acute causes**

  Ruptured papillary muscle, ruptured chordae tendineae, infective endocarditis

Pathophysiology

- Acute MR (Figure 6-2)
- Chronic MR (Figure 6-3)

DIAGNOSIS

Clinical Presentation

History

- Acute MR

  Most prominent symptom is relatively rapid onset of significant shortness of breath, which may lead quickly to respiratory failure.

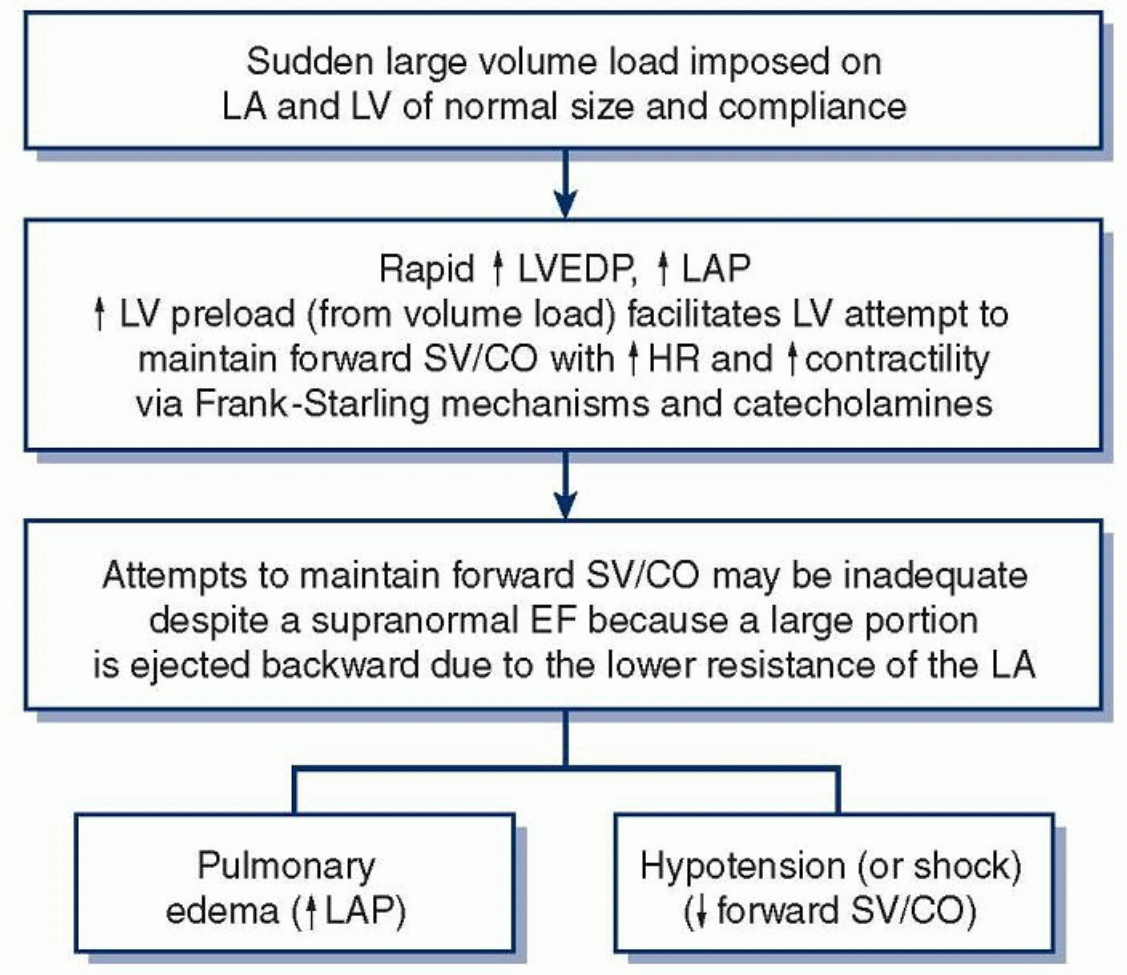


Figure 6-2. Acute mitral regurgitation. CO, cardiac output; EF, ejection fraction; HR, heart rate; LA, left atrium; LAP, left atrial pressure; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; SV, stroke volume.

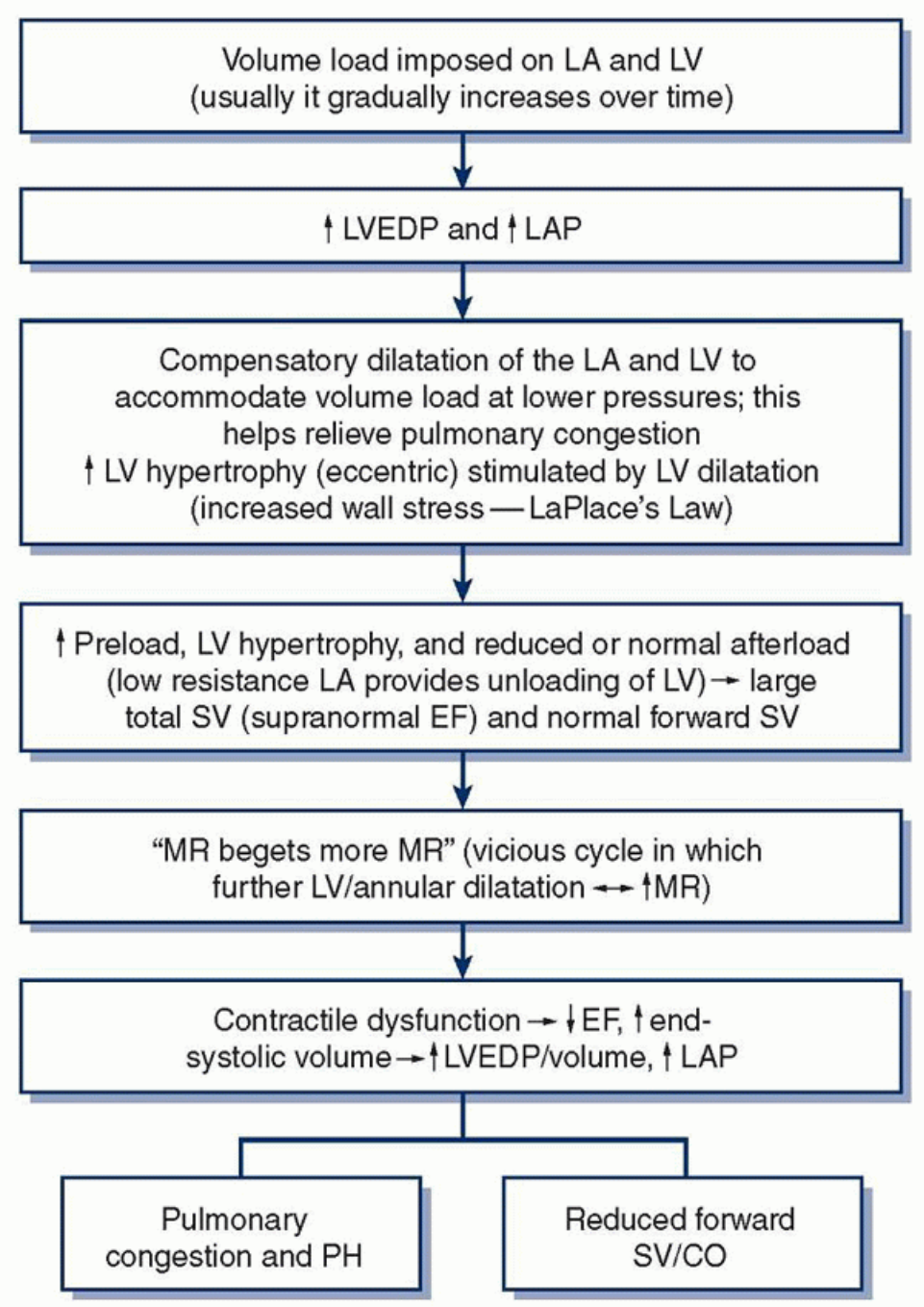


Figure 6-3. Chronic mitral regurgitation. CO, cardiac output; EF, ejection fraction; LA, left atrium; LAP, left atrial pressure; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; MR, mitral regurgitation; PH, pulmonary hypertension; SV, stroke volume.

- Chronic MR
  - The etiology of MR and the time at which the patient presents will influence the symptoms reported.
  - In primary MR (usually degenerative MR) that has gradually progressed, the patient may be asymptomatic even when the MR is severe. As compensatory mechanisms fail, patients may note dyspnea on exertion (may be due to PH and/or pulmonary edema), palpitations (from an atrial arrhythmia), fatigue, and volume overload.

Physical Examination

- Acute MR
  - Tachypnea with respiratory distress, tachycardia, relative hypotension (even shock)
  - Systolic murmur, usually at the apex (may not be holosystolic and may be absent)

- Chronic MR
  - Apical holosystolic murmur that radiates to the axilla.
  - In MV prolapse, there is a midsystolic click heard before the murmur.
  - S_2 may be widely split due to an early A_2.
  - Other signs of CHF (lower extremity edema, increased central venous pressure, crackles, etc.).

Diagnostic Testing

- **ECG**
  - LAE, LVH/LV enlargement, AF
  - Pathologic Q waves from previous myocardial infarction in ischemic MR
- **CXR**

  Enlarged LA, pulmonary edema, enlarged pulmonary arteries, and cardiomegaly
- **TTE**
  - Assess etiology of MR
  - LA size and LV dimensions (should be dilated in chronic severe MR of any etiology)
  - EF (LV dysfunction is present if EF ≤60%)
  - Qualitative and quantitative measures of MR severity
- **TEE**
  - Provides better visualization of the valve to help define anatomy, presence of endocarditis, and feasibility of repair
  - May help determine severity of MR when TTE is nondiagnostic, particularly in the setting of an eccentric jet
- **Cardiac catheterization**
  - Right heart catheterization
    - PH in patients with chronic severe MR, LA filling pressure in patients with unclear symptoms.
    - Giant “V” waves on pulmonary capillary wedge pressure tracing may suggest severe MR.
  - Left heart catheterization
    - May influence therapeutic strategy in ischemic MR
    - Evaluation of CAD in patients with risk factors undergoing MV surgery
  - Left ventriculogram can evaluate LV function and severity of MR.
- **MRI**
  - Assess EF in patients with severe MR but with an inadequate assessment of EF by echocardiography.
  - Assess quantitative measures of MR severity when echocardiography is nondiagnostic.
  - Viability assessment may play a role in considering therapeutic strategy in ischemic MR.
- **Nuclear**
  - Assess EF in patients with severe MR but with an inadequate assessment of EF by echocardiography.
  - Viability assessment may play a role in considering therapeutic strategy in ischemic MR.

TREATMENT

Acute MR

- While awaiting surgery, aggressive afterload reduction with IV nitroprusside or an IABP can diminish the amount of MR and stabilize the patient by promoting forward flow and reducing pulmonary edema.
- These patients are usually tachycardic, but attempts to slow their heart rate should be avoided because they are often heart rate dependent for an adequate forward CO.

Chronic MR

The role for medical therapy may differ depending on the etiology of the MR.

- **Primary MR**
  - In the asymptomatic patient with normal LV function and chronic severe MR due to leaflet prolapse, there is generally no accepted medical therapy.
  - In the absence of systemic hypertension, there is no established indication for vasodilating drugs.
  - Whether angiotensin-converting enzyme (ACE) inhibitors or β-blockers delay ventricular remodeling and the need for surgery is being investigated in prospective studies.
- **Secondary MR**
  - Treat as other patients with LV dysfunction.
  - ACE inhibitors and β-blockers are indicated and have been shown to reduce mortality and the severity of MR.
  - Some patients may also qualify for cardiac resynchronization therapy, which can favorably remodel the LV and reduce the severity of MR.

Other Nonoperative Therapies

Percutaneous

Currently, the most developed device may be the placement of a mitral clip, which pinches the leaflets together in an attempt to enhance coaptation (a percutaneous treatment analogous to the surgical Alfieri stitch), creating a figure-eight orifice.

This procedure is performed via femoral venous access, and a transseptal puncture is used to position the delivery system in the LA. Using fluoroscopy and TEE guidance, the clip is advanced and attempts are made to grasp the leaflet tips of the anterior and posterior MV leaflets and clip them together.

Surgical Management

AHA/ACC recommendations for intervention

- **Primary MR**
  - Symptomatic with chronic severe primary MR (stage D) and LVEF >30% (class I).
  - Asymptomatic with chronic severe primary MR with EF 30-60% or LV end-systolic dimension ≥40 mm) (stage C2; class I).
  - Chronic severe primary MR undergoing cardiac surgery for other indications (class I).
  - Repair is recommended over replacement (class I).
  - Asymptomatic patients with chronic severe primary MR (stage C1) in whom repair is highly likely (>95%) and operative mortality is low (<1%) or in the setting of new-onset AF or PH (class IIa).
- **Secondary MR** (benefits of surgery not well established)

- Chronic severe secondary MR undergoing cardiac surgery for other indications (class IIa).
- Severely symptomatic patients (NYHA III/IV) with chronic severe secondary MR (stage D; class IIb)

- Patients with AF should be considered for a concomitant surgical Maze procedure.

Aortic Regurgitation

GENERAL PRINCIPLES

- Aortic regurgitation (AR) may result from pathology of the aortic valve, the aortic root, or both; it is important that both the valve and the root are evaluated to determine the appropriate management and treatment.
- AR usually progresses insidiously with a long asymptomatic period; when it occurs acutely, patients are often very sick and must be managed aggressively.

Etiology

- **More common**

  Bicuspid aortic valve, rheumatic disease, calcific degeneration, infective endocarditis, idiopathic dilatation of the aorta, myxomatous degeneration, systemic hypertension, dissection of the ascending aorta, Marfan syndrome

- **Less common**

  Traumatic injury to the aortic valve, collagen vascular diseases (ankylosing spondylitis, rheumatoid arthritis, reactive arthritis, giant cell aortitis, and Whipple disease), syphilitic aortitis, discrete subaortic stenosis, ventricular septal defect with prolapse of an aortic cusp

- **Acute**

  Infective endocarditis, dissection of the ascending aorta, trauma

Pathophysiology

- Acute AR (Figure 6-4)
- Chronic AR (Figure 6-5)

DIAGNOSIS

Clinical Presentation

History

- **Acute:** Patients with acute AR may present with **symptoms of cardiogenic shock and severe dyspnea**. Other presenting symptoms may be related to the cause of acute AR.

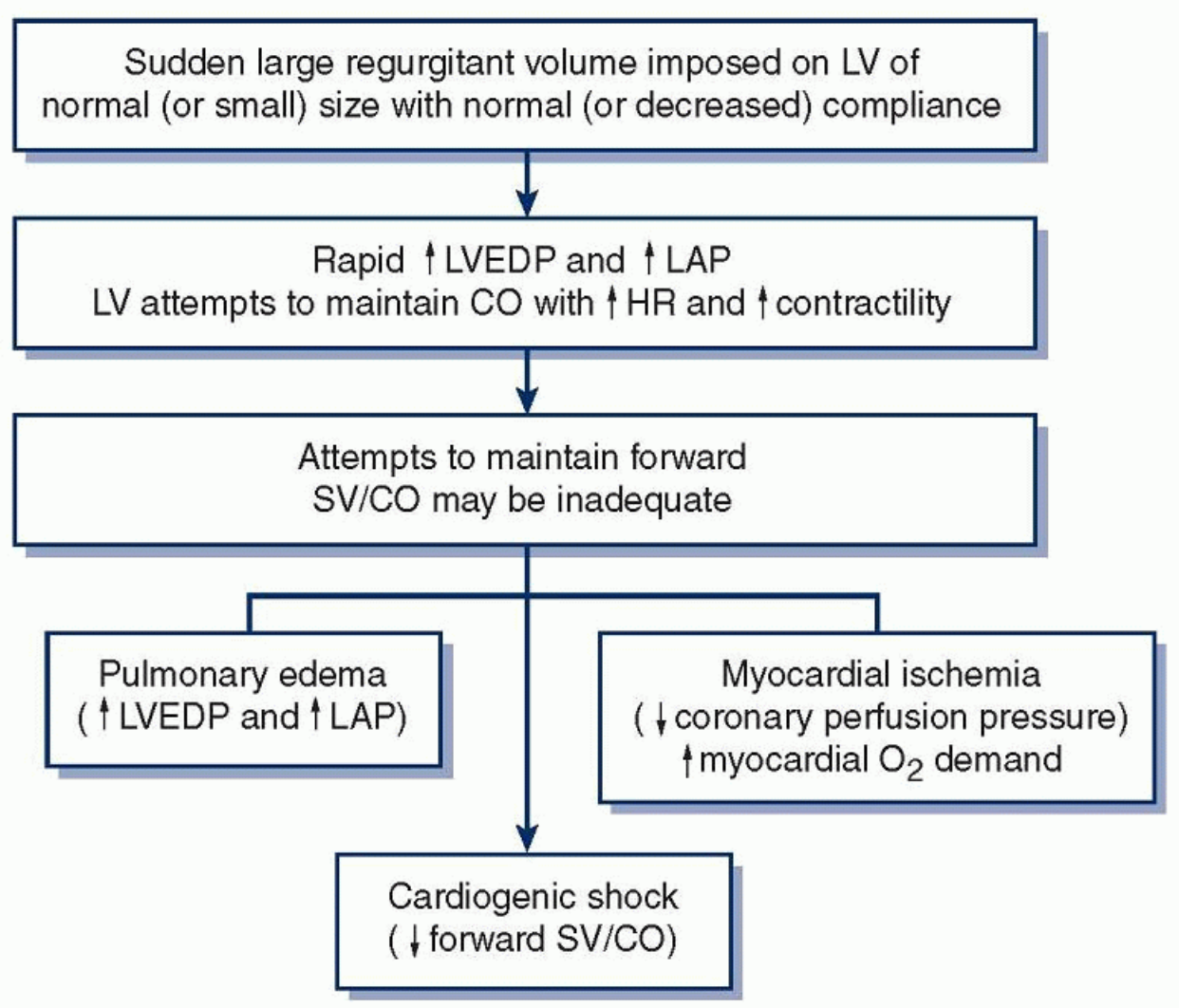


Figure 6-4. Acute aortic regurgitation. CO, cardiac output; HR, heart rate; LAP, left atrial pressure; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; SV, stroke volume.

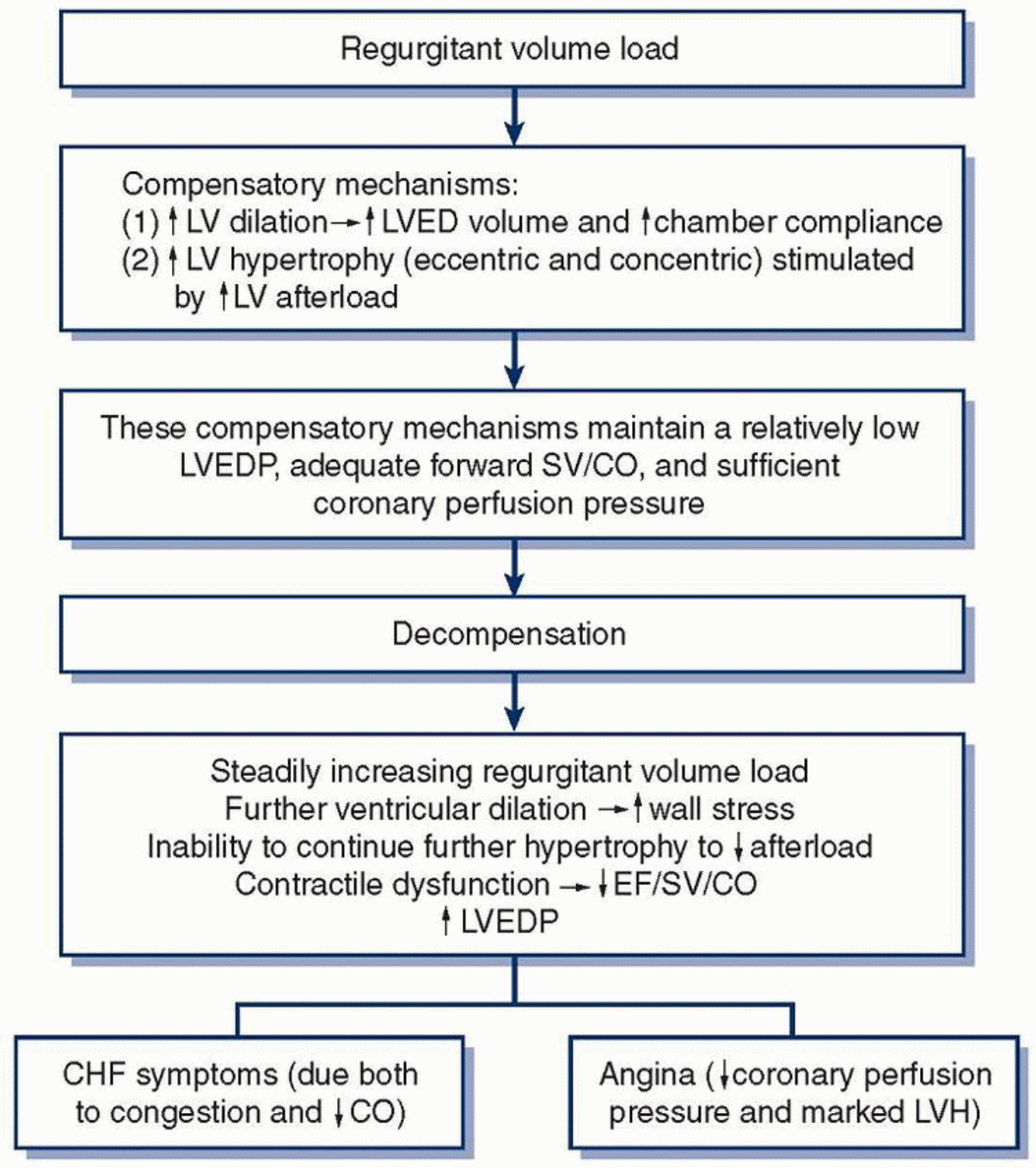


Figure 6-5. Chronic aortic regurgitation. CO, cardiac output; CHF, congestive heart failure; EF, ejection fraction; LV, left ventricle; LVED, left ventricular end-diastolic; LVEDP, left ventricular end-diastolic pressure; LVH, left ventricular hypertrophy; SV, stroke volume.

- **Chronic:** Symptoms depend on the presence of LV dysfunction and whether the patient is in the **compensated versus decompensated stage**. Compensated patients are typically asymptomatic, whereas those in the decompensated stage may note decreased exercise tolerance, dyspnea, fatigue, and/or angina.

Physical Examination

- Acute
  - **Tachycardia:** Wide pulse pressure may be present, but is often not present because forward SV (and therefore systolic blood pressure) is reduced; brief soft diastolic murmur heard best at third left intercostal space (often not heard); systolic flow murmur (due to volume overload and hyperdynamic LV).
  - Look for evidence of aortic dissection, infective endocarditis, and Marfanoid characteristics.

- Chronic
  - LV heave; point of maximal impulse is laterally displaced.
  - Diastolic decrescendo murmur heard best at left sternal border leaning forward at endexpiration (severity of AR correlates with duration, not intensity, of the murmur).

  - Systolic flow murmur (due mostly to volume overload; concomitant AS may also be present).
  - Widened pulse pressure (often >100 mm Hg) with a low diastolic pressure; there are numerous eponyms for the characteristic signs related to a wide pulse pressure.

Diagnostic Testing

- **ECG**
  - Tachycardia, LVH, and LAE (more common in chronic AR).
  - New conduction block may suggest an aortic root abscess.
- **CXR**

  Look for pulmonary edema, widened mediastinum, and cardiomegaly.
- **TTE**

  LV systolic function, LV dimensions at end systole and diastole, leaflet number and morphology, assessment of the severity of AR; look for evidence of endocarditis or aortic dissection; dimension of aortic root.
- **TEE**
  - Clarify whether there is a bicuspid valve if unclear on TTE.
  - Better sensitivity and specificity for aortic dissection than TTE.
  - Clarify whether there is endocarditis with or without root abscess if unclear on TTE.
  - Better visualization of aortic valve in patients with a prosthetic aortic valve.
- **Cardiac catheterization**
  - In patients undergoing AVR who are at risk for CAD.
  - Assessment of LV pressure, LV function, and severity of AR (via aortic root angiography) is indicated in symptomatic patients in whom the severity of AR is unclear on noninvasive imaging or discordant with clinical findings.
- **MRI/CT**
  - Depending on the institution, either of these may be the imaging modality of choice for evaluating aortic dimensions and/or for evaluation of aortic dissection.
  - If echocardiography assessment of the severity of AR is inadequate, MRI is useful for assessing the severity of AR.

TREATMENT

- **The role of medical therapy in patients with AR is limited**; there are currently no randomized, placebo-controlled data showing that vasodilator therapy delays the development of symptoms or LV dysfunction warranting surgery.
- **Vasodilator therapy (i.e., nifedipine, ACE inhibitor, hydralazine)** is indicated to reduce systolic blood

pressure in hypertensive patients with AR.

- Retrospective data suggest that β-blocker use may be associated with a survival benefit in patients with severe AR, but prospective studies are needed.
- When endocarditis is suspected or confirmed, appropriate antibiotic coverage is critical.

Surgical Management

- **AHA/ACC recommendations for intervention**
  - Symptomatic patients with severe AR (stage D) regardless of LV systolic function (class I)
  - Asymptomatic patients with chronic severe AR and LV systolic dysfunction (EF ≤50%) (stage C2; class I)
  - Patients with severe AR (stage C or D) undergoing cardiac surgery for other indications (class I)
  - Asymptomatic patients with severe AR and normal LV systolic function (EF >50%) but with severe LV dilation (LV end-systolic dimension >50 mm) (stage C2; class IIa)

- Acute, severe AR is almost universally symptomatic and is treated surgically.
- If the aortic root is dilated, it may be repaired or replaced at the time of AVR. For patients with a bicuspid valve, Marfan syndrome, or a related genetically triggered aortopathy, surgery on the aorta should be considered at the time of AVR.

OUTCOME/PROGNOSIS

- Asymptomatic patients with normal LV systolic function
  - Progression to symptoms and/or LV dysfunction <6% per year
  - Progression to asymptomatic LV dysfunction <3.5% per year
  - Sudden death <0.2% per year
- Asymptomatic patients with LV dysfunction

  Progression to cardiac symptoms >25% per year
- Symptomatic patients

  Mortality rate >10% per year

Prosthetic Heart Valves

GENERAL PRINCIPLES

The choice of valve prosthesis depends on many factors including the patient, surgeon, cardiologist, and clinical scenario. With improvements in bioprosthetic valves, the recommendation for a mechanical valve in patients <65 years of age is no longer as firm, and bioprosthetic valve use has increased in younger patients.

- **Mechanical**
  - Ball-and-cage (Starr-Edwards): rarely, if ever, used today
  - Bileaflet (i.e., St. Jude, Carbomedics): most commonly used
  - Single tilting disk (i.e., Björk-Shiley, Medtronic Hall, Omnicarbon)

- **Advantages:** structurally stable, long lasting, relatively hemodynamically efficient (particularly bileaflet)
- **Disadvantages:** need for anticoagulation, risk of bleeding, risk of thrombosis/embolism despite anticoagulation, severe hemodynamic compromise if disk thrombosis or immobility occurs (single tilting disk), risk of endocarditis

- **Bioprosthetic**
  - Porcine aortic valve tissue (i.e., Hancock, Carpentier-Edwards)
  - Bovine pericardial tissue (i.e., Carpentier-Edwards Perimount)
  - **Advantages:** no need for anticoagulation, low thromboembolism risk, low risk of catastrophic valve failure
  - **Disadvantages:** structural valve deterioration, imperfect hemodynamic efficiency, risk of endocarditis, still a small risk (0.7% per year) of thromboembolism without anticoagulation
- **Homograft (cadaveric)**

  Rarely used for atrioventricular surgery; most commonly used to replace the pulmonic valve

TREATMENT

- **AHA/ACC recommendations for anticoagulation for prosthetic valves**
  - Anticoagulation with a vitamin K antagonist and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve (class I).
  - Anticoagulation with a vitamin K antagonist to achieve an INR of 2.5 is recommended in patients with a mechanical AVR (bileaflet or current-generation single tilting disk) and no risk factors for thromboembolism (class I).

  - Anticoagulation with a vitamin K antagonist is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older generation mechanical AVR (such as ball-in-cage) (class I).
  - Anticoagulation with a vitamin K antagonist is indicated to achieve an INR of 3.0 in patients with a mechanical MV replacement (class I).
  - Aspirin 75-100 mg daily is recommended in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis (class I).
  - Aspirin 75-100 mg daily is reasonable in all patients with a bioprosthetic aortic valve or MV (class IIa).
  - Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should **not** be used in patients with mechanical valve prostheses (class III).
- **AHA/ACC recommendations for bridging therapy for prosthetic valves**
  - Continuation of vitamin K antagonist anticoagulation with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures (i.e., dental extractions) where bleeding is easily controlled (class I).
  - Temporary interruption of vitamin K antagonist anticoagulation, without bridging agents while the INR is subtherapeutic, is recommended in patients with bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures (class I).
  - Bridging anticoagulation with either IV unfractionated heparin or SC low-molecularweight heparin is

recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with mechanical AVR and any thromboembolic risk factor, older generation mechanical AVR, or mechanical MV replacement (class I).

7
Cardiac Arrhythmias

Daniel H. Cooper
Mitchell N. Faddis

TACHYARRHYTHMIAS

Approach to Tachyarrhythmias

GENERAL PRINCIPLES

- Tachyarrhythmias are commonly encountered in the inpatient setting.
- Recognition and analysis of these rhythms in stepwise manner will facilitate initiation of appropriate therapy.
- Clinical decision making is guided by patient symptoms and signs of hemodynamic stability.

Definition

Cardiac rhythms whose ventricular rate exceeds **100 beats per minute** (bpm).

Classification

Tachyarrhythmias are broadly classified based on the width of the QRS complex on the ECG.

- Narrow-complex tachyarrhythmia (QRS <120 msec): Arrhythmia (supraventricular tachycardia) originates within the atria and rapidly activates the ventricles via the His-Purkinje system.
- Wide-complex tachyarrhythmia (QRS ≥120 msec): Arrhythmia originates outside the normal conduction system (ventricular tachycardia [VT]) or travels via an abnormal His-Purkinje system (supraventricular tachycardia with aberrancy) activating the ventricles in an abnormally slow manner.

Etiology

Mechanism divided into disorders of **impulse conduction** and **impulse formation**:

- **Disorders of impulse conduction:** Reentry is the most common mechanism of tachyarrhythmias. A reentrant mechanism can occur when differential refractory periods and conduction velocities allow for propagation of an activation wavefront in a unidirectional manner around a zone of scar or refractory cardiac tissue. Reentry of the activation wavefront around a myocardial circuit sustains the arrhythmia (e.g., VT).
- **Disorders of impulse formation: Enhanced automaticity** (e.g., accelerated junctional and accelerated idioventricular rhythm) **and triggered activity** (e.g., long QT syndrome and digitalis toxicity) are other less common mechanisms of tachyarrhythmias.

DIAGNOSIS

Clinical Presentation

- Tachyarrhythmias often produce symptoms that lead to patient presentation at an outpatient or acute care setting.
- They can be associated with systemic illnesses in patients who are being evaluated in the emergency department or are being treated in an inpatient setting.

History

- Symptoms generally guide clinical decision making.
- **Dyspnea, angina, lightheadedness or syncope, and decreased level of consciousness** are severe symptoms that mandate urgent treatment.
- Baseline symptoms that reflect **poor left ventricular (LV) function**, such as dyspnea on exertion (DOE), orthopnea, paroxysmal nocturnal dyspnea (PND), and lower extremity swelling, are critical to elucidate.
- **Palpitations:** Common symptom of tachyarrhythmias. The pattern of onset and termination is useful to suggest the presence of a primary arrhythmia. Sudden onset and termination is highly suggestive of a tachyarrhythmia.
- Termination of palpitations with breath holding or the Valsalva maneuver is suggestive of a supraventricular tachyarrhythmia.
- History of **organic heart disease** (i.e., ischemic, nonischemic, valvular cardiomyopathy) or **endocrinopathy** (i.e., thyroid disease, pheochromocytoma) should be sought.
- History of **familial or congenital causes of arrhythmias** such as hypertrophic cardiomyopathy (HCM), long QT syndrome, or other congenital heart disease should be addressed as well.
  - **Hypertrophic obstructive cardiomyopathy** (HOCM) is associated with atrial arrhythmias (atrial fibrillation [AF] in 20-25%), as well as malignant ventricular arrhythmias.
  - **Mitral valve prolapse** (MVP) is associated with supraventricular and ventricular arrhythmias.
- **Medications history should be carefully taken**, including over-the-counter and herbal medications, to assess a possible causal link.

Physical Examination

- Signs of clinical stability or instability, including vital signs, mental status, peripheral perfusion, etc., are critical in guiding initial decision making.
- If clinically stable, then physical exam should be focused on determining underlying cardiovascular abnormalities that may make certain rhythms more or less likely.
- Findings of **congestive heart failure (CHF)**, including elevated jugular venous pressure (JVP), pulmonary rales, peripheral edema, and S_3 gallop, make the diagnosis of malignant ventricular arrhythmias more likely.
- If arrhythmia is sustained, here are some special considerations during physical exam:

- **Palpate the pulse** and assess for rate and regularity.
  - If rate is about 150 bpm, suspect atrial flutter (AFl) with 2:1 block.
  - If pulse is irregular with no pattern, suspect AF.
  - Irregular pulse with a discernible pattern (group beating) suggests the presence of second-degree heart block.
- **"Cannon" A waves:** Revealed on inspection of JVP reflect atrial contraction against a closed tricuspid valve. If irregular, then suggestive of underlying atrioventricular (AV) dissociation and possible presence of VT.
- If regular in 1:1 ratio with peripheral pulse, then suggestive of AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), or a junctional tachycardia, all leading to retrograde atrial activation occurring simultaneously with ventricular contraction.

Diagnostic Testing

Laboratories

Serum electrolytes, complete blood count (CBC), thyroid function tests, serum concentration of digoxin (when applicable), and a urine toxicology screen should be considered for all patients.

Electrocardiography

- **A 12-lead ECG, in the presence of the rhythm abnormality and in normal sinus rhythm,** is the most useful initial diagnostic test.
- If the patient is clinically stable, obtain a 12-lead ECG and a **continuous rhythm strip** with leads that best demonstrate atrial activation (e.g., V_1, II, III, aVF).
- Examine the ECG for evidence of conduction abnormalities, such as preexcitation or bundle branch block, or signs of structural heart disease such as prior myocardial infarction (MI).
- Comparison of the ECG obtained during arrhythmia with that at baseline can highlight subtle features of the QRS deflection that indicate the superposition of atrial and ventricular depolarization.
- Rhythm strip is very useful to document the response to interventions (e.g., vagal maneuvers, antiarrhythmic drug therapy, or electrical cardioversion).

Imaging

Chest radiographs and **transthoracic echocardiograms** can help provide evidence of structural heart disease that may make ventricular arrhythmias more likely.

Diagnostic Procedures

- **Continuous ambulatory ECG monitoring**
  - One or more days; useful for documenting symptomatic transient arrhythmias that occur with sufficient frequency.
  - Recording mode useful for assessment of patient's heart rate response to daily activities or antiarrhythmic drug treatment.
  - Correlation between patient-reported symptoms in a time-marked diary and heart rhythm recordings is the key to determining if symptoms are attributable to an arrhythmia.
- **In-hospital telemetry monitoring**

  Mainstay of surveillance monitoring during the course of hospitalization for cardiac arrhythmia patients who are seriously ill or are having life-threatening arrhythmias.
- **Event recorders**
  - Weeks to months; useful for documenting symptomatic transient arrhythmias that occur infrequently.
  - A "loop recorder" is worn by the patient and continuously records the ECG. When activated by the patient or via an autodetection feature, the ECG recording is saved with several minutes of preceding rhythm data.
  - An **implantable loop recorder or insertable loop recorder (ILR)** is a subcutaneous monitoring device used to provide an automated or patient-activated recording of significant arrhythmic events that occur very infrequently over many months or used for patients who are unable to activate external recorders.
- **Exercise ECG**

  Useful for studying exercise-induced arrhythmias or to assess the sinus node response to exercise.
- **Electrophysiology study (EPS)**
  - Invasive, catheter-based procedure that is used to study a patient's susceptibility to arrhythmias or to investigate the mechanism of a known arrhythmia.
  - EPS is also combined with catheter ablation for curative treatment of many arrhythmia mechanisms.
  - The efficacy of EPS to induce and study arrhythmias is highest for reentrant mechanisms.

TREATMENT

Please refer to the treatment of individual tachyarrhythmias for hemodynamically stable patients and advanced cardiac life support (ACLS) algorithm for tachycardias in Appendix C.

Supraventricular Tachyarrhythmias

GENERAL PRINCIPLES

- **Supraventricular tachyarrhythmias (SVTs)** are often recurrent, rarely persistent, and a frequent cause of visits to emergency departments and primary care physician offices.
- The evaluation of patients with SVT should always begin with prompt assessment of hemodynamic stability and clinical "substrate."

- The diagnostic and therapeutic discussion that follows is aimed at the hemodynamically stable patient. If a patient is deemed clinically unstable based on clinical signs and symptoms, one should immediately proceed to cardioversion per ACLS guidelines.

Definition

- Tachyarrhythmias that require atrial or AV nodal tissue, or both, for their initiation and maintenance are termed SVT.
- The QRS complex in most SVTs is narrow (QRS <120 msec). However, they can certainly present as a wide-complex tachycardia (QRS ≥120 msec) in SVT with aberrancy or an accessory pathway-mediated tachycardia.

Classification

- SVT is initially classified by ECG appearance in an effort to understand the likely underlying arrhythmia mechanism.
- A diagnostic approach, based on the ECG, is summarized in Figure 7-1.

Epidemiology

Published incidence data vary widely between studies, and the prevalence of asymptomatic episodes is not known.

DIAGNOSIS

A general understanding of the prevalence of various arrhythmia mechanisms is useful to guide evaluation of an individual patient.

- **AF** is the most common narrow-complex tachycardia seen in the inpatient setting. **AFl** can often accompany AF and is diagnosed one-tenth as often as AF but is twice as prevalent as the paroxysmal SVTs. The other atrial tachyarrhythmias are far less common.
- In one case series, **AVNRT** was reported as the most common diagnosis of the paroxysmal SVTs (60%), followed by AVRT (30%) (*Crit Care Med 2000;28(10 suppl):N129*).
- However, if the patient is younger than age 40, then AVRT, often in the context of Wolff-Parkinson-White (WPW) syndrome, is the most common arrhythmia mechanism.

Clinical Presentation

The clinical presentation for SVT is similar to tachyarrhythmias in general and has been previously outlined in this section.

Differential Diagnosis

- **AF**

  The most common sustained tachyarrhythmia and discussed as a separate topic in this section.
- **AFl**
  - AFl is the second most common atrial arrhythmia, with an estimated 200,000 new cases in the United States annually, and is associated with increasing age, underlying heart disease, and male gender (*J Am Coll Cardiol 2000;36:2242*).
  - AFl usually presents as a **regular rhythm** but can be **irregularly irregular** when associated with variable AV block (2:1 to 4:1 to 3:1, etc.).

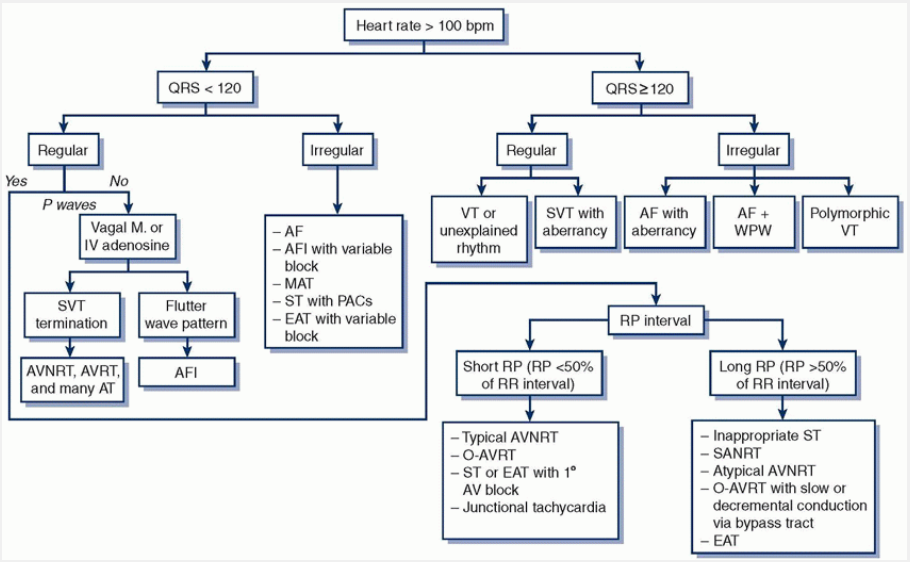


Figure 7-1. Diagnostic approach to tachyarrhythmias. AF, atrial fibrillation; AFl, atrial flutter; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; EAT, ectopic atrial tachycardia; MAT, multifocal atrial tachycardia; O-AVRT, orthodromic AVRT; PAC, premature atrial complex; SANRT, sinoatrial nodal reentrant tachycardia; ST, sinus tachycardia; SVT, supraventricular tachyarrhythmia; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White; AT, atrial tachycardia.

  - **Mechanism:** Reentrant circuit usually within the right atrium around the perimeter of the tricuspid valve. This form of AFl is called "typical" AFl. Atrial rate is 250-350 bpm with conduction to ventricle that is usually not 1:1, but most often 2:1. **(SVT with regular ventricular rate of 150 bpm should raise suspicion for AFl.)**
  - AFl commonly coexists with AF and is associated with the same risk factors (obesity, hypertension, diabetes mellitus, and obstructive sleep apnea).
  - **ECG:** In typical AFl, "saw tooth" pattern best visualized in leads II, III, and aVF with negative deflections in V_1.

- **Multifocal atrial tachycardia (MAT)**
  - **Irregularly irregular** SVT seen generally in elderly hospitalized patients with multiple comorbidities.
  - MAT is most often associated with chronic obstructive pulmonary disease (COPD) and heart failure but also associated with glucose intolerance, hypokalemia, hypomagnesemia, drugs (e.g., theophylline), and chronic renal failure.
  - **ECG:** SVT with at least **three distinct P-wave morphologies**, generally best visualized in leads II, III, and V_1.
- **Sinus tachycardia (ST)**
  - ST is the most common mechanism of **long RP tachycardia**.
  - Usually, ST is a normal physiologic response to hyperadrenergic states (fever, pain, hypovolemia, anemia, hypoxia, etc.) but can also be induced by illicit drugs (cocaine, amphetamines, methamphetamine) and prescription drugs (theophylline, atropine, β-adrenergic agonists).
  - **Inappropriate ST** refers to persistently elevated sinus rate in the absence of an identifiable physical, pathologic, or pharmacologic influence.
- **Ectopic atrial tachycardia (EAT)**
  - EAT with variable block can present as an **irregularly irregular** rhythm and can be distinguished from AFl by an **atrial rate of 150-200 bpm**.
  - EAT with variable block is associated with **digoxin toxicity**.
  - EAT is characterized by a regular atrial activation pattern with a P-wave morphology originating outside of the sinus node complex resulting in a **long RP tachycardia**.
  - **Mechanism:** Enhanced automaticity, triggered activity, and possibly microreentry.
- **AVNRT**
  - This reentrant rhythm requires functional dissociation of the AV node into two pathways with antegrade conduction down the "slow" pathway and retrograde conduction up the "fast" pathway. AVNRT can occur at any age, with a predilection for **middle age** and **female gender**. AVNRT is not correlated with structural heart disease.

    "Typical" AVNRT is a major cause of **short RP tachycardia**. **ECG appearance has characteristic absent P waves** because atrial activation is coincident with the QRS complex. Commonly, atrial activation can occur at the terminal portion of the QRS to create a pseudo-r' (V_1) or pseudo-s' (II) compared to the sinus rhythm QRS.
  - **"Atypical" AVNRT**
    - Less common; antegrade conduction proceeds down the fast AV nodal pathway with retrograde conduction up the slow AV nodal pathway, leading to a **long RP tachycardia**.
    - **ECG:** The retrograde P wave is inscribed well after the QRS complex in the second half of the RR interval.
- **AVRT**
  - **Orthodromic AVRT (O-AVRT)** is the most common AVRT, accounting for about 95% of all AVRT.
    - Accessory pathway-mediated reentrant rhythm with antegrade conduction to the ventricle down the AV node and retrograde conduction to the atrium up an accessory or "bypass" tract, leading to a **short RP tachycardia**.
    - **ECG:** Retrograde P waves are frequently seen after the QRS complex and are usually distinguishable from the QRS (i.e., separated by >70 msec).

    - O-AVRT is the most common mechanism of SVT in patients with WPW syndrome who have preexcitation (defined by short PR and a delta wave on upstroke of QRS) present on sinus rhythm ECG.
    - O-AVRT can occur without preexcitation when conduction through the bypass tract occurs only during tachycardia in a retrograde fashion ("concealed pathway").
    - Less commonly, retrograde conduction over the accessory pathway to the atrium proceeds slowly enough for atrial activation to occur in the second half of the RR interval, leading to a **long RP tachycardia**. The associated incessant tachycardia can cause tachycardia-induced cardiomyopathy.
  - **Antidromic AVRT:** This reentrant form of SVT occurs when conduction to the ventricle is down an accessory bypass tract with retrograde conduction through the AV node or a second bypass tract.
    - **ECG:** The QRS seems consistent with VT; however, the presence of preexcitation on the baseline QRS should be diagnostic for WPW syndrome.
    - Antidromic AVRT is seen in <5% of patients with WPW syndrome.
- **Junctional tachycardia**
  - Due to enhanced automaticity of the AV junction. The electrical impulses conduct to the ventricle and atrium simultaneously, similar to typical AVNRT, so that the retrograde P waves are frequently concealed in the QRS complex.
  - Uncommon in adults.
  - Common in young children, particularly after cardiac surgery.
- **Sinoatrial nodal reentrant tachycardia (SANRT)**
  - Reentrant circuit is localized at least partially within the sinoatrial node.
  - Abrupt onset and termination, triggered by a premature atrial complex.
  - **ECG:** P-wave morphology and axis are identical to the native sinus P wave during normal sinus rhythm.

TREATMENT

- Please refer to Table 7-1 for general therapeutic approach to common SVTs.
- Acute treatment of symptomatic SVT should follow the **ACLS protocol** as outlined in Appendix C.
- Chronic treatment is guided by the severity of associated symptoms, the frequency, and the duration of recurrent events.

- Many SVTs can be terminated by **AV nodal blocking agents or techniques** (Table 7-2), whereas AF, AFl, and some atrial tachycardias will persist with a slowing of the ventricular rate due to partial AV nodal blockade.
- **Radiofrequency ablation (RFA):** Definitive cure with high success rates from 85-95% for many SVTs, including AVNRT, accessory bypass tract-mediated tachycardias, focal atrial tachycardia, and AFl. Complication risk is generally <1%. This risk includes major bleeding, cardiac perforation or tamponade, stroke, pulmonary embolism, and complete heart block requiring permanent pacemaker (PPM).
- There is limited evidence, but no large randomized trials with long-term follow-up, that suggests catheter ablation compared to antiarrhythmic therapy improves quality of life and is more cost-effective in the long term (*Am J Cardiol 1998;82:589*).

Atrial Fibrillation

GENERAL PRINCIPLES

The medical management of **AF** requires careful consideration of three issues: **rate control, prevention of thromboembolic events, and rhythm control**.

TABLE 7-1 Treatment of Common Supraventricular Tachyarrhythmias

Treatment Strategies	
Atrial flutter (AFl)	Anticoagulation similar to AF; risk of thromboembolic complications is similar. Rate control with same agents as AF. If highly symptomatic or rate control difficult, electrical or chemical cardioversion is appropriate. If pacemaker present, overdrive atrial pacing can achieve cardioversion. Catheter ablation of typical right AFl with long-term success above 90% and rare complications.
Multifocal atrial tachycardia (MAT)	Therapy targeted at treatment of underlying pathophysiologic process. Maintain potassium and magnesium electrolyte balance. Antiarrhythmic, if symptomatic rapid ventricular response. Individualize β-adrenergic blockers vs. calcium channel blocker therapy. DC cardioversion is not effective.
Sinus tachycardia (ST)	Therapy targeted at treatment of underlying pathophysiologic process.
Ectopic atrial tachycardia (EAT)	**Acute therapy:** Identify and treat precipitating factors like digoxin toxicity; if hemodynamically stable, then β-blockers and calcium channel blockers. In rare cases, amiodarone, flecainide, or sotalol. **Chronic therapy:** Rate control with β-adrenergic blockers and calcium channel blockers. If unsuccessful, options include catheter ablation (86% success rate), flecainide, propafenone, sotalol, or amiodarone.
AV nodal reentrant tachycardia (AVNRT)	Catheter ablation highly successful (96%) but has to be individualized to each patient. If medical therapy more desirable—β-adrenergic blockers, calcium channel blockers, and digoxin; then consider propafenone, flecainide, etc.
Orthodromic AV reentrant tachycardia (O-AVRT)	**Acute therapy:** Vagal maneuvers, adenosine, calcium channel blockers. If ineffective, then procainamide or β-blockers. **Chronic suppressive therapy:** Catheter ablation highly successful (95%) but has to be individualized to each patient. If medical therapy more desirable for prevention, flecainide and procainamide are indicated.
Antidromic AV reentrant tachycardia (A-AVRT)	**Acute therapy:** Avoid adenosine or other AV node-specific blocking agents. Consider ibutilide, procainamide, or flecainide. **Chronic suppressive therapy:** Accessory pathway catheter ablation is preferred and successful (95%). If medical therapy desired, consider flecainide and propafenone.

AF, atrial fibrillation; AV, atrioventricular; DC, direct current.

From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines. *J Am Coll Cardiol* 2003;42:1493.

TABLE 7-2 Common Vagal Maneuvers and Adenosine

	Patient Preparation[a]	Mechanism	Dose/Duration/Details	Toxicity	Contraindication	Potentiators/Antagonists	Common Side Effects
Valsalva	Describe the procedure.	Vagal stimulation during relaxation phase.	Exhale forcefully against a closed airway for several seconds followed by relaxation.	Well tolerated.	Patient unable to follow commands.	—	—

Carotid sinus massage	Check for carotid bruits and history of CVA; then place in recumbent position with neck extended.	Vagal stimulation.	First, apply enough pressure to simply feel carotid pulse with index and middle fingers. If no effect, then use rotating motion for 3-5 s.	Well tolerated. Risk of embolizing carotid plaque. **Never massage both carotids.**	Recent TIA or stroke, or ipsilateral significant carotid artery stenosis or carotid artery bruit.	—	—
Adenosine	Explain the potential side effects to the patient.	AV nodal blocking agent. Short-acting (serum half-life 4-8 min).	Initial: 6 mg IV rapid bolus via antecubital vein, followed by 10-30 mL saline flush. If desired or effect not achieved, can repeat 12 mg followed by 12 mg after 1- to 2-min intervals. Central venous line: 3 mg IV initial dose.	Precipitate prolonged asystole in patients with sick sinus syndrome or second- or third-degree AV block.	Significant bronchospasm.	Potentiators: Dipyridamole and carbamazepine. **Effect pronounced in heart transplant recipients.** Antagonists: Caffeine and theophylline.	Facial flushing, palpitations, chest pain, hypotension, exacerbation of bronchospasm.

AV, atrioventricular; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and many atrial tachycardias will terminate with vagal maneuvers or adenosine, and in atrial flutter, the appearance of flutter waveform will help diagnosis.

Water immersion, eyeball pressure, coughing, gagging, deep breathing, etc., are other alternative vagal maneuvers.

[a]Patients should be under continuous ECG monitoring for each of these procedures. To enhance diagnostic value of rhythm strip, use leads V_1 and II (atrial activity).

Definition

AF is an atrial tachyarrhythmia characterized by chaotic activation of the atria with loss of atrial mechanical function. AF has a pattern on 12-lead ECG characterized by the absence of consistent P waves. Instead, rapid, low-amplitude oscillations or fibrillatory waves are noted in the baseline of leads that best demonstrate atrial activation (V_1, II, III, aVF). The ventricular response to AF is characteristically irregular and often rapid in the presence of intact AV conduction. AF is the most common cardiac arrhythmia.

Classification

AF has been classified into four forms based on the clinical presentation: first occurrence, paroxysmal, persistent, and permanent forms.

- **First occurrence** may be symptomatic or asymptomatic. The spontaneous conversion rate is high, measured >60% in hospitalized patients.
- **Paroxysmal** AF describes a recurrent form of AF in which individual episodes are <7 days and usually <48 hours in duration.
- **Persistent** AF describes a recurrent form of AF in which individual episodes are >7 days in duration or require electrical cardioversion to terminate.
- **Longstanding persistent** AF describes the form of AF that has failed attempts at cardioversion, electrical or pharmacologic, or has been accepted due to contraindications for cardioversion or a lack of symptoms.

Epidemiology

- AF is the most common sustained tachyarrhythmia for which patients seek treatment and the most likely etiology for an irregularly irregular rhythm discovered on an inpatient ECG. AF is typically a disease of the elderly, affecting >10% of those >75 years old.
- Independent risk factors for AF, in addition to advanced age, include male sex, diabetes mellitus, cardiovascular disease such as CHF, valvular heart disease, hypertension (HTN), and previous MI (*JAMA 1994;271:840*). Below age 65, obesity and obstructive sleep apnea are important risk factors for new-onset AF (*J Am Coll Cardiol 2007;49(5):565*). Although clinical hyperthyroidism is associated with new-onset AF, the prevalence is low in a population of patients with AF (*J Epidemiol 2008;18(5):209*).
- Following cardiothoracic surgery, AF occurs in 20-50% of patients (*J Am Coll Cardiol 2006;48(4):8540*).

Pathophysiology

The precise mechanisms giving rise to AF are incompletely understood. The initiation of AF is commonly due to rapid, repetitive firing of an ectopic focus within the pulmonary veins with fibrillatory conduction to the bodies of the atria. The maintenance of persistent AF likely requires multiple reentrant circuits varying in location and timing to explain the self-perpetuating characteristic of AF. Structural and electrical remodeling of the left atrium associated with cardiovascular disease promotes ectopic activity and heterogeneous conduction patterns that provide the substrate for AF. AF, when present, also promotes structural and electrical remodeling in the atria that stabilizes the rhythm. Inflammation and fibrosis may play a major role in initiation and maintenance of AF. Inflammatory markers, such as interleukin-6 and C-reactive protein, are raised in AF and correlate with the duration of AF, success of cardioversion, and thrombogenesis.

Prevention

- Currently, there is a lack of prospective clinical trials that examine the value of primary prevention of non-postoperative AF through treatment of associated conditions or risk factor modification. Some analyses suggest that statins may reduce recurrent AF by 61%, independent of their lipid-lowering effect (*J Am Coll Cardiol 2008;51:828*). Angiotensin-converting

P.195

enzyme **(ACE)** inhibitors and angiotensin receptor blockers **(ARBs)** have been shown to prevent atrial remodeling in animals via suppression of the renin-angiotensin system. A meta-analysis of patients with CHF and HTN treated with either ACEIs or ARBs demonstrated a reduction in new-onset AF by 20-30% (*J Am Coll Cardiol 2005;45:1832*).

- A number of pharmacologic and nonpharmacologic strategies have been evaluated to prevent postoperative AF. Perioperative continuation of **β-adrenergic antagonists** has been shown to reduce postoperative AF rates. **Amiodarone, sotalol, magnesium, and omega-3 fatty acids** used in the perioperative period have demonstrated a reduction in postoperative AF (*Ann Pharmacother 2007;41:587*).

DIAGNOSIS

AF is diagnosed by 12-lead ECG with a stereotypical pattern of an irregularly fluctuating baseline with an irregular, and often rapid, ventricular rate (>100 bpm). AF should be distinguished from other tachycardia mechanisms with an irregular ventricular response such as MAT and AFl with variable conduction.

Clinical Presentation

Symptoms associated with AF can range from severe (acute pulmonary edema, palpitations, angina, syncope) to nonspecific (fatigue) to none at all. Symptoms are usually secondary to the rapid ventricular response to AF rather than the loss of atrial systole. However, patients with significant ventricular systolic or diastolic dysfunction can have symptoms directly attributable to the loss of atrial systole. Prolonged episodes of tachycardia due to AF may lead to a **tachycardia-induced cardiomyopathy**.

TREATMENT

The medical management of AF is directed at three therapeutic goals: **rate control, prevention of thromboembolic events, and rhythm control** through maintenance of sinus rhythm. Previous studies have shown that there is no mortality advantage to a management strategy aimed at maintaining sinus rhythm (*N Engl J Med 2002;347:1825*). Therefore, rate control and management of thromboembolic risk are the preferred strategy in minimally symptomatic patients. Rhythm control is reserved for patients who remain symptomatic despite reasonable efforts at pharmacologic rate control.

Medications

Medical management begins with consideration of appropriate antithrombotic therapy. Warfarin has been shown to be consistently superior to aspirin (ASA) or ASA in combination with clopidogrel for prevention of thromboembolus. The novel oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban have been directly compared to warfarin in randomized prospective trials that documented a lower rate of stroke and systemic emboli compared to warfarin. Rate control of the ventricular response to AF is achieved with medications that limit conduction through the AV node such as **verapamil, diltiazem, β-adrenergic antagonists, and digoxin**. Rhythm control through maintenance of sinus rhythm can be attempted with selected antiarrhythmic drugs. Pharmacologic control with antiarrhythmic drugs is most effective at preventing recurrence of AF and less effective at chemical cardioversion of AF (Table 7-3).

First Line

- **Prevention of stroke and systemic emboli** is a central tenet of AF management guided by individual risk assessment in each patient. Systemic anticoagulation with warfarin or an NOAC will attenuate the risk of stroke or systemic emboli associated with AF; however, the use of any one of these agents requires a careful risk-benefit analysis to identify

P.196

P.197

P.198

patients who are at sufficient risk for thromboembolic events to outweigh the increased risk of hemorrhagic complications.

TABLE 7-3 Pharmacologic Agents Used for Heart Rate Control in Atrial Fibrillation

Drug	Loading Dose	Onset of Action	Maintenance Dose	Major Side Effects	Recommendation
Without evidence of accessory pathway					
Esmolol[a]	IV: 0.5 mg/kg over 1 min	5 min[b]	0.06-0.2 mg/kg/min	↓BP, ↓HR, HB, HF, bronchospasm	I
Metoprolol[a]	IV: 2.5-5.0 mg bolus over 2 min (up to three doses) PO: Same as maintenance	5 min	NA 25-100 mg bid	↓BP, ↓HR, HB, HF, bronchospasm	I
Propranolol[a]	IV: 0.15 mg/kg	4-6 h 5 min	NA	↓BP, ↓HR, HB, HF, bronchospasm	I
	PO: Same as	60-90	80-240 mg/d in		

	maintenance	min	divided doses		
Diltiazem	IV: 0.25 mg/kg over 2 min PO: Same as maintenance	2-7 min 2-4 h	5-15 mg/h 120-360 mg/d in divided doses; slow release available	↓BP, HB, HF	I
Verapamil	IV: 0.075-0.15 mg/kg over 2 min	3-5 min 1-2 h	NA	↓BP, HB, HF	I
	PO: Same as maintenance		120-360 mg/d in divided doses; slow release available		
With evidence of accessory pathway[c]					
Amiodarone	IV: 150 mg over 10 min	Days	1 mg/min × 6 h, then 0.5 mg/min	See below	IIa
In patients with heart failure and without accessory pathway					
Digoxin	IV: 0.25 mg q2h, up to 1.5 mg	60 min or more	0.125-0.375 mg/d IV or orally	Digoxin toxicity, HB, ↓HR	I
Amiodarone[d]	PO: 0.5 mg/d IV: 150 mg over 10 min PO: 800 mg/d for 1 wk, 600 mg/d for 1 wk, 400 mg/d for 1 wk,	2 days Days 1-3 wk	1 mg/min × 6 h, then 0.5 mg/min 100-400 mg PO daily	↓BP, HB, ↓HR, warfarin interaction; see text for description of dermatologic, thyroid, pulmonary, corneal, and liver side effects	Acute setting: IIa (IV) Nonacute/chronic: IIb (PO)

↓BP, hypotension; ↓HR, bradycardia; HB, heart block; HF, heart failure; NA, not applicable.

[a]Only representative β-blockers are included in the table, but other similar agents could be used for this indication in appropriate doses.

[b]Onset is variable, and some effects occur earlier.

[c]Conversion to sinus rhythm and catheter ablation of the accessory pathway are generally recommended; pharmacologic therapy for rate control may be appropriate therapy in certain patients. See text for discussion of atrial fibrillation in setting of preexcitation/Wolff-Parkinson-White syndrome.

[d]Amiodarone can be useful to control the heart rate in patients with atrial fibrillation when other measures are unsuccessful or contraindicated.

Adapted from Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *Circulation* 2006;114:e257-e354.

- The **CHA_2DS_2-VASc score** is a validated, risk stratification tool in nonvalvular AF that predicts stroke or systemic embolus risk based on the presence of the following risk factors: **C**HF, **H**TN, **a**ge >65 or >75 years, **d**iabetes mellitus, female **s**ex, prior **s**troke/transient ischemic attacks (TIAs), and history of **v**ascular disease (Table 7-4).
- Antithrombotic therapy can be omitted in patients with a **CHA_2DS_2-VASc score = 0.**
- In patients with a **CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or ASA may be considered.**
- Systemic anticoagulation with warfarin or an NOAC is recommended for patients with a CHA_2DS_2-VASc risk of ≥2 and no contraindications for anticoagulation.
- Measurement of renal function is critical to assess the safety and dosing of NOACs in patients with a **CHA_2DS_2-VASc score of ≥2 and chronic kidney disease.**
- The role of antithrombotic therapy leading up to and after restoration of sinus rhythm is discussed in the following text in the context of cardioversion.

- **Rate control** of AF can be achieved with drugs that prolong conduction through the AV node. These include the nondihydropyridine calcium channel blockers (diltiazem, verapamil), β-adrenergic blockers, and digoxin. Refer to Table 7-3 for loading and dosing recommendations.
  - **Digoxin** is useful in controlling the resting ventricular rate in AF in the setting of LV dysfunction and CHF. Its utility in other clinical settings is limited by reduced efficacy of rate control during exertion. **Digitalis toxicity** is characterized by symptoms of **nausea, abdominal pain, vision changes, confusion, and delirium**. Patients with renal

dysfunction are at high risk as are patients on agents known to increase digoxin levels (e.g., verapamil, diltiazem, erythromycin, cyclosporine). **Paroxysmal atrial tachycardia with varying degrees of AV block and bidirectional VT** are the most commonly seen arrhythmias in association with digitalis toxicity. Treatment is supportive, by withholding the drug, insertion of temporary pacemakers for AV block, and **IV phenytoin for bidirectional VT**.

TABLE 7-4 Annual Stroke Risk in Patients with Nonvalvular Atrial Fibrillation Not Treated with Anticoagulation According to the CHA_2DS_2-VASc Score

CHA_2DS_2-VASc Score	Stroke Risk (%)[a]
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	12.5
9	15.2

CHA_2DS_2-VASc, cardiac failure, hypertension, age 65-74 or age >74 (doubled), diabetes, female sex, stroke (doubled), and a history of vascular disease.

[a]The adjusted stroke rate was derived from multivariate analysis assuming no aspirin usage.

Adapted from Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factorbased approach: The Euro Heart Survey on atrial fibrillation. *Chest* 2010;137:263-72.

- **Nonpharmacologic rate control** of AF can be accomplished by AV nodal ablation in association with PPM implantation. This strategy should be reserved for patients who have failed pharmacologic rate control and in whom rhythm control is either ineffective or contraindicated.

Second Line

Rhythm control of AF is accomplished pharmacologically with antiarrhythmic drugs that modify impulse formation or propagation to prevent initiation of AF. Antiarrhythmic drugs are less effective at restoration of sinus rhythm through **pharmacologic cardioversion**. **The risk of thromboembolus associated with a pharmacologic cardioversion should be considered before beginning antiarrhythmic drug therapy.** Guidelines for anticoagulation are discussed in the following text:

- **Pharmacologic cardioversion** should be done in the hospital setting with continuous ECG monitoring because of a small risk of life-threatening tachyarrhythmias or bradyarrhythmias. **Ibutilide** is the only drug that is approved by the U.S. Food and Drug Administration for pharmacologic cardioversion. Clinical trials have shown a 45% conversion rate for AF and a 60% conversion rate for AFl. Ibutilide is associated with a 4-8% risk for torsades de pointes (TdP), especially in the first 2-4 hours after administration of the drug. Because of this risk, patients must be monitored on telemetry with an external defibrillator immediately available during ibutilide infusion and for at least 4 hours after the infusion. The risk for TdP is higher in patients with cardiomyopathy and CHF. Ibutilide is given via an IV, at a dosage of 1 mg (0.01 mg/kg if patient is <60 kg), **infused slowly over 10 minutes**. Faster administration can promote TdP. The efficacy of antiarrhythmics to achieve pharmacologic conversion drops sharply when AF is >7 days in duration. For shorter duration AF episodes, dofetilide, sotalol, flecainide, and propafenone have some efficacy, whereas amiodarone has limited efficacy to achieve pharmacologic cardioversion.
- **Maintenance of sinus rhythm** with antiarrhythmic agents is associated with a small risk for life-threatening proarrhythmia. As a result, antiarrhythmic therapy should be reserved for patients who have highly symptomatic AF despite adequate rate control. Commonly used antiarrhythmic agents, their major route of elimination, and dosing regimens are listed in Table 7-5. The most effective agents for maintenance of sinus rhythm are flecainide, propafenone, sotalol, dofetilide, amiodarone, and dronedarone.
  - **Flecainide** and **propafenone** can be considered for maintenance of sinus rhythm in patients with **structurally normal hearts**. In patients with structural heart disease, these agents are associated with an increased mortality rate (*N Engl J Med 1989;321:406*), and both agents are potent negative inotropes that can provoke or exacerbate heart failure. Both agents prolong the QRS duration as an early manifestation of toxicity. Toxicity increases with heart rate due to preferential blockade of active sodium channels. This property is described as **positive use dependence**. Exercise ECG can be used to give additional information about dose safety at higher heart rates. Flecainide should be used with caution without concomitant dosing with an AV nodal blocker because a paradoxical increase in the ventricular rate may occur due to drug-induced conversion of AF to AFl. Propafenone is less prone to this phenomenon due to intrinsic β-adrenergic antagonism.
  - **Sotalol** is useful for the maintenance of sinus rhythm. Sotalol is a mixture of stereoisomers (DL-); D-sotalol is a potassium channel blocker, whereas L-sotalol is a β-antagonist.

P.200

P.201

P.202

Side effects reflect both mechanisms of action. In addition to QT interval prolongation leading to TdP, DL-sotalol may result in sinus bradycardia or AV conduction abnormalities. Sotalol should not be used in patients with decompensated CHF (due to the negative inotropic effect) or with a prolonged QT interval.

Initiation of sotalol should be done in an inpatient monitored setting.

TABLE 7-5 Commonly Used Antiarrhythmic Drugs

Class	Drug	Route of Administration (Elimination)	Initial/Loading Dose	Maintenance Dose	Major Adverse Effects[a]/Comments
Ia	Procainamide	IV (R, H) PO (R, H)	15-18 mg/kg at 20 mg/min 50 mg/kg/24 h, Max: 5 g/24 h	1-4 mg/min IR: 250-500 mg q3-6h SR: 500 mg q6h Procanbid: 1000-2500 mg q12h	GI, CNS, +ANA/SLE-like syndrome, fever, hematologic, anticholinergic. Follow QT_c, serum procainamide (4-8 mg/L) and NAPA levels (<20 mg/mL)
	Quinidine	PO (H)	Sulfate, 200-400 mg q6h; gluconate, 324-972 mg q8-12h	NA	↑QT, TdP, ↓BP, thrombocytopenia, cinchonism, GI upset
	Disopyramide	PO (H, R)	300-400 mg	IR: 100-200 mg q6h SR: 200-400 mg q12h	Anticholinergic, HF
Ib	Lidocaine	IV (H)	1 mg/kg over 2 min (may repeat × 2 up to 3 mg/kg total)	1-4 mg/min	↓HR, CNS, GI; adjust dose in patients with hepatic failure, AMI, HF, or shock
	Mexiletine	PO (H)	400 mg one-time dose	200-300 mg q8h	GI, CNS
Ic	Flecainide	PO (H, R)	50 mg q12h	Increase by 50-100 mg/d every 4 days to max 400 mg/d	HF, GI, CNS, blurred vision
	Propafenone	PO (H)	IR: 150 mg q8h ER: 225 mg q12h	IR: Increase at 3- to 4-day intervals up to 300 mg q8h; ER: May increase at 5-day intervals, up to 425 mg q12h	GI, dizziness
III	Sotalol	PO (R)	80 mg q12h	May increase every 3 days up to 240-320 mg/d in two to three divided doses	↓HR, ↓BP, CHF, CNS Limit QT_c prolongation to <550 ms
	Dofetilide	PO (R, H)	CrCl (mL/min): Dose (µg bid): >60: 500 40-60: 250 20-39: 125 <20: Contraindicated	Dose adjusted based on QT_c 2-3 h after inpatient doses 1 through 5 Chronic therapy requires calculation of QT_c and CrCl every 3 months with adjustment as necessary	↑QT, VT/TdP, HA, dizziness; see text for further details on initiating and monitoring treatment
	Ibutilide	IV (H)	1 mg (0.01 mg/kg if patient <60 kg) over 10 min; can repeat if no response 10 min after initial infusion	NA	↑QT, TdP, AV block, GI, HA
	Amiodarone	IV (H) PO (H)	IV: 150 mg over 10 min PO: 800 mg/d for 1 wk, then 600 mg/d for 1 wk, then 400 mg/d for 1 wk	1 mg/min × 6 h, then 0.5 mg/min 100-400 mg PO daily	↓BP, HB, ↓HR, warfarin interaction; see text for description of dermatologic, thyroid, pulmonary, corneal, and liver effects

AMI, acute myocardial infarction; ANA, antinuclear antibodies; ↓BP, hypotension; CNS, central nervous system; CHF, congestive heart failure; CrCl, creatinine clearance; ER, extended release; GI, gastrointestinal; H, hepatic; HA, headache; HB, heart block; HF, heart failure; ↓HR, bradycardia; IR, immediate release; NA, not applicable; NAPA, *N*-acetylprocainamide; R, renal; SLE, systemic lupus erythematosus; SR, sustained release; TdP, torsades de pointes; VT, ventricular tachycardia.

[a]Either common or life-threatening adverse effects of these medications are listed. This is not a comprehensive list of all possible adverse effects.

- **Dofetilide** is useful for the maintenance of sinus rhythm. Dofetilide is a pure potassium channel blocker. Initiation of dofetilide should be done in an inpatient, monitored setting.

- QT prolongation with sotalol or dofetilide is intensified by bradycardia, a characteristic known as "**reverse use dependence**." The main risk of dofetilide is TdP. Dofetilide is contraindicated in patients with a baseline corrected QT interval (QT_c) >440 msec, or >500 msec in patients with bundle branch block. Initial dosing of dofetilide is based on the creatinine clearance. A 12-lead ECG should be obtained before the first dose of dofetilide and 1-2 hours after each dose. If the QT_c interval after the first dose is prolonged by 15% of the baseline or exceeds 500 msec, a 50% dosage reduction is indicated. If the QT_c exceeds 500 msec after the second dose, dofetilide must be discontinued. Several medications block the renal secretion of dofetilide (verapamil, cimetidine, prochlorperazine, trimethoprim, megestrol, ketoconazole) and are contraindicated with dofetilide. The advantages of dofetilide are that it is not associated with increased CHF or mortality in patients with LV dysfunction (*N Engl J Med 1999;341:857*) and it does not cause sinus node dysfunction or conduction abnormalities.
- **Dronedarone** is the newest antiarrhythmic agent approved for treatment of AF. Like amiodarone, from which it was derived, dronedarone shares properties with Vaughan Williams classes I-IV antiarrhythmic drugs. Dronedarone has been shown to be more effective than placebo at maintaining sinus rhythm after cardioversion but less effective than amiodarone at maintenance of sinus rhythm. The incidence of proarrhythmia is low with dronedarone, as is the incidence of organ toxicity. A trend toward increased mortality has been shown in patients with advanced heart failure symptoms, and it is contraindicated in this patient group. Dronedarone is metabolized in the liver and should not be used in patients with significant hepatic dysfunction. Dronedarone can be used in patients with significant renal dysfunction because clearance is predominantly in the feces.
- **Amiodarone** is arguably the most effective antiarrhythmic agent for maintenance of sinus rhythm. **Because of the extensive toxicity profile of amiodarone, it should not be considered as a first-line agent for rhythm control of AF in patients in whom an alternative antiarrhythmic can be safely used.** IV amiodarone has a low efficacy for acute conversion of AF, although conversion after several days of IV amiodarone has been observed. Given its common use and relatively high incidence of side effects, a more detailed discussion of these effects is required.
  - Adverse effects of oral amiodarone are partially dose dependent and may occur in up to 75% of patients treated at high doses for 5 years. At lower doses (200-300 mg/d), adverse effects that require discontinuation occur in approximately 5-10% of patients per year.
  - **Pulmonary toxicity** occurs in 1-15% of treated patients but appears less likely in those who receive <300 mg/d (*Circulation 1990;82:580*). Patients characteristically have a dry cough and dyspnea associated with pulmonary infiltrates and rales. The process appears to be reversible if detected early, but undetected cases may result in a mortality rate of up to 10% of those affected. A CXR and pulmonary function tests should be obtained at baseline and every 12 months or when patients complain of shortness of breath. The presence of interstitial infiltrates on the chest radiograph and a decreased diffusing capacity raise concern of amiodarone pulmonary toxicity.

  - **Photosensitivity** is a common adverse reaction, and in some patients, a violaceous skin discoloration develops in sun-exposed areas. The blue-gray discoloration may not resolve completely with discontinuation of therapy.
  - **Thyroid dysfunction** is a common adverse effect. Hypothyroidism and hyperthyroidism have been reported, with an incidence of 2-5% per year. Thyroid-stimulating hormone should be obtained at baseline and monitored every 6 months. If hypothyroidism develops, concurrent treatment with levothyroxine may allow continued amiodarone use.
  - **Corneal microdeposits**, detectable on slit-lamp examination, develop in virtually all patients. These deposits rarely interfere with vision and are not an indication for discontinuation of the drug. Optic neuritis, leading to blindness, is rare but has been reported in association with amiodarone.
  - The most common **ECG changes** are lengthened PR intervals and bradycardia; however, high-grade AV block may occur in patients who have preexisting conduction abnormalities. Amiodarone may prolong QT intervals, although usually not extensively, and **TdP is rare**. Other agents that prolong the QT interval, however, should be avoided in patients who are taking amiodarone.
  - **Liver dysfunction** usually manifests in an asymptomatic and transient rise in hepatic transaminases. If the increase exceeds three times normal or doubles in a patient with an elevated baseline level, amiodarone should be discontinued or the dose should be reduced. Aspartate transaminase (AST) and alanine transaminase (ALT) should be monitored every 6 months in patients who are receiving amiodarone.
  - **Drug interactions.** Amiodarone may raise the blood levels of warfarin and digoxin; therefore, these drugs should be reduced routinely by one-half when amiodarone is started, and levels should be followed closely.

Other Nonpharmacologic Therapies

Nonpharmacologic methods of rhythm control include catheter or surgical ablation techniques that block the initiation and maintenance of AF.

- **Direct current cardioversion (DCCV)** is the safest and most effective method of acutely restoring sinus rhythm. Prior to cardioversion, consideration of thromboembolic risk and anticoagulation is critical, when possible, to minimize thromboembolic events triggered by the cardioversion process. AF with a rapid ventricular response in the setting of ongoing myocardial ischemia, MI, hypotension, or respiratory distress should receive prompt cardioversion regardless of the anticoagulation status.
  - If the duration of AF is documented to be **<48 hours**, cardioversion may proceed without anticoagulation. If AF has persisted for **>48 hours** (or for an unknown duration), patients should be anticoagulated for at least 3 weeks before cardioversion, and anticoagulation should be continued in the same therapeutic range following successful cardioversion.
  - An alternative to anticoagulation for 3 weeks before cardioversion is to perform a **transesophageal echocardiogram** to rule out left atrial appendage thrombus before cardioversion. This method is safe and has the advantage of a shorter time to cardioversion than 3 weeks of anticoagulation. Therapeutic anticoagulation is indicated after the cardioversion for a minimum of 4 weeks (*Am J Cardiol 1998;82:1545*).
  - When practical, sedation should be accomplished with midazolam (1-2 mg IV q2min to a maximum of 5 mg), methohexital (25-75 mg IV), etomidate (0.2-0.6 mg/kg IV), or propofol (initial dose, 5 mg/kg/h IV).
  - Proper synchronization of the DC shock to the QRS is critical to avoid induction of VT by a cardioversion shock delivered during a vulnerable period of the ventricle.
  - For cardioversion of atrial arrhythmias, the anterior patch electrode should be positioned just right of the sternum at the level of the third or fourth intercostal space, with

    the second electrode positioned just below the left scapula posteriorly. **Care should be taken to position patch electrodes at least 6 cm from PPM or defibrillator generators.** If electrode paddles are used, firm pressure and conductive gel should be applied to minimize contact impedance. Direct contact with the patient or the bed should be avoided. Atropine (1 mg IV) should be readily available to treat prolonged pauses. Reports of serious arrhythmias, such as VT, ventricular fibrillation (VF), or asystole, are rare and are more likely in the setting of improperly synchronized cardioversions, digitalis toxicity, or concomitant antiarrhythmic drug therapy.

- **Curative catheter ablation of AF** has been shown to be highly effective in young patients with structurally normal hearts and a paroxysmal pattern of AF. Cure rates in this patient category are in the range of 70%. Cure rates are diminished in patients with structural heart disease, advanced age, and persistent AF. A significant fraction of patients require more than one ablation procedure to achieve cure. The goal of the catheter ablation procedure in paroxysmal AF patients is to achieve electrical isolation of the pulmonary veins. In patients with persistent AF, this goal is frequently combined with substrate modification strategies whereby regions of the atria are targeted for ablation to block reentry or the presence of focal drivers of AF. Because of potential complications and modest success, patients should undergo at least one trial of an antiarrhythmic drug for maintenance of sinus rhythm. If this trial is ineffective or poorly tolerated, curative catheter ablation can be contemplated.

Surgical Management

Surgical techniques for cure of AF have been evaluated since the 1980s. Of these techniques, the Cox-Maze procedure has the highest demonstrated efficacy and the most substantial published follow-up data documenting sustained efficacy. Including patients with persistent AF and structural heart disease, cure rates approach 90%. Because of its highly invasive nature, surgical treatment is usually reserved for patients who have failed a catheter ablation strategy or who have planned concomitant cardiac surgery.

Ventricular Tachyarrhythmias

GENERAL PRINCIPLES

- Ventricular tachyarrhythmias should be initially approached with the assumption that they will have a malignant course until proven otherwise.
- Characterization of the arrhythmia involves consideration of hemodynamic stability, duration, morphology, and presence or lack of underlying structural heart disease.
- Ultimately, this characterization will aid in determining the patient's risk for **sudden cardiac arrest** and need for device or ablation-based therapy.

Definitions

- **Nonsustained VT:** Three or more consecutive ventricular complexes (>100 bpm) that terminate spontaneously within 30 seconds.
- **Sustained monomorphic VT:** Tachycardia of ventricular origin with single QRS morphology that lasts longer than 30 seconds or requires cardioversion due to hemodynamic compromise.
- **Polymorphic VT:** VT characterized by an ever-changing QRS morphology. **TdP** is a variant of polymorphic VT that is typically preceded by a prolonged QT interval in sinus rhythm. Polymorphic VT is associated with hemodynamic collapse or instability.
- **VF** is associated with disorganized mechanical contraction, hemodynamic collapse, and sudden death. The ECG reveals irregular and rapid oscillations (250-400 bpm) of highly variable amplitude without uniquely identifiable QRS complexes or T waves.

- Ventricular arrhythmias are the major cause of **sudden cardiac death (SCD)**. **SCD** is defined as death that occurs within 1 hour of the onset of symptoms. In the United States, approximately 350,000 cases of SCD occur annually. Among patients with aborted SCD, ischemic heart disease is the most common associated cardiac structural abnormality. Most cardiac arrest survivors do not have evidence of an acute MI; however, >75% have evidence of previous infarcts. A nonischemic cardiomyopathy is also associated with an elevated risk for SCD.

Etiology

- **VT associated with structural heart disease**
  - Most ventricular arrhythmias are associated with structural heart disease, typically related to active ischemia or history of infarct.
    - Scar and the peri-infarct area provide the substrate for reentry that produces sustained monomorphic VT.
    - Polymorphic VT and VF are commonly associated with ischemia and are the presumed cause of most out-of-hospital SCDs.
  - Nonischemic cardiomyopathy typically involves progressive dilation and fibrosis of the ventricular myocardium, providing an arrhythmogenic substrate.
  - Infiltrative cardiomyopathies (sarcoid, hemochromatosis, amyloid) represent a smaller patient population that is at significant risk for ventricular arrhythmias whose management is less clearly defined.
  - Adults with prior repair of congenital heart disease are commonly afflicted with both VT and SVT.
  - Arrhythmogenic right ventricular (RV) dysplasia or cardiomyopathy is marked by fibrofatty replacement of the RV (and sometimes LV) myocardium that gives rise to left bundle branch block (LBBB) morphology VT and is associated with sudden death, particularly in young athletes.
  - Bundle branch reentry VT is a form of VT that uses the His-Purkinje system in a reentrant circuit and is typically associated with cardiomyopathy and an abnormal conduction system.
- **VT in the absence of structural heart disease**
  - Inherited ion channelopathies, such as those seen in Brugada and long QT syndromes, can lead to polymorphic VT and sudden death in patients without evidence of structural heart disease on imaging.
  - Catecholaminergic polymorphic VT involves familial, exercise-induced VT that is related to irregular calcium processing.
  - **Idiopathic VT** is a diagnosis of exclusion that requires the documented absence of structural heart disease, genetic disorders, and reversible etiologies (i.e., ischemia, electrolyte/metabolic abnormalities). Most idiopathic VTs originate from the RV outflow tract (RVOT) and are amenable to ablation. Less commonly, LV outflow tract (LVOT) VT or fascicular VT (using anterior and posterior divisions of the left bundle branch) may be discovered on EPS.

DIAGNOSIS

Clinical Presentation

- The evaluation of wide-complex tachyarrhythmias (WCTs) should always begin with prompt assessment of vital signs and clinical symptoms. If the arrhythmia is poorly tolerated, postpone further detailed evaluation and proceed to acute management per ACLS guidelines. If stable, there are several important questions to address that can guide one toward the most likely diagnosis. A common mistake is the assumption that hemodynamic stability supports the diagnosis of SVT over

VT.

- VT represents the vast majority of WCT seen in the inpatient setting with reported prevalence upward of 80%. With that in mind, one can then proceed to elicit several historical points of emphasis and scrutinize ECG properties of the arrhythmia to further delineate the mechanism of the underlying rhythm disturbance. Begin with the following questions:
  - Does the patient have a history of structural heart disease? Patients with structural heart disease are much more likely to have VT rather than SVT as the etiology of a WCT. In one report, 98% of patients with WCT who had prior MI proved to have VT (*Am J Med 1988;84:53*).
  - Does the patient have a pacemaker, implantable cardioverter-defibrillator (ICD), or wide QRS at baseline?
    - The presence of either a pacemaker or an ICD should raise suspicion for a device-mediated WCT.
    - **Device-mediated WCT** can be due to ventricular pacing at a rapid rate either due to device tracking of an atrial tachyarrhythmia or an "endless loop tachycardia" created by tracking of the retrograde atrial impulses created by the preceding ventricular paced beat. In either case, the tachycardia rate is a clue to the mechanism because this is typically equal to the programmed upper rate limit (URL) of the device. A commonly programmed URL is 120 paces per minute (ppm). A tachycardia rate above the URL effectively excludes a device-mediated WCT.
    - Device can be confirmed by inspection of the chest wall (usually left chest for righthanded patients), chest radiograph (CXR), or the presence of pacing spikes seen on ECG.
    - Patients with known right bundle branch block (RBBB), LBBB, or intraventricular conduction delay (IVCD) at baseline who present with WCT will have a QRS morphology identical to baseline in the presence of SVT. In addition, some patients with a narrow QRS at baseline will manifest a WCT due to SVT when a rate-related bundle branch block is present (SVT with aberrancy).
  - What medications is the patient taking?
    - The medication list should be scanned for any medication with proarrhythmic side effects, especially those that can prolong the baseline QT interval. These medicines include many of the class I and III antiarrhythmics, certain antibiotics, antipsychotics, and many more.
    - Medications that can lead to electrolyte abnormalities, such as loop and potassiumsparing diuretics, ACEIs, ARBs, etc., should be ascertained. Also, digoxin toxicity is always an important consideration in the setting of any arrhythmia.

Differential Diagnosis

- WCT may be due to either SVT with aberrant conduction or VT. Differentiation between these mechanisms is of the utmost importance. **The pharmacologic agents used in the management of SVT (i.e., adenosine, β-blockers, calcium channel blockers) can cause hemodynamic instability if used in the setting of VT.** Therefore, all WCTs are considered to be ventricular in origin until proven otherwise.

  Other less common mechanisms of WCT include **antidromic AVRT, hyperkalemiainduced arrhythmia, or pacemaker-induced tachycardia**.
- **Telemetry artifact** due to poor lead contact or repetitive patient motion (tremor, shivering, brushing teeth, chest physical therapy, etc.) can mimic VT or VF.

Diagnostic Testing

Laboratories

Laboratory studies should include basic metabolic panel, magnesium, CBC, and serial troponins.

Electrocardiography

- **Differentiation of SVT with aberrancy from VT** based on ECG analysis is critical in the determination of appropriate acute and chronic therapy. Features that are diagnostic of VT are **AV dissociation**, **capture or fusion beats**, an absence of RS morphology in the precordial leads (V_1-V_6), and **LBBB morphology with right axis deviation**. In the absence of these features, examination of an RS complex in a precordial lead for an RS interval >100 msec is consistent with VT. In addition, characteristic QRS morphologies that are suggestive of VT may be sought, as shown in Figure 7-2.
- **ECG pearls**
  - **Classic Brugada pattern**
    - Baseline: Pseudo-RBBB with ST-segment elevation and T-wave inversion in V_1, V_2
    - May be unmasked by stress, illness, fever, illicit drug use, etc.
  - **Arrhythmogenic RV dysplasia**
    - Baseline: Epsilon wave (late potential just after QRS), ± wide QRS, ± T-wave inversion (V_1, V_2)
    - VT: Reflects RV origin, likely LBBB configuration; may present with polymorphic VT
  - **Bundle branch reentrant VT**
    - Baseline: IVCD
    - VT: LBBB morphology typically ("down" the right bundle; "up" the left bundle)
  - **Fascicular VT**

    VT: Superior axis, RBBB morphology
  - **Long QT syndrome**
    - Baseline: QT >50% of the RR interval if HR 60-100 bpm; QT_c ≥440 msec
    - VT: TdP degenerating into VF
  - **Outflow tract VT**

    VT: Inferior axis, LBBB morphology. R/S transition in the precordial leads can aid in localization. Early transition (V_1 or V_2) suggests an LVOT origin; later transition (V_4) suggests RVOT origin.

Imaging

- The presence or absence of structural heart disease should be initially evaluated by transthoracic echocardiography.
- Further imaging (cardiac MRI, noninvasive stress test, coronary angiogram, etc.) should be obtained based on suspected etiology.

TREATMENT

- **Differentiation of SVT with aberrancy from VT** based on analysis of the surface ECG is critical in the determination of appropriate acute and chronic therapy.
  - For acute therapy of SVT, IV medications such as adenosine, calcium channel blockers, or β-blockers are used. However, calcium channel blockers and β-blockers can produce hemodynamic instability in patients with VT.
  - Chronically, many SVTs are amenable to RFA, whereas most VTs are malignant and require an antiarrhythmic agent and/or ICD implantation.
- Immediate unsynchronized DCCV is the primary therapy for pulseless VT and VF.

Other Nonpharmacologic Therapies

- **ICDs** provide automatic recognition and treatment of ventricular arrhythmias. ICD implantation improves survival in patients resuscitated from ventricular arrhythmias (secondary prevention of SCD) and in individuals without prior symptoms who are at high risk for SCD (primary prevention of SCD).

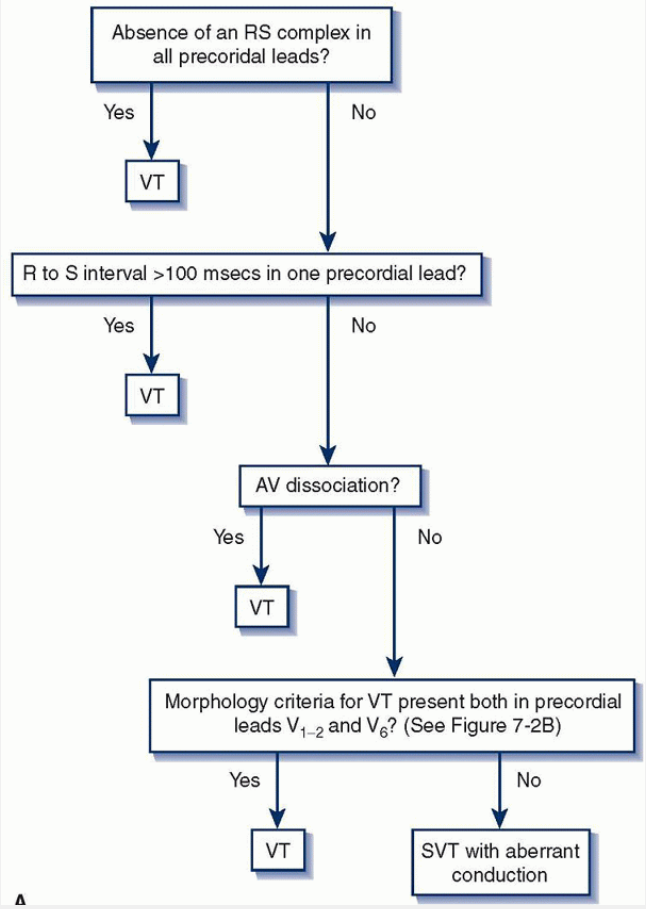


Figure 7-2. A and B. Brugada criteria for distinguishing ventricular tachycardia from supraventricular tachycardia with aberrancy in wide-complex tachycardias. LBBB, left bundle branch block; RBBB, right bundle branch block; SVT, supraventricular tachyarrhythmia; VT, ventricular tachycardia. (From Sharma S, Smith TW. Advanced electrocardiography: ECG 201. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.)

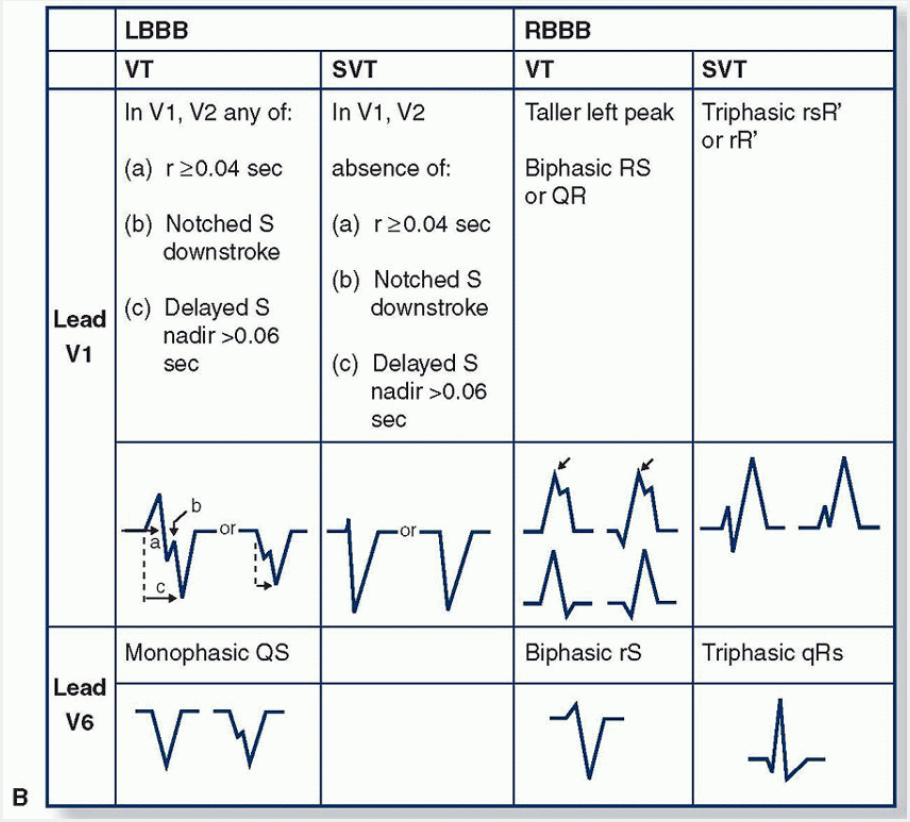


Figure 7-2. (*Continued*).

- **Secondary prevention of SCD** with ICD implantation is indicated for most patients who survive SCD outside of the peri-MI setting. The superiority of ICD therapy to chronic antiarrhythmic drug therapy has been demonstrated (AVID trial; *N Engl J Med 1997;337:1576*).
- **Primary prevention of SCD** with ICD implantation is indicated for patients who are at high risk of SCD. The efficacy of ICD implantation for primary prevention of SCD in the setting of cardiomyopathy has been established in multiple prospective clinical trials (see Multicenter Automatic Defibrillator Implantation Trial **[MADIT]**, *N Engl J Med 1996;335:1933*; Multicenter Un-Sustained Tachycardia Trial **[MUSTT]**, *N Engl J Med 1999;341:1882*; **MADIT II Trial**, *N Engl J Med 2002;346:877*; and **SCD-HeFT**, *N Engl J Med 2005;352(3):225*). Most patients with an LV ejection fraction of <35% for more than 3 months on optimal medical therapy meet current indications for prophylactic ICD implantation.
  - **Other indications for ICD**
  - Phenotypes associated with **HCM, arrhythmogenic RV cardiomyopathy, congenital long QT syndrome, or Brugada syndrome have a higher risk of SCD**. ICD implantation is indicated if patients with one of these syndromes have had a resuscitated cardiac arrest or documented ventricular arrhythmia. Prophylactic ICD implantation is based on disease-specific risk factors.

  - Patients who are awaiting cardiac transplantation are at high risk for SCD, especially if they are receiving an intravenous inotrope. Prophylactic ICD implantation is reasonable to protect against SCD prior to transplantation.

    ICDs are **contraindicated** in patients who have incessant VT, recent MI <40 days or revascularization <3 months in the case of primary prevention, significant psychiatric illnesses, or life expectancy of <12-24 months.

- **Radiofrequency catheter ablation of VT** is most successfully performed in patients with hemodynamically stable forms of idiopathic VT that is not associated with structural heart disease. Long-term cure rates in these patients are similar to those achieved for catheter ablation of SVT. In the presence of structural heart disease, catheter ablation has a lower efficacy and a higher morbidity but is an important treatment option, particularly in drug-refractory, symptomatic VT that is leading to ICD therapy.
  - **Idiopathic VT is usually associated with a structurally normal heart, but an associated tachycardia-mediated cardiomyopathy has been described.**
    - **Outflow tract VT** often presents as repetitive, nonsustained bursts of VT that originates most commonly from the RV (RVOT) and less commonly from the LV near the coronary cusps or aorto-mitral continuity. These can be responsive to β-adrenergic blockers, diltiazem, verapamil, and adenosine.
    - Both forms of idiopathic VT are thought to be benign in the absence of structural heart disease. Therefore, ICD implantation is not appropriate. All forms of idiopathic VT are amenable to treatment with RFA or drug therapy.
  - **VT associated with ischemic heart disease** can also be treated by catheter ablation by targeting the scar-based substrate. Emergent catheter ablation in the setting of frequent hemodynamically unstable VT requiring defibrillation (VT storm) can be life-saving. Ablation has been shown to be reduce ICD therapy and improve quality of life.
  - **Ablation of VT in nonischemic cardiomyopathy** is also reasonable, particularly in drug-refractory patients, but VT circuits may be intramyocardial or epicardial. As a result, success rates are typically lower than those associated with ischemic VT, and referral to a center that routinely performs both endocardial and epicardial ablations should be considered.

Medications

- VF that is resistant to external defibrillation requires the addition of IV antiarrhythmic agents.
  - IV lidocaine is frequently used; however, IV amiodarone appears to be more effective in increasing survival of VF when used in conjunction with defibrillation (*N Engl J Med 2002;346:884*).
  - After successful defibrillation, continuous IV infusion of effective antiarrhythmic therapy should be maintained until any reversible causes have been corrected.

- Chronic antiarrhythmic drug therapy is indicated for the treatment of recurrent symptomatic ventricular arrhythmias. In the setting of hemodynamically unstable ventricular arrhythmias treated with an ICD, antiarrhythmic drug therapy is often necessary to prevent frequent device discharges.

First Line

- **Amiodarone** is safe and well tolerated for the acute management of ventricular arrhythmias. Amiodarone has complex pharmacokinetics and is associated with significant toxicities arising from chronic therapy (*Am Heart J 1993;125:109*).

  After oral loading, amiodarone prevents the recurrence of sustained VT or VF in up to 60% of patients. A therapeutic latency of more than 5 days exists before beneficial antiarrhythmic effects are observed with oral dosing, and full suppression of arrhythmias may

  not occur for 4-6 weeks after therapy is initiated. Unfortunately, recurrence of ventricular arrhythmias during long-term follow-up is common.
- **Class II** agents, the β-adrenergic antagonists, are the only class of antiarrhythmic agents to have consistently shown improved survival in post-MI patients.
  - β-Adrenergic blockers reduce postinfarction total mortality by 25-40% and SCD by 32-50% (*Lancet 1981;2:823*; *Lancet 1999;353:9*; *Lancet 1999;353:2001*; *N Engl J Med 2001;344:1651*; *Lancet 2001;357:1385*).
  - After acute therapy of VT/VF and stabilization, β-adrenergic blockers should be initiated and titrated as blood pressure and heart rate allow.
- **ACEIs** have also been shown to reduce sudden death and overall mortality in patients with coronary artery disease (CAD) or CHF.

Second Line

- **Sotalol** is a **class III** agent indicated for the chronic treatment of VT/VF. Sotalol prevents the recurrence of sustained VT and VF in 70% of patients (*N Engl J Med 1993;329:452*) but must be used with caution in individuals with CHF.
- **Class I** agents in general have not been shown to reduce mortality in patients with VT/VF. In fact, the class Ic agents, **flecainide** and **propafenone**, are associated with increased mortality in patients with ventricular arrhythmias after MI (*N Engl J Med 1991;324:781*).
- **Lidocaine** is a **class Ib** agent available only in IV form with efficacy in the management of sustained and recurrent VT/VF. The prophylactic use of lidocaine for suppression of premature ventricular contractions and nonsustained VT in the otherwise uncomplicated post-MI setting should be avoided. Toxicities of lidocaine include central nervous system (CNS) effects (convulsions, confusion, stupor, and, rarely, respiratory arrest), all of which resolve with discontinuation of therapy. Serum levels should be followed during prolonged use.
- **Mexiletine** is similar to lidocaine but is available in oral form. **Mexiletine is most often used in combination with either amiodarone or sotalol for chronic treatment of refractory ventricular arrhythmias.** CNS toxicity includes tremor, dizziness, and blurred vision. Higher levels may result in dysarthria, diplopia, nystagmus, and an impaired level of consciousness. Nausea and vomiting are common.
- **Phenytoin** can be used in the treatment of **digitalis-induced ventricular arrhythmias**. It may have a limited role in the treatment of ventricular arrhythmias associated with congenital long QT syndromes and those with structural heart disease.

SPECIAL CONSIDERATIONS

- **Class IV** agents have no role in the chronic management of VT associated with structural heart disease.
- Primary therapy for VF that occurs secondary to ischemia in the setting of an MI is complete revascularization. In the absence of complete revascularization, the patient remains at high risk for recurrent VT/VF.
- In the case of **TdP associated with long QT syndrome**, acute therapy is immediate defibrillation.
- Bolus administration of magnesium sulfate in 1- to 2-g increments up to 4-6 g IV is effective.
- In cases of acquired long QT, identification and treatment of the underlying condition should be undertaken, if possible.
- Elimination of long-short triggering sequences and shortening of the QT interval can be achieved by increasing the heart rate to the range of 90-120 bpm by either IV isoproterenol infusion (initial rate at 1-2 μg/min) or temporary transvenous pacing.

BRADYARRHYTHMIAS

GENERAL PRINCIPLES

- Bradyarrhythmias are commonly encountered rhythms in the inpatient setting that result in a ventricular rate of <60 bpm.
- **Anatomy of the conduction system**
  - The **sinus node** is a collection of specialized pacemaker cells located in the high right atrium. Under normal conditions, it initiates a wave of depolarization that spreads inferiorly and leftward via atrial myocardium and intranodal tracts, producing atrial systole.
  - The wave of depolarization then reaches another grouping of specialized cells, the **AV node**, located in the right atrial side of the interatrial septum. Normally, the AV node should serve as the lone electrical connection between the atria and ventricles.
  - From the AV node, the wave of depolarization travels down the **His bundle**, located in the membranous septum, and into the **right and left bundle branches** before reaching the **Purkinje fibers** that depolarize the rest of the ventricular myocardium.

Etiology

Common causes of bradycardia are listed in Table 7-6.

TABLE 7-6 Causes of Bradycardia

Intrinsic
Congenital disease (may present later in life)
Idiopathic degeneration (aging)

Infarction or ischemia
Cardiomyopathy
Infiltrative disease: sarcoidosis, amyloidosis, hemochromatosis
Collagen vascular diseases: systemic lupus erythematosus, rheumatoid arthritis, scleroderma
Surgical trauma: valve surgery, transplantation
Infectious disease: endocarditis, Lyme disease, Chagas disease

Extrinsic

Autonomically mediated
Neurocardiogenic syncope
Carotid sinus hypersensitivity
Increased vagal tone: coughing, vomiting, micturition, defecation, intubation
Drugs: β-blockers, calcium channel blockers, digoxin, antiarrhythmic agents
Hypothyroidism
Hypothermia
Neurologic disorders: increased intracranial pressure
Electrolyte imbalances: hyperkalemia, hypermagnesemia
Hypercarbia/obstructive sleep apnea
Sepsis

From Fansler DR, Chen J. Bradyarrhythmias and permanent pacemakers. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.

DIAGNOSIS

Clinical Presentation

When evaluating a suspected bradyarrhythmia, one should efficiently use the history, physical exam, and available data to address stability, symptoms, reversibility, site of dysfunction, and need for pacing.

History and Physical Examination

- If the patient is demonstrating signs of poor perfusion (hypotension, confusion, decreased consciousness, cyanosis, etc.), immediate management per ACLS protocol should be initiated. The clinical manifestations of bradyarrhythmias are variable, ranging from asymptomatic to nonspecific (lightheadedness, fatigue, weakness, exercise intolerance) to overt (syncope).
- Emphasis should be placed on delineating **whether the presenting symptoms have a direct temporal relationship to underlying bradycardia**. Other historical points of emphasis include the following:
  - Ischemic heart disease, particularly involving the right-sided circulation, can precipitate a number of bradyarrhythmias. Therefore, symptoms of acute coronary syndrome should always be sought.
  - **Precipitating circumstances** (micturition, coughing, defecation, noxious smells) surrounding episodes may help identify a neurocardiogenic etiology.
  - **Tachyarrhythmias**, particularly in patients with underlying sinus node dysfunction, can be followed by long pauses due to sinus node suppression during tachycardia.
  - History of structural heart disease, hypothyroidism, obstructive sleep apnea, collagen vascular disease, infections (bacteremia, endocarditis, Lyme, Chagas), infiltrative diseases (amyloid, hemochromatosis, and sarcoid), neuromuscular diseases, and prior cardiac surgery (valve replacement, congenital repair) should be sought.
  - **Medications** should be reviewed with emphasis on those that affect the sinus and AV nodes (i.e., calcium channel blockers, β-adrenergic blockers, digoxin).
- After hemodynamic stability is confirmed, a more thorough examination with particular emphasis on the cardiovascular exam and any findings consistent with the above comorbidities is appropriate (Figure 7-3).

Diagnostic Testing

Laboratories

Laboratory studies should include serum electrolytes and thyroid function tests in most patients. Digoxin levels and serial troponins should be drawn when clinically appropriate.

Electrocardiography

- The **12-lead ECG** is the cornerstone for diagnosis in any workup where arrhythmia is suspected.
  - Rhythm strips from leads that provide the best view of atrial activity (II, III, aVF, or V_1) should be examined.
  - Emphasis should be placed on identifying evidence of **sinus node dysfunction** (P-wave intervals) or **AV conduction abnormalities** (PR interval).
  - Evidence of both old and acute manifestations of ischemic heart disease should be sought as well.
- **Sinus node dysfunction**, or sick sinus syndrome, represents the most common reason for pacemaker implantation in the United States. Manifestations of sick sinus syndrome include (Figure 7-4):
  - **Sinus bradycardia** is defined as a regular rhythm with QRS complexes preceded by “sinus” P waves (upright in II, III, aVF) at a rate <60 bpm. Young patients and athletes

    often have resting sinus bradycardia that is well tolerated. Nocturnal heart rates are lower in all patients, but the elderly tend to have higher resting heart rates and sinus bradycardia is a far less common normal variant.

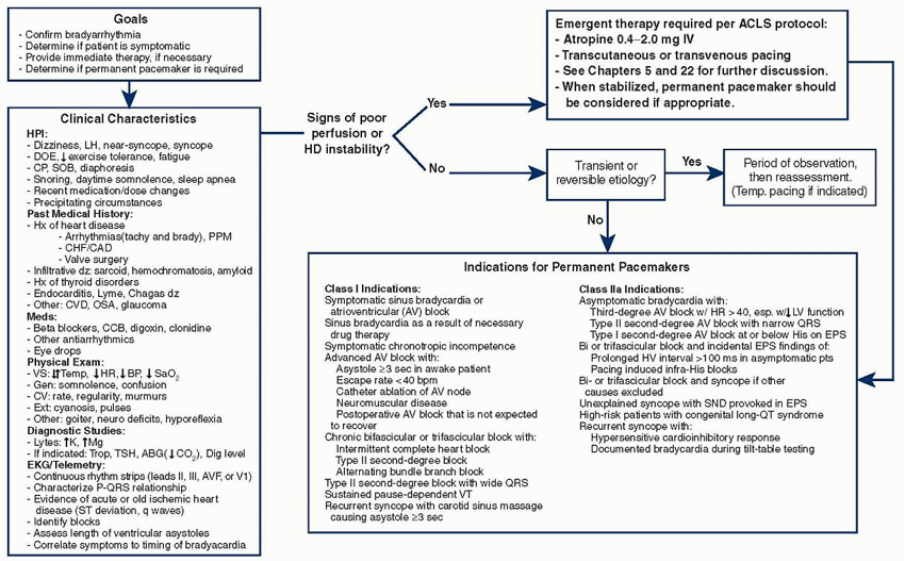


Figure 7-3. Approach to bradyarrhythmias. ABG, arterial blood gas; ACLS, advanced cardiac life support; ↓BP, hypotension; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CP, chest pain; CVD, cerebrovascular disease; DOE, dyspnea on exertion; dz, disease; EPS, electrophysiologic study; HD, hemodynamic; HPI, history of present illness; ↓HR, bradycardia; Hx, history; ↑K, hyperkalemia; LH, lightheadedness; ↑Mg, hypermagnesemia; OSA, obstructive sleep apnea; PPM, permanent pacemaker; ↓SaO_2, hypoxia; SND, sinus node dysfunction; SOB, shortness of breath; TSH, thyroid-stimulating hormone; VS, vital signs; VT, ventricular tachycardia. (From Fansler DR, Chen J. Bradyarrhythmias and permanent pacemakers. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.)

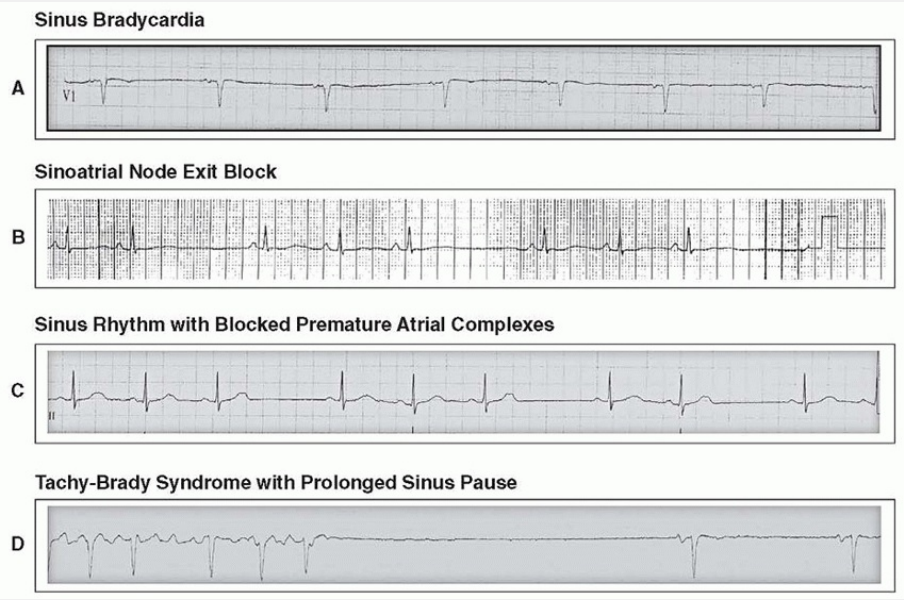


Figure 7-4. Examples of sinus node dysfunction. **A.** Sinus bradycardia. The sinus rate is approximately 45 bpm. **B.** Sinoatrial node exit block. Note that the PP interval in which the pause occurs is exactly twice that of the nonpaused PP interval. **C.** Blocked premature atrial complexes. This rhythm is often confused for sinus node dysfunction or atrioventricular block. Note the premature, nonconducted P waves inscribed in the T wave that resets the sinus node leading to the observed pauses. **D.** Tachy-brady syndrome. Note the termination of the irregular tachyarrhythmia followed by a prolonged 4.5-second pause prior to the first sinus beat. (From Fansler DR, Chen J. Bradyarrhythmias and permanent pacemakers. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.)

- **Sinus arrest** and **sinus pauses** refer to failure of the sinus node to depolarize, which manifest as periods of atrial asystole (no P waves). This may be accompanied by ventricular asystole or escape beats from junctional tissue or ventricular myocardium. Pauses of 2-3 seconds can be found in healthy, asymptomatic people, especially during sleep. Pauses >3 seconds, particularly during daytime hours, raise concern for significant sinus node dysfunction.
- **Sinus exit block** represents the appropriate firing of the sinus node, but the wave of depolarization fails to traverse past the perinodal tissue. It is indistinguishable from sinus arrest on surface ECGs except that the R-R interval will be a multiple of the R-R preceding the bradycardia.
- **Tachy-brady syndrome** occurs when tachyarrhythmias alternate with bradyarrhythmias, especially AF.
- **Chronotropic incompetence** is the inability to increase the heart rate appropriately in response to metabolic need.

- **AV conduction disturbances**
  - AV conduction can be **diverted** (fascicular or bundle branch blocks); **delayed** (first-degree AV block); **occasionally interrupted** (second-degree AV block); **frequently, but**

not always, interrupted (advanced or high-degree AV block); or **completely absent** (third-degree AV block). Assignment of the bradyarrhythmia under investigation to one of these categories allows one to better determine prognosis and, therefore, guide therapy.

  - **First-degree AV block** describes a conduction delay that results in a PR interval >200 msec on the surface ECG.
  - **Second-degree AV block** is present when there are periodic interruptions (i.e., "dropped beats") in AV conduction. Distinction between Mobitz I and II is

important because they possess differing natural histories of progression to complete heart block.

- **Mobitz type I block (Wenckebach)** is represented by a progressive delay in AV conduction with successive atrial impulses until an impulse fails to conduct. On surface ECG, classic Wenckebach block manifests as:

  Progressive prolongation of the PR interval of each successive beat, before the dropped beat.

  Shortening of each subsequent RR interval before the dropped beat.

  A regularly irregular grouping of QRS complexes (group beating).

  Type I block is usually within the AV node and portends a more benign natural history with progression to complete heart block unlikely.

- **Mobitz type II block** carries a less favorable prognosis and is characterized by abrupt AV conduction block without evidence of progressive conduction delay.

  On ECG, the PR intervals remained unchanged preceding the nonconducted P wave.

  The presence of type II block, particularly if a bundle branch block is present, often antedates progression to complete heart block.

- The presence of **AV 2:1 block** makes the differentiation between Mobitz type I or II mechanisms difficult. Diagnostic clues to the site of block include the following:

  Concomitant first-degree AV block, periodic AV Wenckebach, or improved conduction (1:1) with enhanced sinus rates or sympathetic input suggests a more proximal interruption of conduction (i.e., Mobitz type I mechanism).

  Concomitant bundle branch block, fascicular block, or worsened conduction (3:1, 4:1, etc.) with enhanced sympathetic input localizes the site of block more distally (Mobitz type II mechanism).

- **Third-degree (complete) AV block** is present when all atrial impulses fail to conduct to the ventricles. There is complete dissociation between the atria and ventricles ("A > V" rates). This should be distinguished from dissociation with competition at the AV node ("V > A" rates).
- **Advanced or high-degree AV block** is present when more than one consecutive atrial depolarization fails to conduct to the ventricles (i.e., 3:1 block or greater). On ECG, consecutive P waves will be seen without associated QRS complexes. However, there will be demonstrable P:QRS conduction somewhere on the record to avoid a "third-degree" designation (Figure 7-5).

Imaging

- The presence or absence of structural heart disease should be initially evaluated by transthoracic echocardiography.
- Further imaging should be obtained based on suspected etiology.

TREATMENT

Pharmacologic Therapy

- Bradyarrhythmias that lead to significant symptoms and hemodynamic instability should be managed emergently as outlined in ACLS guidelines (see Appendix C).

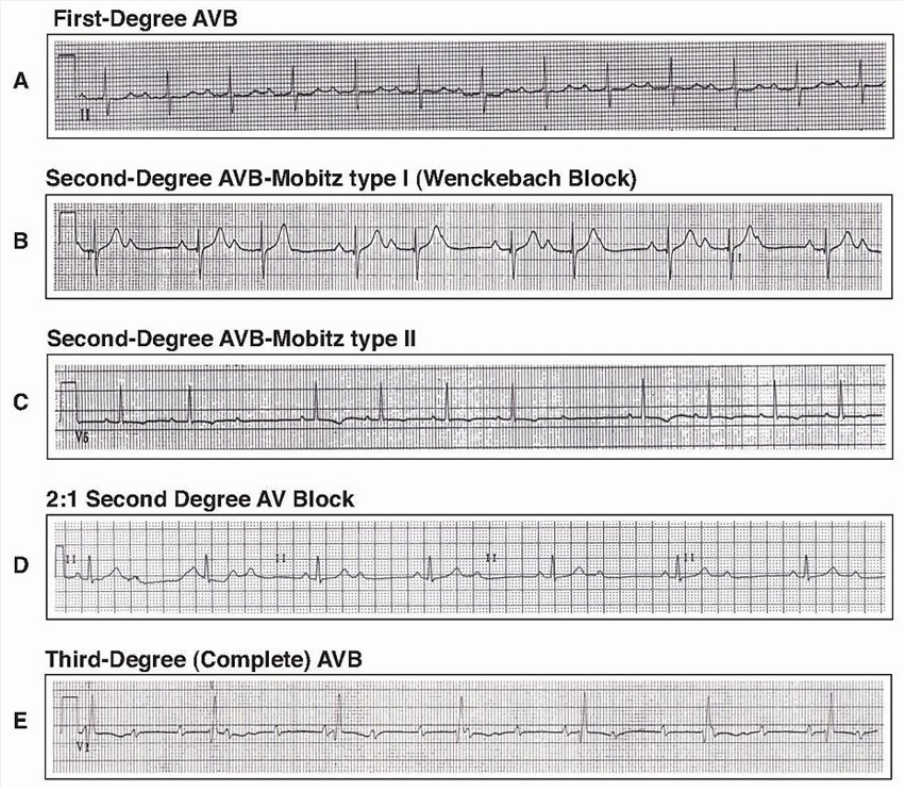


Figure 7-5. Examples of atrioventricular block (AVB). **A.** First-degree AVB. There are no dropped beats, and the PR interval is >200 msec. **B.** 3:2 Second-degree AVB-Mobitz I. Note the "group beating" and the prolonging PR interval prior to the dropped beat. The third P wave in the sequence is subtly inscribed in the T wave of the preceding beat. **C.** Second-degree AVB-Mobitz II. Note the abrupt atrioventricular conduction block without evidence of progressive conduction delay. **D.** 2:1 AVB. This pattern makes it difficult to distinguish between Mobitz I versus II type mechanisms of block. Note the narrow QRS complex, which supports a more proximal origin of block (type I mechanism). A wider QRS (concomitant bundle branch or fascicular block) would suggest a type II mechanism. **E.** Complete heart block. Note the independent regularity of both the atrial and ventricular rhythms (junctional escape) with no clear association with each other throughout the

rhythm strip. (From Fansler DR, Chen J. Bradyarrhythmias and permanent pacemakers. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.)

- **Atropine**, an anticholinergic agent given in doses of 0.5-2.0 mg IV, is the cornerstone pharmacologic agent for emergent bradycardia treatment.
  - Dysfunction localized more proximally in the conduction system (i.e., symptomatic sinus bradycardia, first-degree AV block, Mobitz I second-degree AV block) tends to be responsive to atropine.
  - Distal disease is not responsive and can be worsened by atropine.
- Reversible causes of bradyarrhythmias should be identified, and any agents (digoxin, calcium channel blockers, β-adrenergic blockers) that caused or exacerbated the underlying dysrhythmia should be withheld.

Other Nonpharmacologic Therapies

- For bradyarrhythmias that have irreversible etiologies or that are secondary to medically necessary pharmacologic therapy, pacemaker therapy should be considered.
  - Temporary pacing is indicated for symptomatic second-degree or third-degree heart block caused by transient drug intoxication or electrolyte imbalance and complete heart block or Mobitz II second-degree AV block in the setting of an acute MI.
  - Sinus bradycardia, AF with a slow ventricular response, or Mobitz I second-degree AV block should be treated with temporary pacing only if significant symptoms or hemodynamic instability is present.
  - Temporary pacing is achieved preferably via insertion of a transvenous pacemaker. Transthoracic external pacing can be used, although the lack of reliability of capture and patient discomfort make this a second-line modality.
- Once hemodynamic stability has been established, attention turns to the indications for PPM placement.
  - In symptomatic patients, the key determinants include **potential reversibility of causative factors** and **temporal correlation of symptoms to the arrhythmia**.
  - In asymptomatic patients, the key determinant is based on whether the **discovered conduction abnormality has a natural history of progression to higher degrees of heart block** that portends a poor prognosis.
- **Permanent pacing**
  - Permanent pacing involves the placement of anchored, intracardiac pacing leads for the purpose of maintaining a heart rate sufficient to avoid symptoms and hemodynamic instability. Current devices, through maintenance of AV synchrony and rate-adaptive programming, more closely mimic normal physiologic heart rate behavior.
    - Class I (general agreement/evidence for benefit) and IIa (weight of conflicting opinion/evidence in favor of benefit) indications for permanent pacing are listed in Figure 7-3.
    - Pacemakers are designed to provide an electrical stimulus to the heart whenever the rate drops below a preprogrammed **lower rate limit**. Therefore, the ECG appearance of a PPM varies depending on the heart rate and state of AV conduction.
    - The pacing spikes produced by modern pacemakers are low amplitude, sharp, and immediately preceding the generated P wave or QRS complex indicating capture of the chamber. Figure 7-6 illustrates some common ECG appearances of normally and abnormally functioning pacemakers.
  - The pacemaker generator is commonly placed subcutaneously in the pectoral region on the side of the nondominant arm. The electronic lead(s) is placed in the cardiac chamber(s) via central veins. Complications of placement include **pneumothorax, device infection, bleeding, and rarely, cardiac perforation with tamponade**.
    - Before implantation, the patient must be free of any active infections, and anticoagulation issues must be carefully considered. Hematomas in the pacemaker pocket develop most commonly in patients who are receiving IV heparin or SC low-molecular-weight heparin. In severe cases, surgical evacuation is required.
    - Following implantation, **posteroanterior (PA) and lateral CXRs** are obtained to confirm appropriate lead placement. The pacemaker is interrogated at appropriate intervals—typically, before discharge, 2-6 weeks following discharge, and every 6-12 months thereafter.
  - **Pacing modes** are classified by a sequence of three to five letters. Most pacemakers are referred to by the three-letter code alone.
    - **Position I denotes the chamber that is paced:** A for atria, V for ventricle, or D for dual (A + V).
    - **Position II refers to the chamber that is sensed:** A for atria, V for ventricle, D for dual (A + V), or O for none.

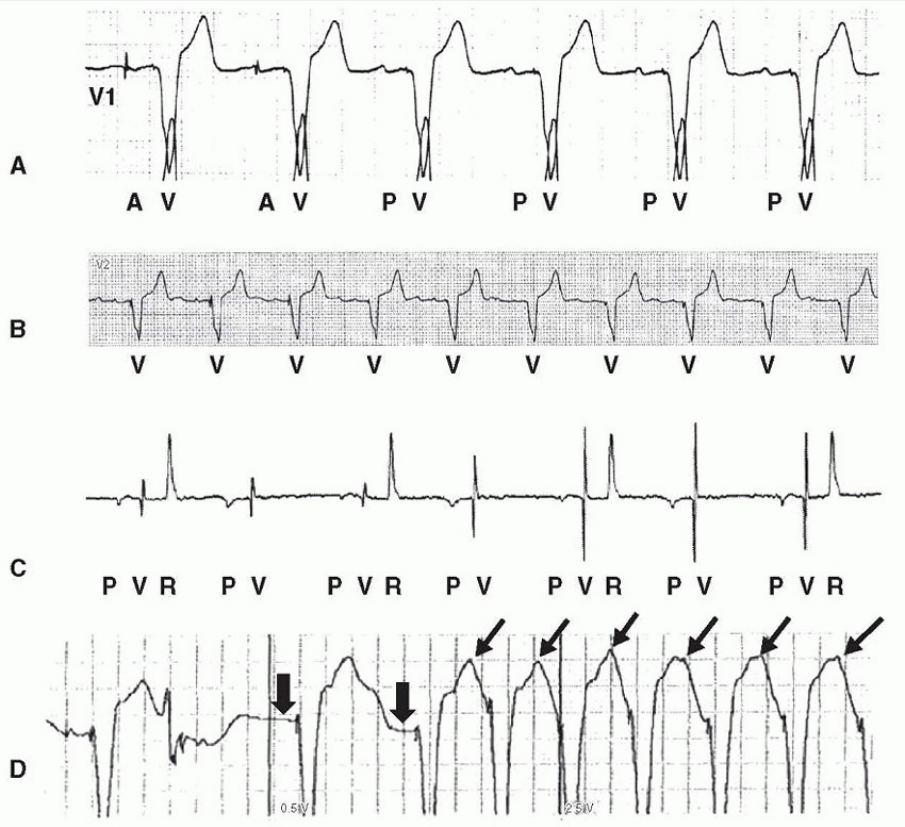


Figure 7-6. Pacemaker rhythms. **A.** Normal dual-chamber (DDD) pacing. First two complexes are atrioventricular (AV) sequential pacing, followed by sinus with atrial sensing and ventricular pacing. **B.** Normal single-chamber (VVI) pacing. The underlying rhythm is atrial fibrillation (no distinct P waves), with ventricular pacing at 60 bpm. **C.** Pacemaker malfunction. The underlying rhythm is sinus (P) at 80 bpm with 2:1 heart block and first-degree AV block (long PR). Ventricular pacing spikes are seen (V) after each P wave, demonstrating appropriate sensing and tracking of the P waves; however, there is failure to capture. **D.** Pacemaker-mediated tachycardia. A, paced atrial events; V, paced ventricular events; P, sensed atrial events; R, sensed ventricular events. (**D,** From Fansler DR, Chen J. Bradyarrhythmias and permanent pacemakers. In: Cuculich PS, Kates AM, eds. *The Washington Manual Cardiology Subspecialty Consult*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2014.)

- **Position III denotes the type of response the pacemaker will have to a sensed signal:** I for inhibition, T for triggering, D for dual (I + T), or O for none.
- **Position IV is used to signify the presence of rate-adaptive pacing (R)** in response to increased metabolic need.

- The most common pacing systems used today include VVI, DDD, or AAI.
  - AAI systems should be used only for sinus node dysfunction in the absence of any AV conduction abnormalities.
  - The presence of AV nodal or His-Purkinje disease makes a dual-chamber device (i.e., DDD) more appropriate.
  - Patients in chronic AF warrant a single ventricular lead with VVI programming.
- Modern-day pacemakers also have the capability of **mode switching**. This is useful in patients with DDD pacers who have paroxysmal tachyarrhythmias. When these

patients develop an atrial arrhythmia faster than a programmed mode switch rate, the device will switch to a mode (i.e., VVI) that does not track atrial signals. It will return to DDD when the tachyarrhythmia resolves.

- Although infrequent, **pacemaker malfunction** is a potentially life-threatening situation, particularly for patients who are pacemaker dependent. The workup of suspected malfunction should begin with a 12-lead ECG.
  - If no pacing activity is seen, one can place a magnet over the pacemaker to assess for output failure and ability to capture. **Application of the magnet switches the pacemaker to an asynchronous pacing mode.** For example, VVI mode becomes VOO (ventricular asynchronous pacing), and DDD mode becomes DOO (asynchronous AV pacing).
  - If malfunction is obvious or if the ECG is unrevealing and malfunction is still suspected, then a formal interrogation of the device should be done. **Patients are given a card to carry upon implantation that will identify the make and model of the device to facilitate this evaluation.**
  - **Chest radiograph (two views)** should also be obtained to assess for evidence of overt lead abnormalities (dislodgement, fracture, migration, etc.).
- General categories of pacemaker malfunction include failure to pace (output failure), failure to capture, failure to sense (undersensing), and pacemaker-mediated dysrhythmias.

SPECIAL CONSIDERATIONS

- Often, episodes of bradycardia are transient and episodic; therefore, a baseline ECG may not be sufficient to capture the bradycardia. Some form of continuous monitoring is often required.
  - In the inpatient setting, **continuous central telemetry monitoring** can be used.
  - If further workup is done as an outpatient, **24- to 72-hour Holter monitoring** can be used if the episodes occur somewhat frequently. If infrequent, **an event recorder** or **ILR** should be considered.
  - Again, it is vital to correlate symptoms with the rhythm disturbances discovered via continuous monitoring—a task easily accomplished during inpatient care but

more difficult as an outpatient. Therefore, the importance of accurate symptom diaries in the ambulatory setting should be emphasized to patients.

- To evaluate the sinus node's response to exertion (chronotropic competence), walking the patient in the hallway or up a flight of stairs under appropriate supervision is easy and inexpensive. A formal **exercise ECG** can be ordered if necessary.
- An **EPS** can also be used to assess sinus node function and AV conduction, but it is rarely necessary if the rhythm is already discovered via noninvasive modalities.

SYNCOPE

GENERAL PRINCIPLES

Syncope is a common clinical problem, and a primary goal of evaluation is to determine whether the patient is at increased risk of death.

Definition

Sudden, self-limited loss of consciousness and postural tone caused by transient global cerebral hypoperfusion and followed by spontaneous, complete, and prompt recovery.

Classification

Syncope can be classified into four major categories based on etiology:

- **Neurocardiogenic** (most common): vasovagal, carotid sinus hypersensitivity, and situational

- **Orthostatic hypotension:** hypovolemia, medication induced (iatrogenic), and autonomic dysfunction
- **Cardiovascular:**
  - **Arrhythmia:** sinus node dysfunction, AV block, pacemaker malfunction, VT/VF, SVT (rare)
  - **Mechanical:** HCM, valvular stenosis, aortic dissection, myxomas, pulmonary embolism, pulmonary HTN, acute MI, subclavian steal, etc.
- **Miscellaneous** (not true syncope): seizures, stroke/TIA, hypoglycemia, hypoxia, psychogenic, etc. Atherosclerotic cerebral artery disease is a rare cause of true syncope; the exception is severe obstructive four-vessel cerebrovascular disease (expect focal neurologic findings prior to syncope).

Epidemiology

- Common in the general population—**6% of medical admissions and 3% of emergency room visits**.
- Incidence is similar among men and women; one of the largest epidemiologic studies revealed an 11% incidence during an average follow-up of 17 years, with a sharp rise after age 70 years (*N Engl J Med 2002;347:878*).

Pathophysiology

- The two components of **neurocardiogenic syncope** are described as **cardioinhibitory**, in which bradycardia or asystole results from increased vagal outflow to the heart, and **vasodepression**, where peripheral vasodilation results from sympathetic withdrawal to peripheral arteries. Most patients have a combination of both components as the mechanism of their syncope.
- Specific stimuli may evoke a neurocardiogenic mechanism, leading to **situational syncope** (e.g., micturition, defecation, coughing, swallowing).

Risk Factors

Cardiovascular disease, history of **stroke or TIA**, and **HTN**. Also, low body mass index, increased alcohol intake, and diabetes are associated with syncope (*Am J Cardiol 2000;85:1189*; *N Engl J Med 2002;347:878*).

DIAGNOSIS

- A syncopal event may herald an otherwise unsuspected, potentially lethal cardiac condition, and therefore, a careful evaluation of the patient with syncope is warranted.
- A meticulous history and physical exam are key to an accurate diagnosis of the etiology of syncope. In 40% of episodes, the mechanism of syncope remains unexplained (*Ann Intern Med 1997;126:989*).

Clinical Presentation

History

Special attention should be focused on the **events or symptoms** that **precede and follow** the syncopal event, **eyewitness** accounts during the event, the **time course** of loss and resumption of consciousness (abrupt vs. gradual), and the patient's **medical history**.

- A characteristic prodrome of nausea, diaphoresis, visual changes, or flushing suggests neurocardiogenic syncope, as does the identification of a particular emotional or situational trigger and postepisode fatigue.
- Alternatively, an unusual sensory prodrome, incontinence, or a decreased level of consciousness that gradually clears suggests a seizure as a likely diagnosis.

- With transient ventricular arrhythmias, an abrupt loss of consciousness may occur with a rapid recovery.
- Syncope with exertion is a matter of concern for structural heart disease, pulmonary HTN, and CAD.

Physical Examination

The **cardiovascular** and **neurologic** exams should be the primary focus of initial evaluation.

- Orthostatic vital signs can reveal orthostatic hypotension. All patients should have blood pressure checked in both arms.
- Cardiac exam findings may help detect valvular heart disease, LV dysfunction, pulmonary HTN, etc.

- Neurologic findings are often absent but, if present, may point to a possible neurologic etiology of the syncopal event.
- Carotid sinus massage for 5-10 seconds with reproduction of symptoms and consequent ventricular pause >3 seconds is considered positive for carotid sinus hypersensitivity. It is critical to take proper precautions of telemetry monitoring, availability of bradycardia treatments, and avoiding the procedure in patients with known or suspected carotid disease.

Diagnostic Testing

- The presence of known **structural heart disease**, **abnormal ECG**, **age >65 years**, **focal neurologic findings**, and **severe orthostatic hypotension** suggest a potentially more ominous etiology. Therefore, these patients should be admitted for their workup to avoid delay and adverse outcomes.
- After the history and physical exam, the ECG is the most important diagnostic tool in the evaluation of the patient. It will be abnormal in 50% of cases but alone will yield a diagnosis in only 5% of these patients.
- If the patient has no history of heart disease or baseline ECG abnormalities, **tilt-table testing** has been used to evaluate a patient's hemodynamic response during transition from supine to upright state to precipitate a neurocardiogenic response. In an unselected population, the predictive value of this test is low.
- Please refer to Figure 7-7 for the diagnostic approach to syncope.

TREATMENT

In general, therapy is tailored to the underlying etiology of syncope with goals of preventing recurrence and reducing risk of injury or death.

- **Neurocardiogenic syncope:**
  - **Counsel** patients to take steps to avoid injury by being aware of prodromal symptoms and maintaining a **horizontal position** at those times.
  - Avoid known precipitants and maintain adequate **hydration**.
  - Employ **isometric muscle contraction** during prodrome to abort episode.
  - Evidence suggests that β-adrenergic blockers are probably unhelpful (*Circulation 2006;113:1164*); **selective serotonin reuptake inhibitor (SSRI) antidepressants** and **fludrocortisone** have a debatable effect; and **midodrine** (started at 5 mg PO tid and can be increased to 15 mg tid) is probably helpful in the treatment of neurocardiogenic syncope (*Am J Cardiol 2001;88:80*; *Heart Rhythm 2008;5:1609*).
  - In general, **PPMs** have no proven benefit (*JAMA 2003;289:2224*); however, permanent dual-chamber pacemakers with a hysteresis function (high-rate pacing in response to a detected sudden drop in heart rate) have been shown to be useful in highly selected patients with recurrent neurocardiogenic syncope with a prominent cardioinhibitory component (*J Am Coll Cardiol 1990;16:165*).

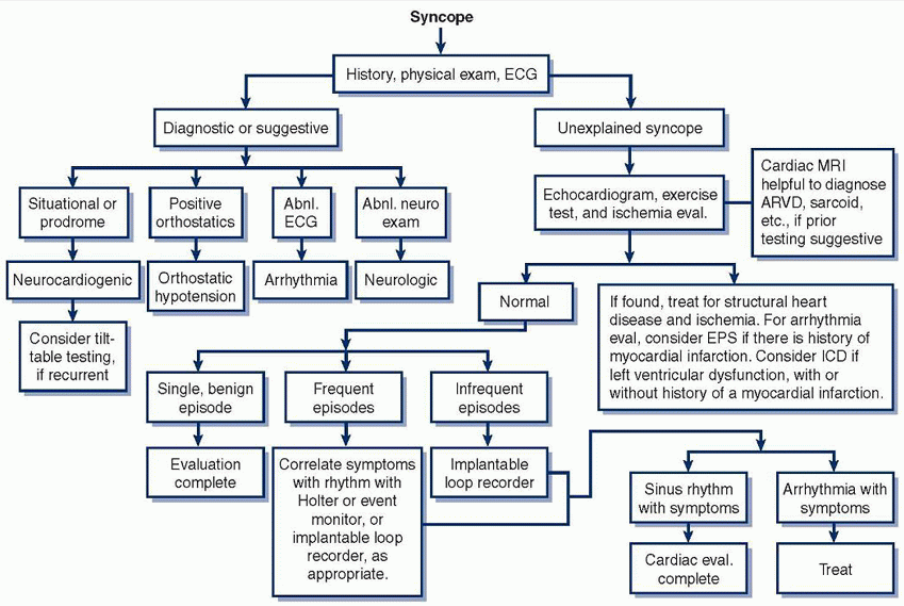


Figure 7-7. Algorithm for the evaluation of syncope. ARVD, arrhythmogenic right ventricular dysplasia; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator. (Data from Holley C. Evaluation of syncope. In: Cooper DH, et al., eds. *The Washington Manual of Medical Therapeutics*. 32nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007; and Strickberger SA, Benson DW, Biaggioni I, et al.; American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke; Quality of Care and Outcomes Research Interdisciplinary Working Group; American College of Cardiology Foundation; Heart Rhythm Society; American Autonomic Society. AHA/ACCF Scientific Statement on the evaluation of syncope: From the American Heart Association Councils on Clinical Cardiology, Cardiovascular Nursing, Cardiovascular Disease in the Young, and Stroke, and the Quality of Care and Outcomes Research Interdisciplinary Working Group; and the American College of Cardiology Foundation: In collaboration with the Heart Rhythm Society: endorsed by the American Autonomic Society. *Circulation* 2006;113[2]:316-27.)

  - **Cardiac pacing** for **carotid sinus hypersensitivity** is appropriate in syncopal patients.
  - In general, neurocardiogenic syncope is not associated with increased risk of mortality.
- **Orthostatic hypotension:**
  - **Adequate hydration** and elimination of offending drugs.
  - Salt supplementation, compressive stockings, and counseling on standing slowly.
  - Midodrine and fludrocortisone can help by increasing systolic BP and expanding plasma volume, respectively.
- **Cardiovascular (arrhythmia or mechanical):**

- Treatment of **underlying disorder** (valve replacement, antiarrhythmic agent, coronary revascularization, etc.)
- **Cardiac pacing** for sinus node dysfunction or high-degree AV block
- Discontinuation of QT-prolonging drugs
- Catheter **ablation** procedures in select patients with syncope associated with SVT

- **ICD** for documented VT without correctable cause and for syncope in presence of significant LV dysfunction even in absence of documented arrhythmia.

8
Critical Care

Catherine Chen
Vladimir Despotovic
Marin H. Kollef

Respiratory Failure

GENERAL PRINCIPLES

Definitions

- **Hypercapnic respiratory failure:** Occurs with acute elevation of carbon dioxide (arterial carbon dioxide tension [$PaCO_2$] >45 mm Hg), producing a respiratory acidosis (pH <7.35).
- **Hypoxemic respiratory failure:** Occurs when normal gas exchange is seriously impaired, causing hypoxemia (arterial oxygen tension [PaO_2] <60 mm Hg or arterial oxygen saturation [SaO_2] <90%).

  Usually associated with tachypnea and hypocapnia; however, progression can lead to hypercapnia as well.
  - **Acute respiratory distress syndrome (ARDS)** is a form of hypoxemic respiratory failure caused by acute lung injury. The common end result is disruption of the alveolocapillary membrane, leading to increased vascular permeability and accumulation of inflammatory cells and protein-rich edema fluid within the alveolar space.
  - The ARDS Definition Task Force redefined ARDS as follows (*JAMA 2012;307:2526*):
    - Onset within 1 week of a known clinical insult or new or worsening respiratory symptoms;
    - Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules;
    - Respiratory failure not fully explained by cardiac failure or volume overload; and
    - Impaired oxygenation with low PaO_2 to fraction of inspired oxygen (FIO_2) ratio (PaO_2/FIO_2 ≤300 mm Hg)
  - Severity of ARDS stratified based on PaO_2/FIO_2:
    - Mild: 200 mm Hg < PaO_2/FIO_2 ≤300 mm Hg with positive end-expiratory pressure (PEEP) ≥5 cm H_2O
    - Moderate: 100 mm Hg < PaO_2/FIO_2 ≤200 mm Hg with PEEP ≥5 cm H_2O
    - Severe: PaO_2/FIO_2 ≤100 mm Hg with PEEP ≥5 cm H_2O

Pathophysiology

- **Hypercapnic respiratory failure** primarily occurs due to ventilatory failure, resulting in an elevated $PaCO_2$:

$$PaCO_2 = \frac{\dot{V}CO_2}{\dot{V}_A} = \frac{\dot{V}CO_2}{\dot{V}_E - \dot{V}_D}$$

where [V with dot above]CO_2 = CO_2 production, [V with dot above]$_A$ = alveolar ventilation, [V with dot above]$_E$ = expired total ventilation, and [V with dot above]$_D$ = dead space ventilation. Rarely, increased carbon dioxide production may contribute to hypercapnia. The differential diagnosis for ventilator failure can be categorized as follows:

- Central nervous system: Hypoventilation/apnea causing decreased respiratory rate (“won't breathe”); e.g., opiate overdose, central apnea/hypoventilation
- Peripheral nervous system: Neuromuscular failure causing decreased tidal volume (“can't breathe”); e.g., Guillain-Barré, myasthenia gravis, amyotrophic lateral sclerosis
- Intercostal muscles: Muscle weakness causing decreased tidal volume; e.g., muscular dystrophies, myopathies
- Thoracic cavity: Anatomic abnormalities causing decreased tidal volume; e.g., scoliosis, thoracoplasty
- Airways: Airway pathologies causing increased dead space; e.g., asthma, chronic obstructive pulmonary disease (COPD)

- **Hypoxemic respiratory failure** usually is the result of the lung's reduced ability to deliver oxygen across the alveolocapillary membrane. The severity of gas exchange impairment is determined by calculating the P(A-a)O_2 gradient using the alveolar gas equation:

$$PaO_2 = FIO_2 (P_{ATM} - P_{H_2O}) - \frac{PACO_2}{R}$$

where FIO_2 = the fraction of inspired oxygen, P_{ATM} = atmospheric pressure, P_{H_2O} = water vapor pressure, and R = the respiratory quotient. Hypoxemia is caused by:

  - **Ventilation-perfusion (V/Q) mismatch:** Occurs when perfusion does not compensate for a change in ventilation or vice versa (e.g., pulmonary embolism and emphysema). Administration of supplemental oxygen increases PaO_2, although it should be noted that oxygen administration paradoxically worsens V/Q matching in emphysema via reversing hypoxic vasoconstriction of pulmonary capillaries, leading to hypercarbia.
  - **Shunt:** An extreme of V/Q mismatch. Occurs when mixed venous blood bypasses lung units and enters systemic arterial circulation. Congenital shunts are due to developmental anomalies of the heart and great vessels. Acquired shunts are due to pus, water, blood, or atelectasis. Acquired cardiac and peripheral vascular shunts also can occur (Table 8-1). Shunts are associated with a widened P(A-a)O_2 gradient, and the resultant hypoxemia is resistant to correction with supplemental oxygen alone.

TABLE 8-1 Causes of Shunt

Cause	Examples
Pulmonary shunts	

Pus	Pneumonia
Water	Cardiogenic pulmonary edema
	Acute myocardial infarction
	Systolic or diastolic left ventricular failure
	Mitral regurgitation or stenosis
	Noncardiogenic pulmonary edema
	Primary acute respiratory distress syndrome
	Aspiration
	Inhalational injury
	Near drowning
	Secondary acute respiratory distress syndrome
	Sepsis
	Pancreatitis
	Reperfusion injury
	Upper airway obstruction pulmonary edema
	Neurogenic pulmonary edema
	High-altitude pulmonary edema
Blood	Diffuse alveolar hemorrhage
Atelectasis	Pleural effusion with atelectasis
	Mucous plugging with lobar collapse
Cardiac shunts	Patent foramen ovale
	Atrial septal defect
	Ventricular septal defect

Vascular shunts	Arteriovenous malformation

- **Diffusion impairment:** Diseases that cause thickening of the interstitium, such as idiopathic pulmonary fibrosis, result in hypoxemia due to gas equilibration time exceeding red blood cell transit time. Hypoxemia usually responds to supplemental oxygen therapy.
- **Hypoventilation:** A decrease in minute ventilation results in an increase in $PACO_2$, displacing oxygen. In pure hypoventilation, the $P(A\text{-}a)O_2$ gradient is normal. Primary treatment is directed at correcting the cause of hypoventilation.
- **Low mixed venous oxygenation:** Normally, the lungs fully oxygenate pulmonary arterial blood, and mixed venous oxygen tension (PvO_2) does not affect PaO_2 significantly. However, a decreased PvO_2 can lower the PaO_2 significantly when either intrapulmonary shunting or V/Q mismatch is present. Factors that can contribute to low mixed venous oxygenation include anemia, hypoxemia, inadequate cardiac output (CO), and increased oxygen consumption. Improving oxygen delivery to tissues by increasing hemoglobin or CO usually decreases oxygen extraction and improves mixed venous oxygen saturation (SvO_2).
- **Low inspired oxygen:** The partial pressure of inspired oxygen is reduced at high altitude secondary to decreased barometric pressure. Inhaled toxic gas decreases FIO_2.

- **Mixed respiratory failure:** Most patients who have respiratory failure have both hypoxemia and hypercarbia. Frequently seen in postoperative patients and patients with COPD exacerbations.

Noninvasive Oxygen Therapy

GENERAL PRINCIPLES

- **Nasal cannulas** are most commonly used, but the exact FIO_2 delivered is unknown because it is influenced by peak inspiratory flow demand. Each additional liter of flow increases FIO_2 by approximately 4%. Flow rates should be limited to ≤5 L/min.
- **Humidified high-flow nasal cannula** can deliver heated and humidified oxygen at higher flows and concentration—up to 50 L/min and 100% FIO_2—than traditional nasal prongs. Optiflow is the most commonly used system.
- **Venturi masks** allow the precise administration of oxygen. Usual FIO_2 values delivered are 24%, 28%, 31%, 35%, 40%, and 50%.
- **Nonrebreathing masks** achieve higher oxygen concentrations (80-90%). A one-way valve prevents exhaled gases from entering the reservoir bag, maximizing the FIO_2.
- **Noninvasive positive-pressure ventilation (NPPV):** Includes continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) ventilation.
  - Decreases the need for endotracheal intubation and mechanical ventilation in patients with neuromuscular disease, COPD, congestive heart failure, and postoperative respiratory insufficiency (*Crit Care Clin 2007;23:201*).

- Use limited to patients who are conscious, cooperative, able to protect their airway, and hemodynamically stable (*N Engl J Med 1998;339:429*).
- May be poorly tolerated due to claustrophobia or aerophagia, so **use should be limited to those with an anticipated short duration of respiratory failure** (e.g., cardiogenic pulmonary edema, COPD exacerbation).
- **Close monitoring is required during its use.**
- **CPAP** prevents alveolar collapse during expiration. Initially, 5 cm H_2O of pressure should be applied, and if hypoxemia persists, the level should be increased by 3-5 cm H_2O up to a level of 10-15 cm H_2O.
- **BPAP** supports both inspiration and expiration to decrease work of breathing. An inspiratory pressure of 5-10 cm H_2O and an expiratory pressure of 5 cm H_2O are reasonable starting points. Ventilation is determined by the difference between inspiratory and expiratory pressures (i.e., "drive pressure"), and inspiratory pressures can be uptitrated to achieve adequate tidal volumes and minute ventilation.

Airway Management and Tracheal Intubation

GENERAL PRINCIPLES

- **Airway management**
  - **Head and jaw positioning:** The oropharynx should be inspected, and all foreign bodies should be removed. If the patient is unresponsive, the head tilt-chin lift maneuver should be performed (see Airway Emergencies in Chapter 26, Medical Emergencies). If neck immobilization is required, jaw thrust should be performed.
  - **Oral and nasopharyngeal airways:** Used when head and jaw positioning fail to establish a patent airway. Initially inserted with the concave curve of the airway facing toward the roof of the mouth. The oral airway then is turned 180 degrees as it is inserted so that the concave curve of the airway follows the natural curve of the tongue. Careful monitoring of airway patency is required, as malpositioning can push the tongue posteriorly and result in oropharyngeal obstruction. Nasopharyngeal airways are made of soft plastic and are passed easily down one of the nasal passages to the posterior pharynx after topical nasal lubrication and anesthesia with viscous lidocaine jelly.
  - **Bag-valve-mask ventilation:** Ineffective respiratory efforts can be augmented with simple bag-valve-mask ventilation. Proper fitting and positioning of the mask using the "EC" hand position—thumb and index finger forming a "C" around the mask, and the remaining fingers forming an "E" to support the jaw—ensure a tight seal around the mouth and nose. Used in conjunction with proper positioning and airway adjuncts, e.g., oral airway.
  - **Laryngeal mask airway (LMA):** The LMA is a supraglottic airway device shaped like an endotracheal tube connected to an elliptical mask. It is designed to be inserted over the tongue and seated in the hypopharynx, covering the supraglottic structures and relatively isolating the trachea. It is a temporary airway and should not be used for prolonged ventilatory support.
- **Endotracheal intubation** (*Int Anesthesiol Clin 2000;38:1*)
  - **Indications:** Initiation of mechanical ventilation, airway protection, inadequate oxygenation with less invasive methods, prevention of aspiration, excessive pulmonary secretions, and hyperventilation as a treatment for increased intracranial pressure

- **Before endotracheal tube intubation** is attempted:
  - Evaluate head and neck positioning: Oral, pharyngeal, and tracheal axes should be aligned by flexing the neck and extending the head, achieving the “sniffing” position.
  - Obese patients may require a shoulder roll or ramp.
  - Necessary equipment must be at the bedside: oxygen tubing, bag-valve-mask device, suction and tubing, endotracheal tube with stylet, 10-mL syringe, direct laryngoscope, direct laryngoscope blades (most commonly Macintosh or Miller size 3 or 4), and end-tidal carbon dioxide (CO_2) colorimeter.
  - Medications that may be used during intubation include neuromuscular blocking agents, opiates, and anxiolytics. Commonly used agents are listed in Table 8-2.
- **Techniques** include:
  - Direct laryngoscopic orotracheal intubation: Most commonly used, requiring only a direct laryngoscope and light source. Procedure available in Table 8-3.
  - Video laryngoscopic orotracheal intubation: Allows for direct visual confirmation of intubation by a second observer via video monitoring.
  - Advanced techniques for specialists include blind nasotracheal intubation and flexible fiber optically guided orotracheal or nasotracheal intubation.
- **Verification of correct endotracheal tube location and positioning:** Proper tube location must be ensured by:
  - Fiber optic inspection of the airways through the endotracheal tube; *or*
  - Direct visualization of the endotracheal tube passing through the vocal cords; *and*

  - Use of an end-tidal CO_2 monitor; *and*
  - CXR
  - Clinical evaluation of the patient (i.e., listening for bilateral breath sounds over the chest and the absence of ventilation over the stomach) and radiographic evaluation alone are unreliable for establishing correct endotracheal tube location.
  - The tip of the endotracheal tube should be 3-5 cm above the carina, depending on head and neck position.
- **After successful intubation:**
  - Tracheal tube cuff pressures: Should be monitored at regular intervals and maintained below capillary filling pressure (25 mm Hg) to prevent ischemic mucosal injury.
  - Sedation: Anxiolytics and opiates are frequently used to facilitate endotracheal intubation and mechanical ventilation. Commonly used agents are listed in Table 8-2.
- **Complications:** Improper endotracheal tube location or positioning is the most important immediate complication to be recognized and corrected.
  - Esophageal intubation should be suspected if no end-tidal CO_2 is detected after three to five breaths, hypoxemia persists or develops, there is a lack of breath sounds, or abdominal distention or regurgitation of stomach contents occurs.

- Mainstem intubation should be suspected if peak airway pressures are elevated or there are unilateral breath sounds.
- Other complications include dislodgment of teeth and upper airway trauma.

- **Surgical airways**
  - **Indications** for surgical airways in critical care:
    - Life-threatening upper airway obstruction (e.g., epiglottitis, angioedema, facial burns, laryngeal/vocal cord edema) preventing bag-valve-mask ventilation and endotracheal intubation cannot be performed.
    - Need for prolonged respiratory support.
  - **Needle cricothyrotomy:** Indicated in emergency settings when the patient cannot be ventilated noninvasively, standard endotracheal intubation is unsuccessful, and a surgical airway cannot be immediately performed. The steps of the procedure are listed in Table 8-3.
  - **Cricothyrotomy:** Indicated in emergency settings when the patient cannot be ventilated noninvasively and standard endotracheal intubation is unsuccessful. The steps of the procedure are listed in Table 8-3.
  - **Tracheostomy:** Most commonly performed due to need for prolonged respiratory support.
    - Recent review demonstrated no benefit of early (≤10 days) tracheostomy over late (>10 days) tracheostomy (*Br J Anaesth 2006 Jan;96(1):127-31*).
    - Tracheostomy should be considered if prolonged ventilatory support is anticipated after 10-14 days of endotracheal intubation.
    - **Complications:** Tracheostomy sites require at least 72 hours to mature, and tube dislodgment prior to maturation can lead to serious, life-threatening complications.

      A tracheostomy tube that has been dislodged prior to stoma maturation **should not be reinserted** due to the risk of creating a false tract.

      Standard orotracheal intubation should be performed if a tracheostomy tube is dislodged prior to stoma maturation.

      Tracheo-innominate artery fistulas are an uncommon but life-threatening complication of tracheostomy that most commonly occurs 7-14 days after the procedure but can occur up to 6 weeks after the procedure. Immediate management includes overinflation of the tracheostomy tube cuff, digital compression of the stoma, and surgical exploration (*Br J Anaesth 2006;96:127*).

TABLE 8-2 Drugs to Facilitate Endotracheal Intubation and Mechanical Ventilation

Drug	Bolus Dosages (IV)	Continuous-Infusion Dosages[a]	Onset	Duration After Single Dose
Succinylcholine[b]	0.3-1 mg/kg	—	45-60 s	2-10 min

Pancuronium	0.05-0.1 mg/kg	1-2 µg/kg/min	2-4 min	60-90 min
Vecuronium	0.08-0.1 mg/kg	0.3-1 µg/kg/min	2-4 min	30-45 min
Atracurium	0.2-0.6 mg/kg	5-15 µg/kg/min	2-4 min	20-35 min
Lorazepam[a]	0.03-0.1 mg/kg	0.01-0.1 mg/kg/h, titrate to effect	5-20 min	2-6 h[c]
Midazolam[a]	0.02-0.08 mg/kg	0.04-0.2 mg/kg/h, titrate to effect	1-5 min	30-60 min[c]
Morphine	0.01-0.15 mg/kg	0.1-0.5 mg/kg/h, titrate to effect	2-10 min	2-4 h[c]
Fentanyl	0.35-1.5 µg/kg	1-10 µg/kg/h, titrate to effect	30-60 s	30-60 min[c]
Etomidate[b]	0.3-0.4 mg/kg	—	10-20 s	4-10 min
Propofol	0.25-0.5 mg/kg	25-80 µg/kg/min	15-60 s	3-10 min[c]
Dexmedetomidine	1 µg/kg	0.2-0.7 µg/kg/h	10 min	30 min

[a]A continuous infusion should be started or titrated upward only after the desired level of sedation is achieved with bolus administration.

[b]Use only in the process of rapid sequence intubation.

[c]Duration is prolonged with continuous IV administration. Frequent titration to the minimum effective dose is required to prevent accumulation of drug.

TABLE 8-3 Procedure for Endotracheal Intubation, Needle Cricothyroidotomy, and Cricothyrotomy

Endotracheal Intubation Using Direct Laryngoscopy

Equipment	Oxygen tubing, bag-valve-mask device, suction and tubing, oral airway, laryngoscope, laryngoscope blades, 7.0-mm inner diameter endotracheal tube with stylet, syringe, end-tidal carbon dioxide colorimeter	
Technique	Step 1	Place the patient in the “sniffing” position, with neck flexed and head extended; obese patients will require shoulder roll or ramp.
	Step 2	Preoxygenate the patient with 100% oxygen through the bag-valve-mask device until saturations are maintained at >95% for 3-5 min, and suction oral secretions as necessary.
	Step 3	During preoxygenation, ensure that all equipment necessary is present and functional: check the endotracheal tube cuff with inflation and deflation, and that the light of the laryngoscope is functional.
	Step 4	Administer IV sedation; once the patient is appropriately sedated, open the mouth with the right hand and insert the laryngoscope blade into the right side of mouth with the left hand, sweeping the tongue to the left.
	Step 5	Advance the blade to the base of the tongue, then lift vertically to visualize the vocal cords; **do not tilt the laryngoscope.**
	Step 6	If vocal cords are visible, insert the endotracheal tube with the stylet with the right hand; once the cuff is past the vocal cords, remove stylet. **Do not attempt intubation if the vocal cords are not visible.**
	Step 7	Advance the endotracheal tube until it is at 21 cm at the gum/teeth for women and 22 cm for men, and inflate the cuff.
	Step 8	**Check tube location** with end-tidal carbon dioxide colorimeter, auscultation over the chest and abdomen, AND chest radiograph.

Needle Cricothyroidotomy (*Br J Hosp Med (Lond) 2009;70:M186*)

Equipment	Large-bore IV catheter with needle stylet, 3-mL Luer lock syringe with plunger removed, 7-mm inner diameter endotracheal tube adapter	
Technique	Step 1	Extend the neck and identify the cricothyroid membrane, located inferior to the thyroid cartilage and superior to the thyroid gland.
	Step 2	Stabilize the thyroid cartilage with the nondominant hand and, using the dominant hand, introduce the IV catheter with the needle stylet at a 45-degree angle through the cricothyroid membrane into the trachea, aspirating air to confirm location.
	Step 3	Advance the catheter to the hub, and remove the needle stylet.

	Step 4	Attach the Luer lock syringe to the catheter, and then the endotracheal tube adapter to the syringe to allow for bag-valve ventilation.

Cricothyrotomy (*Principles of Critical Care, 3e. Chapter 34;2005*)

Equipment	Scalpel, Kelly forceps, 6-mm inner diameter or smaller endotracheal tube	
Technique	Step 1	Extend the neck and identify the cricothyroid membrane, located inferior to the thyroid cartilage and superior to the thyroid gland.
	Step 2	Stabilize the thyroid cartilage with the nondominant hand and, using the dominant hand, make a 1-cm horizontal incision just above the superior border of the cricoid.
	Step 3	Using the Kelly forceps, dissect until the cricothyroid membrane is visualized, and then make a vertical incision through the midline of the membrane, being careful to not pass the blade too deeply.
	Step 4	Widen the incision with Kelly forceps until the endotracheal tube can be inserted, and then inflate the cuff.

Mechanical Ventilation

GENERAL PRINCIPLES

- **Basic modes of ventilation:** Determines how the ventilator initiates a breath (triggering), how the breath is delivered, how patient-initiated breaths are supported, and when to terminate the breath to allow expiration (cycling).
  - **Triggering a breath** occurs after a period of time has elapsed (time-triggered) or when the patient has generated sufficient negative airway pressure or inspiratory flow that exceeds a predetermined threshold (patient-triggered).
  - **Assist-control (AC):** Primary mode of ventilation used in respiratory failure Delivers a fully supported breath whether time- or patient-triggered
  - **Synchronized intermittent mandatory ventilation (SIMV):** Commonly used in surgical patients
    - Delivers a fully supported breath only when time-triggered.
    - Patient-triggered breaths are unassisted or minimally assisted; volumes determined by patient's effort and lung compliance.
  - **Pressure support ventilation (PSV):** A spontaneous mode of ventilation without a set respiratory rate. Delivers a practitioner-determined inspiratory pressure during patient-triggered breathing. **No respiratory rate is set, so no guaranteed minute ventilation.**
  - **Volume control (VC):** Delivers a practitioner-determined tidal volume (V_T) for each breath. Patient airflow is limited to constant or decelerating ramp pattern. When predetermined V_T is delivered, airflow is

terminated and exhalation occurs.

- **Pressure control (PC):** Delivers a practitioner-determined inspiratory pressure for a predetermined inspiratory time for each breath. Airflow is determined by the patient and limited by the inspiratory pressure. When inspiratory time has elapsed, inspiratory

pressure is terminated and exhalation occurs. **Does not deliver a guaranteed V_T and, therefore, minute ventilation.**

- **Basic ventilator settings:** Requires both a mode (AC vs. SIMV) and a control (VC vs. PC).
  - **Respiratory rate**, **FIO_2**, and **PEEP** must be set for all modes of ventilation.
  - For VC, the following must be entered:
    - **V_T:** 6-8 mL/kg ideal body weight (IBW) to prevent barotrauma.

      IBW: Male IBW = 50 kg + 2.3 kg/in × (Height in inches − 60) [imperial], 50 kg + 1.1 kg/cm × (Height in cm − 152.4) [metric]; Female IBW = 45.5 kg + 2.3 kg/in × (Height in inches − 60) [imperial], 45.5 kg + 1.1 kg/cm × (Height in cm − 152.4) [metric]
    - **Inspiratory flow rate:** May be constant (square wave) or ramp (decelerating). Recommend 60 L/min or greater; higher flow rates increase expiration time.
  - For PC, the following must be entered:
    - **Inspiratory pressure:** Should be sufficient to generate V_T of 6-8 mL/kg IBW. Should not exceed 35 cm H_2O due to risk of barotrauma.
    - **Inspiratory time:** Usually <1 second. Shorter inspiratory times increase expiration time.
  - For SIMV, patient-initiated breaths may be assisted with pressure support.
- **Basic ventilator terminology and management:** Flow-time and pressure-time tracings are demonstrated in Figure 8-1.
  - FIO_2: Initial FIO_2 when initiating mechanical ventilation should be 100%, and FIO_2 should be titrated to maintain SaO_2 >87% or PaO_2 >55 mm Hg.
  - **Minute ventilation:** Defined as the product of V_T and respiratory rate (V_T × RR). Normally between 5-10 L/min in resting adults, but may be much higher in high metabolic states, e.g., septic shock.
  - **Peak airway pressure:** Composed of pressures necessary to overcome inspiratory airflow resistance, chest wall recoil resistance, and alveolar opening resistance. Does not reflect alveolar pressure.
  - **Mean airway pressure:** Mean pressures applied during the inspiratory cycle. Approximates alveolar pressure until overdistention occurs.
  - **Plateau pressure:** Reflects alveolar pressure. Checked by performing an end-inspiratory hold maneuver to allow pressures through the tracheobronchial tree to equilibrate.
- **Mechanical ventilation for patients with ARDS:** Due to severe hypoxia associated with ARDS, oxygenation and prevention of barotrauma may have to be prioritized over ventilation, resulting in hypercapnia. Hypercapnia resulting in a pH of 7.20-7.35 may need to be tolerated in order to sufficiently oxygenate the patient ("**permissive hypercapnia**").

- Advanced modes of ventilation: Should be used only after discussion with higher-level practitioners.
  - Volume-assured PSV: Ventilator initially delivers practitioner-determined pressure support; if insufficient to achieve desired V_T within the breath, then ventilator will increase inspiratory pressure to achieve desired V_T.
  - Pressure-regulated VC ventilation: Ventilator determines after each breath if inspiratory pressure was sufficient to achieve targeted V_T; if insufficient or excessive, then ventilator will adjust inspiratory pressure to achieve desired V_T.
  - Inverse-ratio ventilation (IRV): A pressure-controlled method of ventilation most commonly used in ARDS. Inspiratory time exceeds expiratory time to improve oxygenation at the expense of ventilation; patients are permitted to become hypercapnic to pH 7.20. If obstructive lung disease is present, can cause auto-PEEP and excessive hypercapnia.
  - Airway pressure release ventilation (APRV): An extreme version of IRV. Inspiratory pressure (P_{high}) applied for a prolonged period of time (T_{high}) with a short expiratory time (T_{low}, or release time)—usually <1 second—to allow for ventilation. Like IRV, patients are permitted to be hypercapnic to pH 7.20.

    Bilevel ventilation: **Not to be confused with BPAP.** APRV with spontaneous breathing allowed during T_{high} to improve ventilation.

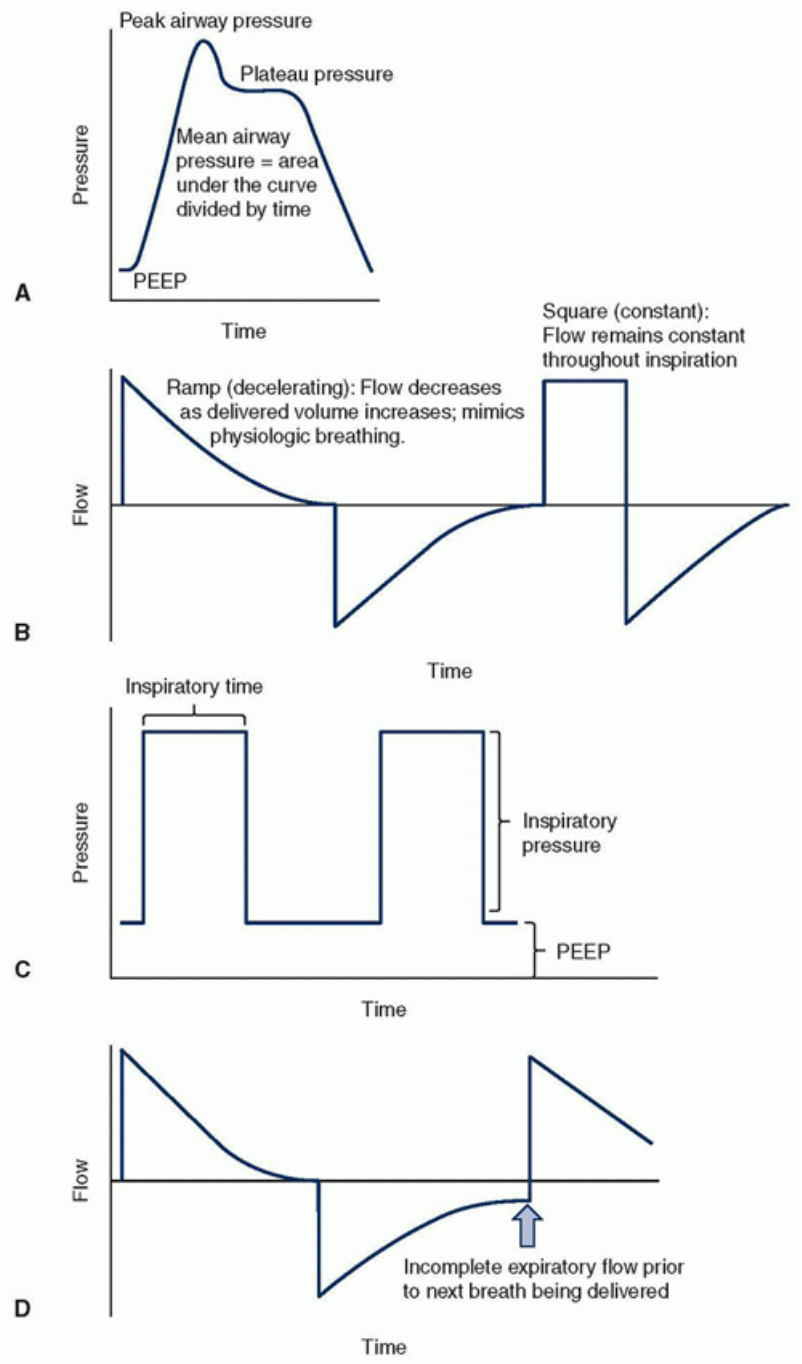


Figure 8-1. Flow-time and pressure-time tracings. **A.** Pressure-time curve for one breath. **B.** Flow-time curve for volume-control ventilation. Pressure varies throughout inspiratory time, depending on lung compliance. **C.** Pressure-time curve for pressurecontrol ventilation. Flow varies throughout inspiratory time, depending on lung compliance. **D.** Pressure-time curve demonstrating auto-positive end-expiratory pressure (auto-PEEP).

- High-frequency oscillatory ventilation: A pressure-controlled form of ventilation. Mean airway pressure set at the mean airway pressure that was previously required to maintain oxygenation. Very small, rapidly delivered breaths at 3-15 Hz allow for CO_2 clearance. Power determines V_T of these very small breaths and should be set at a level that causes vibration of the mid-thigh. Patients must be paralyzed to tolerate this form of ventilation. Previously thought to potentially improve outcomes in ARDS (*BMJ 2010;340:c2327*), but **recent prospective randomized controlled trials demonstrate no reduction** (*N Engl J Med 2013;368:806*) **and possible increase in mortality** (*N Engl J Med 2013;368:795*).

ADJUNCTS TO MECHANICAL VENTILATION

- **Neuromuscular blockade:** Most commonly used in severe ARDS to decrease oxygen consumption from accessory inspiratory muscle use. Recent meta-analysis indicates that its use is associated with lower risk of barotrauma and lower mortality, but more investigation is needed (*Crit Care 2013;17:R43*).
- **Prone positioning:** Improves oxygenation in patients with ARDS by improving V/Q mismatching and decreasing shunt by decreasing amount of atelectatic lung. Early application is associated with improved mortality in ARDS (*N Engl J Med 2013;368:2159*).
  - Patients with moderate to severe ARDS (PaO_2/FIO_2 <150 mm Hg) should be considered.
  - Patients should receive neuromuscular blockade to tolerate proning.
  - Hemodynamic instability an **absolute contraindication**.
  - Morbid obesity a relative contraindication.
  - Patients should remain prone for at least 16 consecutive hours for benefit. Complete proning protocol available online at *New England Journal of Medicine. Available at http://www.nejm.org/action/showMediaPlayer?doi=10.1056%2FNEJMoa1214103&aid=NEJMoa1214103_attach_1&area=*
- Inhaled prostacyclins: Used in ARDS. Theoretically, inhalation of prostacyclins—a class of vasodilators—improves oxygenation by preferential vasodilation of the capillary beds of ventilated lung.
  - Small studies have demonstrated transient improvement in oxygenation (*Pharmacotherapy 2014;34:279*).
  - **No studies have been performed to investigate whether mortality benefit exists.**
  - Has antiplatelet effects, so theoretical concern for worsening diffuse alveolar hemorrhage.
  - Expensive therapy: $150 per day (*J Thorac Cardiovasc Surg 2004;127:1058*).
- Nitric oxide: Used in ARDS. Like inhaled prostacyclins, improves oxygenation by preferential vasodilation of capillary beds of ventilated lung.
  - Transient (24-hour) improvement in oxygenation that resolves by 48 hours (*JAMA 2004;291:1603*)
  - **Does not improve mortality** (*Crit Care Med 2014;42:404*) **and may increase incidence of renal failure** (*Anesth Analg 2011;112:1411*)
  - Very expensive therapy: $3000 per day (*J Thorac Cardiovasc Surg 2004;127:1058*)
- **Helium-oxygen mixture (Heliox):** Used in asthma and severe bronchospasm. Usually, a mixture of 80% helium and 20% oxygen, although also available in other ratios. Theoretically decreases airway resistance due to its low density, thereby decreasing work of breathing. Studies have suggested benefit only in patients with more severe obstruction (*Cochrane Database Syst Rev 2006;(4):CD002884:1-28*).

COMPLICATIONS OF MECHANICAL VENTILATION

- **Airway malpositioning and occlusion:** See Airway Management and Tracheal Intubation section.
- **Troubleshooting ventilator alarms:** See Figure 8-2.

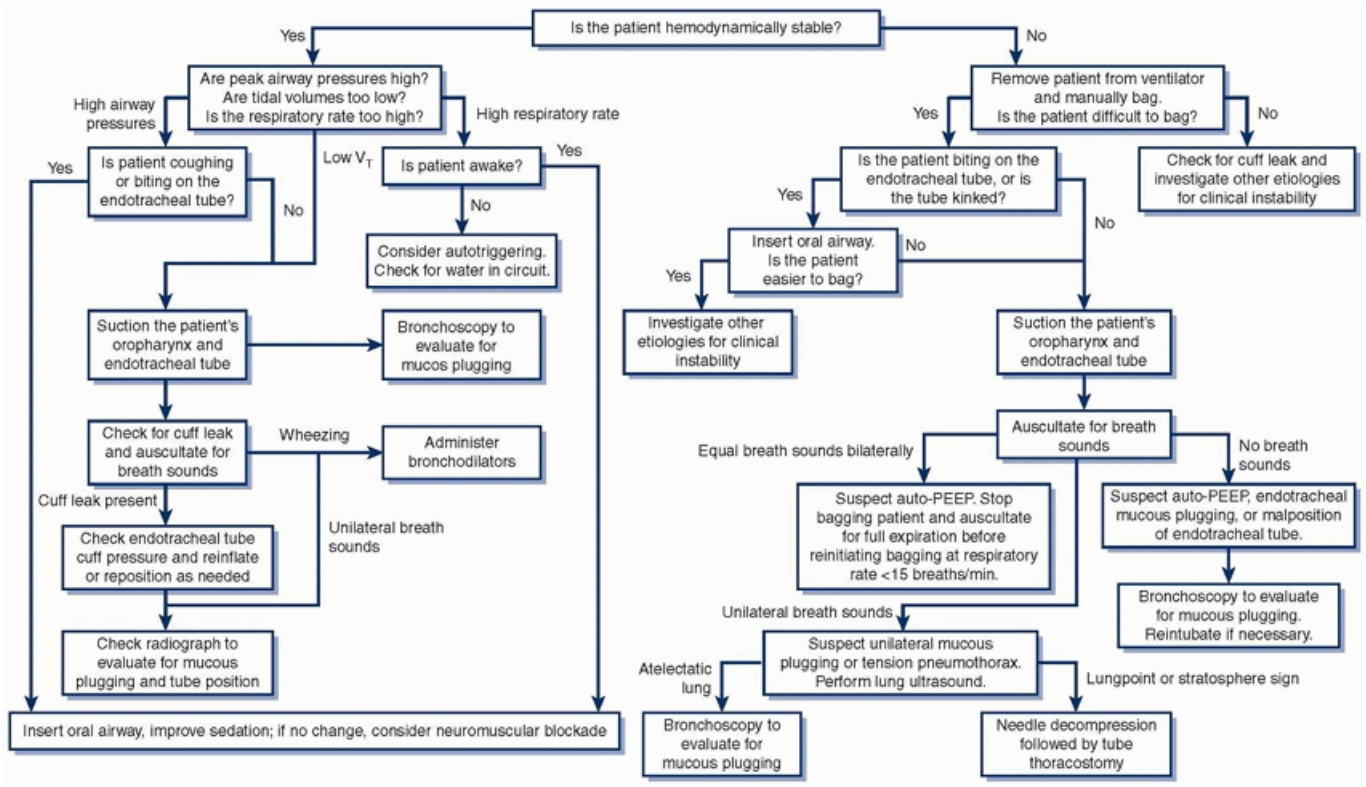


Figure 8-2. Troubleshooting ventilator alarms: what to do when the patient is hypoxic. Auto-PEEP, auto-positive end-expiratory pressure.

- **Auto-PEEP:** Occurs when inspiration is initiated before complete exhalation is complete. May be detected on physical exam by wheezing that does not terminate prior to the next breath. Demonstrated on ventilator flow-time loop by flow not returning to baseline prior to delivery of next breath (Figure 8-1). Excessive auto-PEEP can lead to cardiac decompensation due to tension pneumothorax-like physiology.
- **Barotrauma/volutrauma:** Occurs when excessive PEEP, inspiratory pressures, or tidal volumes are applied, resulting in alveolar rupture and dissection of air along interstitial tissues and causing pneumothorax, pneumomediastinum, pneumopericardium, or pneumoperitoneum. If undetected, can result in life-threatening cardiac decompensation.
- **Ventilator-associated events (VAE):** Encompasses a broad range of conditions and complications that occur in mechanically ventilated patients. Must have a baseline stability of >2 days, defined as stable or decreasing daily minimum PEEP or FIO_2 (*Centers for Disease Control and Prevention 2015 VAE*). Available at *http://www.cdc.gov/nhsn/PDFs/pscManual/10-VAE_FINAL.pdf*
  - **Ventilator-associated condition:** Patient develops worsening oxygenation, defined as requiring increased daily minimum PEEP (≥3 cm H_2O above baseline) or FIO_2 (≥20% above baseline) for ≥2 calendar days
  - **Infection-related ventilator-associated complication:** Within 2 calendar days of worsening oxygenation, **both** of the following criteria are met:
    - Temperature >38°C or < 36°C **or** WBC count ≥12,000 or ≤4000 cells/μL
    - At least one new antimicrobial agent is initiated and continued for ≥4 calendar days
  - **Ventilator-associated pneumonia (VAP):** On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after worsening oxygenation, one of the following criteria are met:

- **Positive culture** from endotracheal aspirate, bronchoalveolar lavage, lung tissue, or protected specimen brush that meets quantitative or semi-qualitative thresholds
- **Purulent respiratory secretions and positive culture** from one of the above specimens that does not meet quantitative threshold
- Positive pleural fluid culture; diagnostic test for *Legionella* species; diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, or coronavirus
- Lung histopathology demonstrating abscess formation, consolidation, parenchymal invasion by fungi, or evidence of infection of the viral pathogens listed above

◦ Daily oral care with chlorhexidine mouthwash decreases risk of VAP.

- Stress-induced peptic ulcer disease: Traditionally thought to be a significant risk of prolonged critical illness and mechanical ventilation, requiring prophylaxis with proton pump inhibitor or H_2 receptor antagonists. However, concerns of increased risk of VAP and recent meta-analyses indicate that stress ulcer prophylaxis needs to be more closely examined (*J Intensive Care Med 2014;40:11*).
- Oxygen toxicity: Breathing high FIO_2 (>60%) for a prolonged period of time (>48 hours) can lead to excessive free radical generation, resulting in lung injury. However, hypoxemia is more dangerous than brief exposure to high FIO_2.

LIBERATION FROM MECHANICAL VENTILATION

- Readiness to wean: Daily assessment of readiness for extubation should begin once underlying disease process begins to resolve and minimal ventilator support is required.
  - Minimal ventilator support: FIO_2 ≤40%, PEEP 5 cm H_2O to maintain SpO_2 >90%.
  - Arterial blood gas: pH and $PaCO_2$ should be at the patient's baseline; particularly important for patients with chronic CO_2 retention.
  - Ventilation requirement: Minute ventilation should be <10 L/min and respiratory rate <30 breaths/min.

  - Mental status: Patient should be awake, alert, and cooperative.
  - Secretions: Secretions should be thin, scant in amount, and easily suctioned; patient should not require suctioning more frequently than every 4 hours prior to extubation.
  - Strength: Patient should have strong cough and be able to lift head off the bed and hold it in flexion for >5 seconds.
  - Breathing trial: Patient should be able to generate spontaneous V_T >5 mL/kg IBW.
  - Rapid shallow breathing index (RSBI): Defined as ratio of respiratory rate to V_T in liters (f/V_T). RSBI >105 accurately predicts weaning failure (*N Engl J Med 1991;23:1445*), but RSBI ≤105 is less accurate at predicting weaning success.
- Methods: **Protocol of daily sedation interruption and breathing trials** is most important predictor of timely liberation from mechanical ventilation (*Cochrane Database Syst Rev 2014;11:CD006904:1-61*), regardless of technique used. Trial times vary between 30 minutes and 2 hours.

- PSV: No time-triggered breaths, but patient remains connected to the ventilator. PEEP is usually at 5 cm H_2O, with low levels of pressure support (5-10 cm H_2O) during spontaneous breathing.
- T-piece/spontaneous breathing trial: Patient is removed from the ventilator but remains intubated. Endotracheal tube is connected to a heated, humidified circuit with minimal or no supplemental oxygen. End-tidal CO_2 monitoring may be used for additional safety.
- SIMV: Used most frequently in surgical and neurosurgical patients. Set respiratory rate is gradually decreased over hours to days until patient is primarily breathing spontaneously. **Has the poorest weaning outcomes of all techniques** (*Chest 2001;120:474S*).

- Extubation: Should be performed early in the day, when full ancillary staff are available.
  - Laryngeal edema: In patients with concern for laryngeal edema (e.g., angioedema, traumatic intubation), cuff leak should be checked prior to extubation. **Absence of cuff leak should preclude extubation**, and patients should be treated with intravenous corticosteroids for 12-24 hours prior to extubation (*Cochrane Database Syst Rev 2009;(3):CD001000:1-24*).

    Cuff leak test is performed by recording the expired tidal volume when the cuff is inflated and then deflating the cuff and recording the expired tidal volume over the next six breaths. The mean of the three lowest tidal volumes is used to calculate the cuff leak volume: the difference between the expired tidal volume with the cuff inflated and expired tidal volume with the cuff deflated. A cuff leak volume <110 mL is predictive of postextubation stridor (*Chest 1996;110:4*).
  - Extubation to NPPV: In patients with COPD who are intubated for acute respiratory failure, extubation to NPPV is associated with a reduction in mortality and health care-associated pneumonia (*Cochrane Database Syst Rev 2013;12:CD004127:1-60*). Similar benefit has **not** been demonstrated in other etiologies of respiratory failure.
- Failure to wean: Defined as inability to liberate from mechanical ventilation 48-72 hours after resolution of underlying disease process. Factors that should be considered include the following:
  - Endotracheal tubes with smaller inner diameter increase airway resistance and may make breathing trials more difficult.
  - Use of neuromuscular blockade is associated with prolonged weakness, particularly when used with corticosteroids (*Curr Opin Crit Care 2004;10:47*).
  - Acid-base disturbances may make liberation from mechanical ventilation difficult.
    - Non-anion gap metabolic acidosis causes compensatory increase in minute ventilation (respiratory alkalosis) to normalize pH, which can lead to tachypnea and respiratory fatigue upon extubation.
    - Metabolic alkalosis causes blunting of ventilatory drive and decrease in minute ventilation (respiratory acidosis) to maintain normal pH, which can lead to hypercapnia upon extubation.

Shock

GENERAL PRINCIPLES

- A process in which blood flow and oxygen delivery to tissues are deranged, leading to tissue hypoxia and resultant compromise of cellular metabolic activity and organ function.
- Main goal of therapy is rapid cardiovascular resuscitation to reestablish tissue perfusion.

- Definitive treatment requires reversal of underlying processes.

Classifications of Shock

- **Distributive:** Shock caused by massive vasodilation and impaired distribution of blood flow, resulting in tissue hypoxia. Usually associated with hyperdynamic cardiac function, unless cardiac function is somehow impaired (see later discussion of cardiogenic shock).
  - **Primary etiologies** are septic shock and anaphylactic shock. Septic shock is most commonly seen in medical intensive care units and will be further discussed in the next section. Anaphylaxis is discussed in Chapter 11, Allergy and Immunology.
  - **Hemodynamic parameters** will demonstrate increased CO, decreased systemic vascular resistance (SVR) due to vasodilation, and elevated central venous oxygen saturation ($ScvO_2$) due to ineffective oxygen extraction by tissue.
  - Primary goals of therapy are:
    - Volume resuscitation: Due to massive peripheral vasodilation, patients have a functionally decreased oxygen-carrying capacity, requiring volume resuscitation. IV crystalloid fluids are primarily used.
    - Treatment of underlying infection: Inadequate initial antimicrobial therapy is an independent risk factor for in-hospital mortality in patients with septic shock (*Chest 1999;115:462*), so timely, effective antimicrobial therapy is a cornerstone of treatment.
    - Removal of offending agent in anaphylactic shock.
    - Cardiovascular support with vasoactive agents (e.g., norepinephrine, epinephrine). Vasoactive agents will be discussed in more detail in a later section.
- **Hypovolemic:** Shock caused by decrease in effective intravascular volume and decreased oxygen-carrying capacity.
  - **Primary etiologies** are hemorrhagic (e.g., trauma, gastrointestinal bleeding) or fluid depletion (e.g., diarrhea, vomiting).
  - **Hemodynamic parameters** will demonstrate an increased CO, increased SVR, and decreased $ScvO_2$ due to increased oxygen extraction by peripheral tissue.
  - Primary goals of therapy are:
    - Volume resuscitation: Traditionally, IV blood product and crystalloid were used for resuscitation of hemorrhagic and fluid depletion shock, respectively, with goal mean arterial pressure (MAP) of 60-65 mm Hg. However, recent studies indicate that overresuscitation may be detrimental in hemorrhagic (*Air Med J 2014;33:172*) and patients without significant comorbidities may tolerate lower hemoglobin levels (7 g/dL) than previously believed. Further investigation of the appropriate fluid volume to give to patients is warranted.
    - Definitive treatment of underlying etiology of volume loss: For hemorrhagic shock, surgical intervention may be necessary for definitive treatment.
- **Obstructive:** Shock caused by obstruction of the heart or great vessels, resulting in decreased left ventricular filling and cardiovascular collapse.
  - **Primary etiology** is **pulmonary embolism** with resulting right ventricular failure.

- **Hemodynamic parameters** will demonstrate decreased CO, normal to increased SVR, and normal to decreased $ScvO_2$.

TABLE 8-4 Hemodynamic Patterns Associated with Specific Shock States

Type of Shock	CI	SVR	PVR	SvO_2	RAP	RVP	PAP	PAOP
Cardiogenic[a]	↓	↑	N	↓	↑	↑	↑	↑
Hypovolemic	↓	↑	N	↓	↓	↓	↓	↓
Distributive	N-↑	↓	N	N-↑	N-↓	N-↓	N-↓	N-↓
Obstructive	↓	↑-N	↑	N-↓	↑	↑	↑	N-↓

CI, cardiac index; N, normal; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVP, right ventricular pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance.

[a]Equalization of RAP, PAOP, diastolic PAP, and diastolic RVP establishes a diagnosis of cardiac tamponade.

- Primary goals of therapy are:
  - Supportive: Although patients are preload dependent, excessive fluid administration can lead to right ventricular overload, thereby worsening shock.
  - In a carefully selected group of patients, **thrombolytic therapy** may be beneficial.

- **Cardiogenic:** Shock caused by left ventricular systolic failure, resulting in decreased CO and subsequent insufficient oxygen distribution.
  - **Primary etiologies** are myocardial infarction, acute mitral regurgitation, myocarditis, pericardial effusion with tamponade, and septal wall rupture.
  - **Hemodynamic parameters** will demonstrate decreased CO, increased SVR, and decreased $ScvO_2$.
  - Primary goals of therapy are:
    - Mitigation of pulmonary edema: NPPV or endotracheal intubation with mechanical ventilation reduces afterload, thereby encouraging forward flow. Additionally, the application of positive pressure to the alveolar space causes pulmonary edema fluid to move to the interstitial space.
    - Careful fluid management: Adequate preload to optimize ventricular function is important, but volume overload will worsen respiratory status, so careful fluid management is necessary.
    - Definitive therapy for underlying cardiac disease: In the event of myocardial infarction, percutaneous revascularization should be performed in a timely fashion.

- Supportive: Inotropic agents such as dobutamine may be used to augment CO. Other inotropes are discussed in Pharmacologic Therapies. Mechanical circulatory assist devices, including **left ventricular assist devices** and **intra-aortic balloon pumps**, may be necessary in patients who do not respond to medical therapy.

- Hemodynamic patterns associated with the different shock states are listed in Table 8-4.

Septic Shock

- **Definition:** Presence of at least two systemic inflammatory response syndrome (SIRS) criteria, with evidence of infection, end-organ dysfunction, and refractory hypotension
  - SIRS criteria: Two of the following four findings must be present:
    - Tachypnea: Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg
    - White blood cell count <4000 cells/μL or >12,000 cells/μL
    - Tachycardia: Pulse >90 bpm
    - Hypo- or hyperthermia: Temperature >38.0°C or <36.0°C
  - End-organ dysfunction, including, but not limited to:
    - Urine output ≤50 mL/kg/h
    - Hepatic dysfunction, as evidenced by abnormal hepatic enzymes

    - Altered mental status
    - Platelet count ≤80,000/μL
    - pH ≤7.30 and plasma lactate ≥4 mmol/L
  - Refractory hypotension defined as systolic blood pressure ≤90 mm Hg or MAP ≤70 mm Hg that does not improve following adequate fluid resuscitation of 30 mL/kg IBW IV crystalloid fluid or requires vasopressors to maintain adequate MAP (*Crit Care Med 2013;31:580*).
- Caused by the systemic release of cytokines and other immunomodulatory mediators by circulating bacteria or bacterial byproducts, resulting in profound vasodilation and compensatory increased CO.
- Management of septic shock:
  - **Volume resuscitation:** Patients should initially receive **30 mL/kg IBW IV crystalloid fluid** within first hour of presentation, with additional volume administered if the patient remains volume responsive. Parameters to determine volume responsiveness (discussed in Hemodynamic Measurements section) should be closely monitored during volume resuscitation to prevent volume overload.
    - Conservative fluid management in acute lung injury is associated with shorter mechanical ventilation time (*N Engl J Med 2005;354:2564*).
    - There is weak evidence that volume overload may be associated with increased mortality in septic shock (*Chest 2000;117:1749*).
  - **Cardiovascular support:** Vasoactive medications may be necessary if volume resuscitation is insufficient to maintain MAP ≥65 mm Hg. **Norepinephrine** has become the first-line agent after it was demonstrated

that dopamine has more adverse events (*N Engl J Med 2010;362:779*). Vasopressin is frequently used as a second-line agent. Mechanisms of action and other agents are discussed in Pharmacologic Therapies.

- **Timely, effective antimicrobial administration:** Duration of hypotension before initiation of effective antimicrobial therapy is independently associated with in-hospital mortality (*Crit Care Med 2006;34:1589*).
- **Source control:** If a specific anatomical source of infection is identified (e.g., necrotizing soft tissue infection), intervention for source control should be performed within the first 12 hours, if possible (*Crit Care Med 2013;41:580*).

- **Early goal-directed therapy:** Protocol for management of the **first 6 hours** of sepsis proposed by Rivers et al. in 2001 (*N Engl J Med 2001;345:1368*). Widely adapted in practice before recent multicenter, prospective, randomized controlled trials called its effectiveness into question (*N Engl J Med 2014;370:1683*; *N Engl J Med 2014;371:1496*); studies limited by practice changes in control group (Figure 8-3).
- **Lactate clearance:** Weak evidence demonstrating that early lactate clearance may be associated with improved outcome in septic shock (*Crit Care Med 2004;32:1637*), although recent multicenter randomized controlled trials did not demonstrate difference in in-hospital mortality (*JAMA 2010;303:739*). Most recent Surviving Sepsis Guidelines recommend targeting resuscitation to normalize lactate in patients with elevated lactate levels (*Crit Care Med 2013;41:580*).

Pharmacologic Therapies

Vasoconstrictive and Inotropic Agents

- **Norepinephrine:** Causes potent vasoconstriction via α_1- and β_1-adrenergic activity. Preferred agent in septic shock due to lack of concomitant tachycardia.
- **Vasopressin:** Causes vasoconstriction via three different G-peptide receptors. Primarily used as an adjunct to norepinephrine. Weak evidence that it may have mortality benefit over norepinephrine in less severe septic shock, defined as requiring treatment with norepinephrine 5-14 μg/min to maintain MAP ≥65 mm Hg (*N Engl J Med 358;9:877*). Standard dosage of vasopressin is 0.04 unit/min.

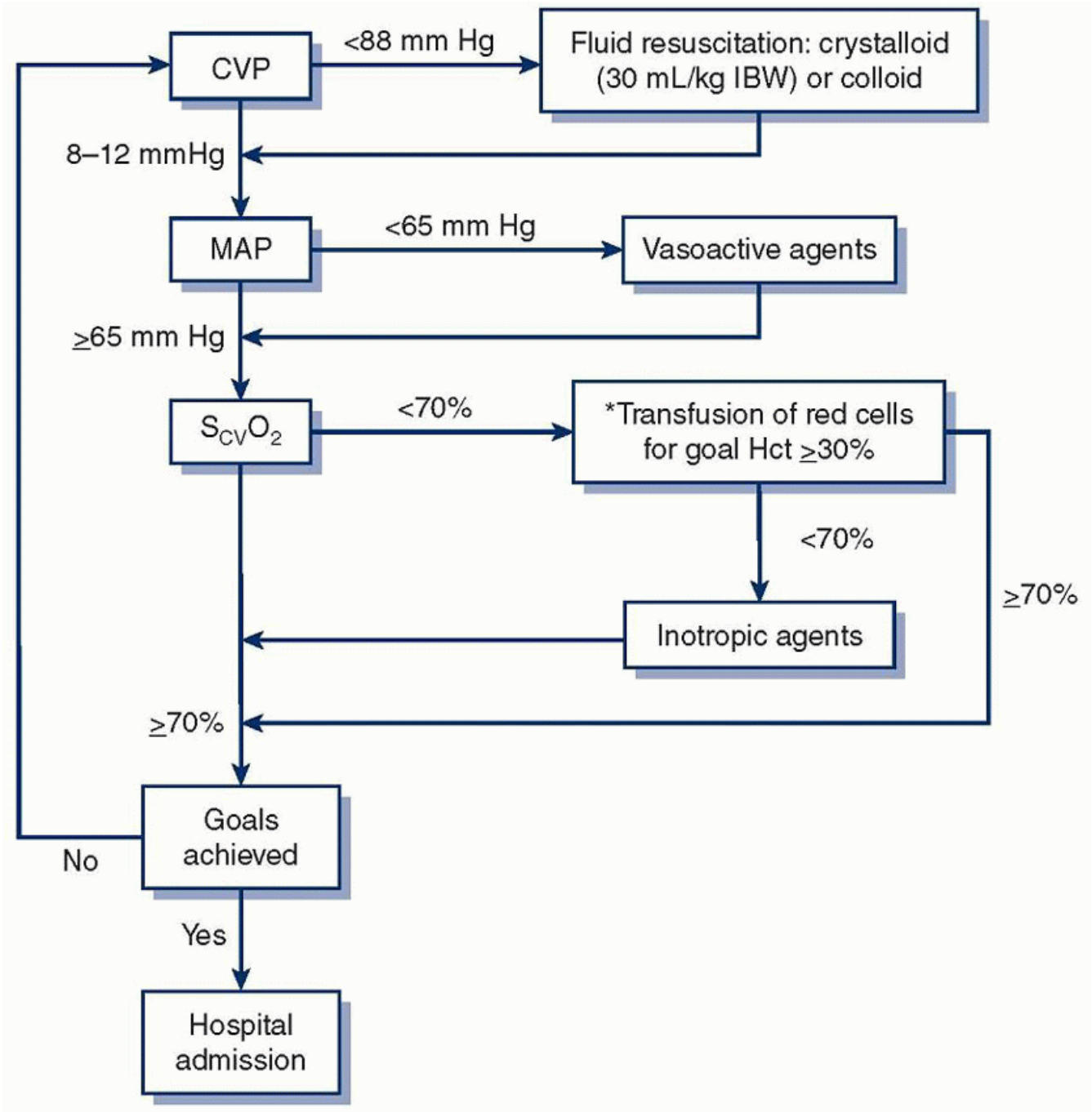


Figure 8-3. Early goal-directed therapy protocol (adapted from *N Engl J Med 2001;345:1368*). *Although included in the original early goal-directed therapy protocol, more recent trials have demonstrated a trend toward increased harm in patients who receive more transfusions; current Surviving Sepsis Guidelines do not recommend transfusing to achieve Hct of 30%. CVP, central venous pressure; Hct, hematocrit; IBW, ideal body weight; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

- **Epinephrine:** Has inotropic and vasoconstrictive properties in a dose-dependent fashion due to α_1- and β-adrenergic activity. At low doses (≤0.05 μg/kg/min), it increases CO and slightly reduces SVR due to predominant β activity. At higher doses (>0.05 μg/kg/min), vasoconstriction predominates due to increased α_1 activity. Preferred agent for anaphylactic shock.
- **Phenylephrine:** Selective α_1-receptor agonist causing vasoconstriction of larger arterioles. Few studies supporting its use in septic shock. May be administered via peripheral intravenous catheters if central venous access has not yet been established.
- **Dobutamine:** Inotropic agent that reduces afterload and increases stroke volume and heart rate via β_1-

agonist activity. Preferred agent for cardiogenic shock but increases risk of cardiac arrhythmias.

- **Dopamine:** Has inotropic, vasodilatory, and vasoconstrictive properties in a dose-dependent fashion due to action on peripheral α_1-receptors, cardiac β_1-receptors, and renal and splanchnic dopaminergic receptors. At doses <5 µg/kg/min, primarily behaves

as a vasodilator, increasing renal blood flow. At doses of 5-10 µg/kg/min, behaves as an inotrope. At doses >10 µg/kg/min, behaves as a vasopressor. Is associated with a higher rate of cardiac arrhythmias than norepinephrine (*N Engl J Med 2010;362:779*).

- **Milrinone:** Phosphodiesterase III inhibitor that has positive inotropic effect, causing increase in CO. Also causes systemic vasodilation, which can worsen hypotension.

Adjunctive Therapies

- **Corticosteroids:** Relative adrenal insufficiency may contribute to refractory hypotension during septic shock. High-dose steroids (methylprednisolone 30 mg/kg or dexamethasone 3-6 mg/kg) are associated with worse outcomes (*Am J Respir Crit Care Med 2012;185:133*), but "stress-dose" steroids (hydrocortisone 50 mg IV q6h) were associated with improved outcomes in one study (*Crit Care Med 2006;34:22*). Most recent Surviving Sepsis Guidelines recommend using hydrocortisone 200 mg IV daily in divided doses only if hypotension is refractory to fluid resuscitation and vasopressor therapy (*Crit Care Med 2013;41:580*).
- **Sodium bicarbonate:** No evidence supports the use of bicarbonate therapy in lactic acidemia from sepsis with pH ≥7.15. Effect of bicarbonate on hemodynamics and vasopressor requirements with more severe acidemia is unknown (*Crit Care Med 2013; 41:580*).
- **Methylene blue:** Selective guanylate cyclase inhibitor, thereby mitigating nitric oxide-mediated vasodilation. Observational studies have demonstrated beneficial effects on hemodynamic parameters, but effects on morbidity and mortality are unknown (*Pharmacotherapy 2010;30:702*).
- **Recombinant human activated protein C:** Previously recommended based on results from one study that demonstrated reduction in mortality (*Crit Care Med 2004;32:2207*), but subsequent studies demonstrated no benefit (*N Engl J Med 2012;366:2055*), and the drug was withdrawn from the market in 2011.
- **Immunoglobulins:** Not recommended due to a lack of benefit (*Crit Care Med 2013; 41:580*).

Hemodynamic Measurements and Critical Care Ultrasound

Although central venous pressure (CVP), MAP, and SvO_2/$ScvO_2$ are used as therapeutic endpoints in treating shock, there is evidence that these parameters do not reflect intravascular volume. There is a growing body of evidence that dynamic parameters, including pulse pressure variation and inferior vena cava (IVC) diameters, may better reflect intravascular volume, but it is unclear that these lead to improved outcomes.

Hemodynamic Measurements

Static Parameters

- **CVP:** An approximation of right atrial pressure and, therefore, preload. Should be measured from an internal jugular or subclavian venous catheter because readings from femoral catheters are influenced by intra-abdominal pressures and thus inaccurate. Poor relationship between CVP and blood volume (*Chest 2008;134:172*), but low values (<4 mm Hg) should lead to fluid resuscitation with careful monitoring (*Intensive Care Med 2007;33:575*).

- **$ScvO_2$:** Percentage of oxygen bound to hemoglobin in blood returning in the superior vena cava. **Not to be confused with SvO_2**; measured from an internal jugular or subclavian venous catheter. Low values indicate inadequate oxygen delivery, either due to inadequate intravascular volume or poor CO.
- **SvO_2:** Percentage of oxygen bound to hemoglobin in blood returning to the right side of the heart. **Not to be confused with $ScvO_2$; can only be measured with pulmonary artery catheter (PAC).** Low values indicate inadequate oxygen delivery, either due to inadequate intravascular volume or poor CO.

- **Pulmonary artery occlusive pressure or wedge pressure:** An approximation of left atrial pressure, which can be used to differentiate between cardiogenic and noncardiogenic pulmonary edema. Measured using PAC. Previously commonly used in the management of septic shock and ARDS, but did not affect mortality or morbidity (*JAMA 2003;290:2713*).
  - Insertion method: Following insertion into a central vein, distal balloon is inflated and PAC is advanced. Bedside waveform analysis or fluoroscopy is used to determine successful passage of the catheter through the right atrium, right ventricle, and into the pulmonary artery (PA).
  - Risks: Overwedging of a PAC can cause **PA rupture with resultant exsanguination** or pulmonary infarct.
- **PAC measurement of CO:** CO can be measured either via thermodilution or Fick principle with a PAC.
  - Thermodilution: An injectate of known volume and temperature is injected into the PAC, and the cooled blood traverses a thermistor at the distal end of the catheter. The CO is inversely proportional to the duration of transit of cooled blood (i.e., the longer the transit time, the lower the CO).
  - Fick principle: CO is the quotient of oxygen consumption and the arteriovenous oxygen difference. To calculate CO, arterial and mixed venous blood are drawn to determine the arteriovenous oxygen difference, and oxygen consumption is determined by respiratory gas analysis or indirect calorimetry.

Dynamic Parameters

- **Aortic Doppler monitoring:** Several systems are available that use Doppler ultrasonography to calculate **CO** and stroke volume. Correlates well with CO as measured by PAC (*Intensive Care Med 2004;30:2060*). **Reliably predicts volume responsiveness in critically ill, ventilated patients without spontaneous breathing** (*Intensive Care Med 2005;31:1195*).
  - Method: Doppler probe is inserted into the esophagus or placed at the suprasternal notch and rotated or tilted until a clear flow-velocity waveform is detected and displayed on the monitor. Aortic diameter is either measured by the system or based on an internally programmed height nomogram.
  - Output parameters: Blood velocity and flow time are measured and used to calculate stroke distance, stroke volume, and CO.
    - Stroke distance: Area under the curve of flow-velocity waveform
    - Stroke volume: Product of stroke distance and aortic cross-sectional area
    - CO: Product of stroke volume and heart rate
- **Pulse pressure variation (ΔPp):** Requires arterial line placement. Calculated as the difference between maximal and minimal systolic blood pressures measured over one respiratory cycle divided by the mean of those values. ΔPp of 13% was an accurate predictor of fluid responsiveness in mechanically ventilated patients without spontaneous breathing (*Am J Respir Crit Care Med 2000;162:134*).

- **IVC distensibility index (dIVC):** Calculated as the difference between maximal and minimal IVC diameter measured over one respiratory cycle divided by the minimal IVC diameter. dIVC of 18% discriminated between volume responders and nonresponders with 90% sensitivity and specificity in mechanically ventilated patients without spontaneous breathing in one study (*Intensive Care Med 2004;30:1740*), but more recent studies have not demonstrated similar reproducibility (*Emerg Med Australas 2012;24:534*).

Critical Care Ultrasound

The use of bedside ultrasonography has greatly expanded recently and is rapidly becoming standard of care in intensive care units. Courses in critical care ultrasonography are

becoming more readily available and are necessary for complete proficiency. This section is intended to serve as an overview of basic concepts only. **Critical care ultrasound is intended to be used as an adjunct to other clinical data.**

- Basic concepts: Air and calcified structures transmit sound waves poorly. Free-flowing fluids transmit sound waves well.
- Basic definitions (*Int J Shoulder Surg 2010;4:55*)
  - Echogenicity: The ability of an object to reflect sound waves.
  - Hyperechoic: Containing structures that reflect sound waves well; shows as white on ultrasound.

    Examples: Bone, pleura, lung
  - Hypoechoic: Containing structures that reflect sound waves poorly; shows as gray on ultrasound. Deeper structures are also more hypoechoic due to attenuation with distance.

    Examples: Lymph nodes, adipose tissue, muscle
  - Anechoic: Containing structures that allow sound waves to pass through freely; shows as black on ultrasound.

    Examples: Blood vessels, transudative pleural effusion
- Ultrasound to facilitate vascular access: More detailed instructions are available in the *Washington Manual of Critical Care*, Section XIX. Use of ultrasound to guide central venous access results in increased success and reduced complication rates.
  - Location: Ultrasound guidance is most commonly used for internal jugular and femoral venous access.
  - Prior to starting the procedure: Both internal jugular and femoral veins should be scanned to evaluate for aberrant anatomy or venous thrombosis. Lung ultrasound can be performed to rule out pneumothorax.
  - After applying the sterile field: The probe is positioned so that the needle is visualized for the entire duration of accessing the vessel.
  - During the procedure: Following insertion of the guidewire, the length of the vessel is scanned to ensure that the guidewire did not inadvertently enter any adjacent arteries.
  - After the procedure: Lung ultrasound is repeated to rule out pneumothorax.
- Cardiac ultrasound: Includes five standard views, reviewed below. Uses body transducer. Intended to facilitate assessment of volume responsiveness, global left and right ventricular systolic function, and valvular function, and indicated for imminently life-threatening causes of hemodynamic failure.

- Parasternal long-axis view: Probe is placed adjacent to the sternum in the left third to fifth intercostal space with the orientation marker pointing toward the patient's right shoulder. The right ventricular outflow tract, left ventricular cavity, ascending aorta, mitral valve, and left atrium should be visualized. Assesses for pericardial effusion, left and right ventricular dysfunction, and valvular pathologies.
- Parasternal short-axis view: Probe remains adjacent to the sternum in the left third to fifth intercostal space, but orientation marker is rotated 90 degrees clockwise to point at the patient's left shoulder. Cross-sectional view of the left and right ventricles at the level of the papillary muscles should be visualized. Assesses for pericardial effusion and left and right ventricular dysfunction.
- Apical four-chamber view: Probe is placed between the midclavicular and midaxillary lines of the left lateral chest between the fifth and seventh intercostal spaces, underneath the left nipple, with the orientation marker pointed at 3 o'clock. The left and right ventricles and atria, as well as the tricuspid and mitral valves, should be visualized. Assesses left and right ventricular size and function.
- Subcostal long-axis view: Probe is placed below the xiphoid process with the orientation marker pointed at 3 o'clock. The left and right ventricles and atria should be visualized. Assesses for pericardial effusion and left and right ventricular dysfunction. May be used for rapid assessment of cardiac function during performance of cardiopulmonary resuscitation.

- IVC longitudinal view: Probe remains below the xiphoid process, but orientation marker is rotated 90 degrees counterclockwise to point at 12 o'clock. IVC in the longitudinal axis should be visualized. Assesses IVC diameter during the respiratory cycle to determine volume responsiveness.

- Thoracic ultrasound: Includes four standard positions, performed bilaterally. Uses the body transducer on the abdominal setting to examine lung parenchyma; vascular transducer may be used for detailed examination of the pleura. Intended to facilitate the diagnosis of pleural effusion, pulmonary edema, pulmonary consolidation, and pneumothorax and to guide safe thoracentesis.
  - Areas of investigation: BLUE protocol, intended for immediate diagnosis of acute respiratory failure, defines four areas for investigation (*Crit Ultrasound J 2011;3:109*). The orientation marker should be pointed toward the patient's head.
    - Upper BLUE point: Midclavicular line, second intercostal space
    - Lower BLUE point: Anterior axillary line, fourth or fifth intercostal space
    - Phrenic point: Midaxillary line, sixth or seventh intercostal space; location of the diaphragm
    - PLAPS point: Posterior to the posterior axillary line, fourth or fifth intercostal space
  - Anatomic landmarks and ultrasound appearance: Knowledge of the normal sonographic appearance of thoracic anatomy is paramount to identifying key structures.
    - Chest wall: Hypoechoic, linear shadows of soft tissue density.
    - Ribs: Hyperechoic, curvilinear structures with a deep, hypoechoic, posterior acoustic shadow.
    - Pleura: Bright, hyperechoic, roughly horizontal line located approximately 0.5 cm below rib shadows.
    - Diaphragm: Curvilinear, hyperechoic line that moves caudally with inspiration. In a seated patient, it is located caudad to the ninth rib.
    - Splenorenal and hepatorenal recesses: Should be confirmed prior to any procedure because its curvilinear appearance is similar to that of the diaphragm. Identified by visualization of the liver or spleen

and the kidney caudally.

- Lung: Air-filled lung appears hyperechoic due to the poor echogenicity of air. Atelectatic or consolidated lung appears hypoechoic relative to normal lung.

- Sonographic artifacts and terminology: A number of sonographic artifacts are caused by air-tissue interfaces, and presence or absence of these artifacts is indicative of disease (*Crit Care Med 2007;35:S250*).

  - **Pleural line:** Brightly echogenic, roughly horizontal line; caused by parietopulmonary interface and indicating the lung surface.
  - **A-lines:** Brightly echogenic horizontal lines roughly parallel to the chest wall; caused by reverberations of the pleural line.
  - **B-lines:** Also called "**comet tails**"; a grouping within one intercostal space is called "**lung rockets**." Hyperechoic line arising perpendicularly from the pleural line that extends across the whole screen without fading, erasing A-lines; moves with lung slide. Caused by thickened interlobular septa or ground-glass areas; isolated B-lines are a normal variant.
  - **Lung slide:** "Twinkling" movement of the pleural line that occurs with the respiratory cycle; caused by movement of the lung along the craniocaudal axis during respiration. In M-mode, lung slide is visualized as the "**seashore sign**," with the chest wall generating the "waves," the aerated lung forming the "sand," and the pleural line as the interface.
  - **Lung pulse:** Pulsation of the pleural line due to transmission of the heartbeat through noninflated lung (*Ann Intensive Care 2014;4:1*).

- Ultrasonography of lung pathology (*Crit Care Med 2007;35:S250*)

  - **Pleural effusion:** A fluid collection bordered by the diaphragm, chest wall, and lung surface. Transudative effusions are typically anechoic; exudative effusions may have

    some echogenicity. If the effusion is loculated, septations—visualized as hyperechoic, web-like structures—may be seen. Atelectatic lung may be seen in the effusion.
  - **Pneumothorax:** Due to air's poor echogenicity, diagnosis of pneumothorax on ultrasound is made by artifact analysis.

    The presence of **lung slide** or **lung pulse** effectively rules out pneumothorax **in the location being investigated**.

    Abolishment of lung slide has a characteristic **stratosphere sign** in M-mode, with loss of the "sand," but is **neither sufficient nor specific for diagnosis of pneumothorax**.

    Lung point is **pathognomonic** for pneumothorax, but has poor sensitivity. Occurs at the interface of the pneumothorax and aerated lung. Characterized by alternation between absent lung slide and present lung slide or B-lines in one location with respirations. In M-mode, will transition between seashore sign and stratosphere sign.
  - **Pneumonia:** Can only be visualized when the consolidation abuts the pleura. A heterogeneous, hypoechoic area with irregular margins where aerated lung abuts the consolidated area. Air bronchograms should be seen to make the diagnosis of pneumonia (*Crit Care Med 2011;39:839*).
  - **Pulmonary edema:** Presence of multiple B-lines within one intercostal space ("lung rockets") may

indicate cardiogenic or noncardiogenic pulmonary edema. Corresponds to the Kerley B lines seen on chest radiograph. Isolated B-lines are a normal variant.

- Abdominal ultrasound: Abdominal ultrasound in critical care is limited and intended to evaluate for intra-abdominal fluid and assess the urinary tract and abdominal aorta.
  - Evaluating for intra-abdominal fluid: Standard evaluation of the trauma patient who may have intra-abdominal bleeding includes the focused assessment with sonography for trauma (FAST) examination. The patient is in the supine position, and four views are obtained:
    - Hepatorenal space: The probe is placed on the right in the tenth or eleventh intercostal space at the posterior axillary line with the orientation mark pointed cephalad.
    - Pelvis: The probe is placed in the suprapubic area with the orientation mark in the 3 o'clock position.
    - Perisplenic space: The probe is placed on the left in the tenth or eleventh space at or slightly posterior to the posterior axillary line with the orientation mark pointed cephalad.
    - Pericardial space: The probe is placed in the subxiphoid position with the orientation marker in the 3 o'clock position.
  - Paracentesis: Paracentesis should be performed under ultrasound guidance because there is evidence supporting a decrease in complications (*Ann Am Thorac Soc 2013;10:713*). More details can be found in the *Washington Manual for Critical Care*, Section XIX.
  - Assessment of the urinary tract: Bedside ultrasonography can identify bladder distention or hydronephrosis.
    - Bladder distention: The probe is placed in the suprapubic position with the orientation marker pointed cephalad for longitudinal dimensions and in the 3 o'clock position for transverse dimensions.
    - Hydronephrosis: The probe should be placed slightly caudad to the locations used for examination of the hepatorenal and perisplenic spaces in the FAST examination. Hydronephrosis is characterized by thinning of the renal cortex as the collecting system dilates.
  - Assessment of the abdominal aorta: The goal is to visualize the entire abdominal aorta to ensure that its diameter from outer wall to outer wall is <3 cm. The examination begins caudad to the xiphoid process, with the probe perpendicular to the abdominal wall and the orientation marker in the 3 o'clock position (*Ann Am Thorac Soc 2013;10:713*).

- Vascular diagnostic ultrasound: Bedside ultrasonography may be performed to evaluate for deep vein thrombosis when clinically indicated. The target vein is visualized in the transverse plane. A vessel with normal blood flow should appear internally anechoic and should be easily compressible. Organized thrombus appears as a discrete, echogenic structure within the venous lumen. A very recently formed thrombus may be anechoic, but the vessel will be incompressible.

9
Obstructive Lung Disease

Jeffrey J. Atkinson

Junfang Jiao

Mario Castro

Chronic Obstructive Pulmonary Disease

GENERAL PRINCIPLES

Definition

Chronic obstructive pulmonary disease (COPD) is a mostly preventable and treatable disorder characterized by expiratory airflow limitation that is not fully reversible. The airflow limitation is often progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, principally cigarette smoke (*GOLD Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Updated 2014]. Available at www.goldcopd.com*). **The airflow obstruction in COPD is caused by emphysema and airway disease.**

- Emphysema is defined pathologically as permanent enlargement of air spaces distal to the terminal bronchiole accompanied by destruction of the alveolar walls and absence of associated fibrosis.
- The airway disease in COPD occurs principally in small airways (i.e., those with an internal diameter of <2 mm). Chronic bronchitis is a common feature of COPD and is defined clinically as productive cough on most days for at least 3 consecutive months per year for at least 2 consecutive years, in the absence of other lung disease that could account for this symptom. Individuals with chronic bronchitis but without airflow obstruction do not have COPD.

Epidemiology

- Although the prevalence of COPD is difficult to determine, it is estimated to affect 10-24 million Americans.
- COPD and other chronic lower respiratory diseases represent the third leading cause of death in the United States (*Natl Vital Stat Rep 2015;64(10):8*).
- In the United States, the age-adjusted mortality rate remains higher among Caucasians compared with African Americans, Hispanics, or Pacific Islanders, but rate differences between men and women have closed.

Etiology

- Most cases of COPD are attributable to **cigarette smoking**. Although only a minority of cigarette smokers develop clinically significant COPD, a much higher proportion develop abnormal lung function (*Lancet 2011;378:991*).
- **Environmental (e.g., wood-burning stoves) and occupational dusts, fumes, gases, and chemicals** are other etiologic agents of COPD. Household indoor air pollution is a major cause of fatal COPD in underdeveloped countries (*Science 2011;334:180*).
- **α_1-Antitrypsin deficiency** is found in 1-2% of COPD patients. Clinical characteristics of affected patients may include a minimal smoking history, early-onset COPD (e.g., younger than 45 years of age), a family

history of lung disease, or lower lobe-predominant emphysema. Despite its relative rarity, some authorities recommend diagnostic testing for this condition in all patients with COPD (*Am J Respir Crit Care Med 2003;168:818*).

Pathophysiology

- Processes in the lungs and airways important in the pathogenesis of COPD include inflammation, immune reactions, imbalance of proteinases and antiproteinases, turnover of extracellular matrix, oxidative stress, and apoptosis.
- Pathologic features include destruction of alveolar tissue and small airways, airway wall inflammation, edema and fibrosis, and intraluminal mucus.
- Pulmonary function changes include decreased maximal expiratory airflow, hyperinflation, air trapping, and alveolar gas exchange abnormalities.
- An increased incidence of osteoporosis, skeletal muscle dysfunction, and coronary artery disease occur in COPD, perhaps indicating a systemic component of inflammation (*Chest 2005;128:2640*).

Prevention

- **Abstinence from smoking is the most effective measure for preventing COPD.**
- In patients with COPD, smoking cessation may result in a reduction in the rate of lung function decline (*Am J Respir Crit Care Med 2002;166:675*) and improve survival (*Ann Intern Med 2005;142:233*).
- Tobacco dependence warrants repeated treatment until patients stop smoking (*N Engl J Med 2011;365:1222*). Most smokers fail initial attempts at smoking cessation, and relapse reflects the nature of the dependence and not the failure of the patient or the physician.
- A multimodality approach is recommended to optimize smoking quit rates.
  - Counseling on the preventable health risks of smoking, providing advice to stop smoking, and encouraging patients to make further attempts to stop smoking even after previous failures
  - Providing smoking cessation materials to patients
  - Prescribing pharmacotherapy (Table 9-1)
- Formal smoking cessation programs, often administered in a group setting, can more be effective than non-face-to-face methods (*Cochrane Database Syst Rev 2005;(2):CD001007*).
- The U.S. Department of Health and Human Services has developed a telephone-based support system (1-800-QUIT NOW) with an Internet analog (smokefree.gov).

DIAGNOSIS

Clinical Presentation

History

- Common symptoms of COPD are dyspnea on exertion, cough, sputum production, and wheezing.
- Typically, dyspnea on exertion progresses gradually over years.
- Significant nocturnal symptoms should lead to a search for comorbidities, such as gastroesophageal reflux, congestive heart failure, or sleep-disordered breathing.

- Clinicians should obtain a lifelong smoking history and quantify exposure to environmental and occupational risk factors.
- Careful assessment of severity of symptoms and frequency of COPD exacerbations is very important, as these will guide treatment choices.
- Some tools used to evaluate dyspnea and symptom severity in COPD include the COPD Assessment Tool (CAT; Table 9-2) and patient-oriented questionnaires like the Modified (British) Medical Research Council questionnaire (mMRC; Table 9-3).
- Weight loss often occurs in patients with end-stage COPD, but other etiologies, such as malignancy and depression, should be sought.
- Although dyspnea contributes predominantly to the morbidity of COPD, death in patients with COPD commonly results from cardiovascular disease, lung cancer, or nonlung cancers (*Chest 2005;128:2640*; *Ann Intern Med 2005;142:233*).

TABLE 9-1 Pharmacotherapy for Smoking Cessation

Product	Dosing	Side Effects/Precautions
Nicotine Replacement Therapy[a]		
Transdermal patch[b]	7, 14, or 21 mg/24 h Usual regimen = 21 mg/d = 6 wk, 14 mg/d × 2 wk, 7 mg/d × 2 wk	Headache, insomnia, nightmares, nausea, dizziness, blurred vision (applies to all nicotine products)
Chewing gum, lozenges	2-4 mg q1-8h Gradually taper use	
Inhaler	10 mg/cartridge (4 mg delivered dose) 6-16 cartridges/d	
Nasal spray	0.5 mg/spray 1-2 sprays in each nostril q1h	
Non-nicotine Pharmacotherapy		
Bupropion ER *(Zyban)*	150 mg/d × 3 days, then bid × 7-12 wk Start 1 wk before quit date	Dizziness, headache, insomnia, nausea, xerostomia, hypertension, seizure Avoid monoamine oxidase inhibitors
Varenicline *(Chantix)*	0.5 mg/d × 3 days, bid × 4 days, then 1 mg bid × 12-24 wk	Nausea, vomiting, headache, insomnia, abnormal dreams Worsening of underlying psychiatric illness

	Start 1 wk before quit date

[a]Combination therapy is often used. A long-acting product (e.g., patch) is used for basal nicotine replacement, with a short-acting product (e.g., inhaler) used for breakthrough cravings.

[b]If patient smokes less than a half pack per day, start at 14-mg dose.

See also *N Engl J Med* 2011;365:1222 for strategies and approach.

Physical Examination

- Until significant reduction of lung function occurs (e.g., forced expiratory volume in 1 second [FEV_1] <50% predicted), physical signs of COPD are usually not present.
- Patients with severe COPD may exhibit prolonged (>6 seconds) breath sounds on a maximal forced exhalation, decreased breath sounds, use of accessory muscles of respiration, and hyperresonance to chest percussion. Expiratory wheezing may or may not be present.
- Signs of pulmonary hypertension (PH) and right heart failure may be present.
- **Clubbing is not a feature of COPD**, so its presence should prompt an evaluation for other conditions, especially lung cancer.

Differential Diagnosis

Airway tumors, asthma, bronchiectasis, chronic pulmonary thromboembolic disease, congestive heart failure, cystic fibrosis, constrictive bronchiolitis, diffuse panbronchiolitis, eosinophilic granuloma, ischemic heart disease, lymphangioleiomyomatosis, mycobacterial infection (tuberculous and nontuberculous), tracheobronchomalacia, and tracheal stenosis all must be considered as part of the differential in the workup of COPD.

TABLE 9-2 Chronic Obstructive Pulmonary Disease Assessment Tool (CAT)

I never cough.	1	2	3	4	5	I cough all the time.
I have no phlegm or mucus in my chest.	1	2	3	4	5	My chest is completely full of mucus or phlegm.
My chest does not feel tight.	1	2	3	4	5	My chest feels tight.
When I walk up a hill or one flight of stairs, I am not breathless.	1	2	3	4	5	When I walk up a hill or one flight of stairs, I am very breathless.
I am not limited doing any activities at home.	1	2	3	4	5	I am limited doing activities at home.

I am confident leaving my home despite my lung condition.	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition.
I sleep soundly.	1	2	3	4	5	I don't sleep soundly because of my lung condition.
I have lots of energy.	1	2	3	4	5	I have no energy at all.

Total score is sum of scores from individual question scales.

From Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648-54.

Diagnostic Testing

- Consider the diagnosis of COPD in any patient with chronic cough, dyspnea, or sputum production as well as any patient with a history of exposure to COPD risk factors, especially cigarette smoking (*GOLD Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Updated 2014]. Available at www.goldcopd.com*).
- **Pulmonary function testing**
  - A definite diagnosis of COPD requires the presence of expiratory airflow limitation on spirometry, measured as the FEV_1/forced vital capacity (FVC) ratio. Although

0.7 is taken as the lower limit of normal for all adults, with advancing age, the ratio may decrease below 0.7 in individuals who are asymptomatic and have never smoked. Therefore, a reduced ratio should not be interpreted automatically as diagnostic of COPD. The FEV_1 is usually reduced.

TABLE 9-3 Modified British Medical Research Council Questionnaire (mMRC)

0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

From Launois C, Barbe Coralie, Bertin E, et al. The modified Medical Research Council scale

for the assessment of dyspnea in daily living in obesity: A pilot study. *BMC Pulm Med* 2012;12:61.

TABLE 9-4 Classification of Severity of Airflow Limitation in Chronic Obstructive Pulmonary Disease (Based on Postbronchodilator FEV_1)

In patients with $FEV_1/FVC < 0.70$:		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

From the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

- The FEV_1 relative to the predicted normal defines the severity of expiratory airflow obstruction (Table 9-4) and is a predictor of mortality.
- The FEV_1 is often used to assess the clinical course and response to therapy.
- Spirometry may assist in the evaluation of worsened symptoms of unclear etiology.
- The total lung capacity, functional residual capacity, and residual volume often increase to supernormal values in patients with COPD, indicating lung hyperinflation and air trapping.
- The diffusing capacity for carbon monoxide (DLCO) may be reduced.

Laboratories

- A baseline arterial blood gas (ABG) is recommended for patients with severe COPD to assess for the presence and severity of hypoxemia and hypercapnia. Annual monitoring may be considered.
- Elevated venous bicarbonate may signify chronic hypercapnia.
- Polycythemia may reflect a physiologic response to chronic hypoxemia and inadequate supplemental oxygen use.

Imaging

- CXRs are not sensitive for determining the presence of COPD, but they are useful for evaluating alternative diagnoses.
- Chest CT without contrast can detect emphysema and other conditions associated with tobacco smoking

and COPD, especially lung cancer (see Complications section). However, routine diagnostic chest CT adds little to management and is not required to exclude many alternative diagnoses, unless historical or examination findings suggest occult thromboembolic or interstitial lung disease.

- With increasing severity of COPD, patients often develop radiographic signs of thoracic hyperinflation, including flattening of the diaphragm, increased retrosternal/retrocardiac air spaces, and lung hyperlucency with diminished vascular markings. Bullae may be visible. In severe disease, chest CT is used to determine candidacy for lung volume reduction surgery (LVRS) (see Treatment: Surgical Therapy section).

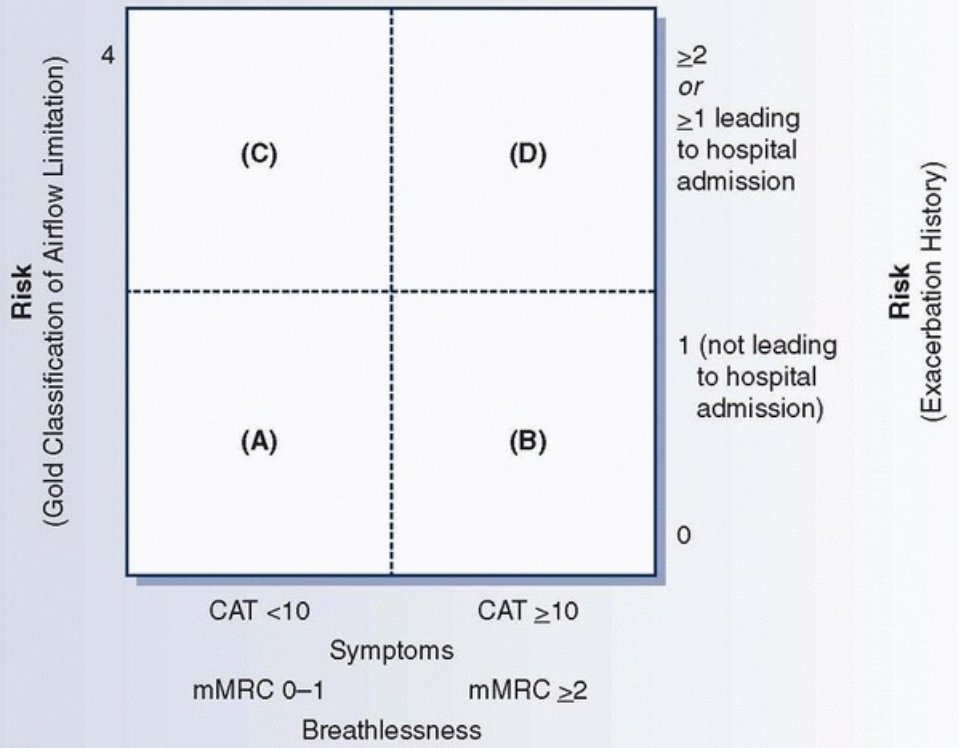
TREATMENT

- Long-term management of patients with COPD aims to improve quality of life, decrease the frequency and severity of acute exacerbations, slow the progression of disease, and prolong survival.
- Of all chronic medical therapies, **smoking cessation and the correction of hypoxemia with supplemental oxygen have the best evidence for improving survival** (*Ann Intern Med 2005;142:233*; *Cochrane Database Syst Rev 2005;(4):CD001744*). Among surgical interventions, LVRS improves survival only in select patients (*Am J Respir Crit Care Med 2011;184:763*).
- COPD should be treated in a stepwise approach based on the combined COPD assessment (Table 9-5) with attention to risk of future exacerbations and symptoms for targeting of therapies with known benefit (Table 9-6).

Medications

A pharmacologic treatment plan (Table 9-7) is based on a patient's disease severity, response to specific medications, frequency of exacerbations, drug availability and affordability, and patient compliance.

TABLE 9-5 Chronic Obstructive Pulmonary Disease Assessment Using Symptoms, Breathlessness, Spirometric Classification, and Risk of Exacerbations



CAT, Chronic Obstructive Pulmonary Disease Assessment Tool; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

From the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

TABLE 9-6 GOLD Category-Based[a] Intervention Strategy

GOLD Category	Intervention
A	Smoking cessation Vaccinations (influenza, pneumococcus) Short-acting bronchodilator as needed
B	All of the above plus: Long-acting bronchodilator Consider fixed-dose combined long-acting bronchodilators
C	All of the above plus: Oxygen if needed Long-acting bronchodilators (or fixed-dose combined) Consider inhaled corticosteroid bronchodilator combination[a] Consider macrolide if frequent exacerbations not controlled

	Consider PDE4 inhibitor if chronic bronchitis and frequent exacerbations not controlled
D	All of the above plus: Pulmonary rehabilitation Consider surgical treatments

GOLD, Global Initiative for Chronic Obstructive Lung Disease; PDE4, phosphodiesterase-4.

[a]Intervention benefit based on exacerbation risk versus risk of pneumonia in individual patient.

Adapted from the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

- **Inhaled bronchodilators**
  - Inhaled bronchodilators are the foundation of COPD pharmacotherapy. They work mainly by relaxing airway smooth muscle tone. This results in a reduction in expiratory airflow obstruction.
  - Proper use of a metered-dose inhaler (MDI) results in equally effective drug delivery as use of a nebulizer in most patients (*Health Technol Assess 2001;5(26):1-149*). Health care providers should routinely assess a patient's MDI technique and provide training.
  - Long-acting inhaled anticholinergic agents result in significant improvements in lung function, quality of life, and COPD exacerbations, although the rate of decline of FEV_1 is unaffected (*N Engl J Med 2008;359:1543*).
  - Long-acting β-adrenergic agonists (LABAs) offer improvements that are at least similar to long-acting anticholinergic agents and inhaled corticosteroids (ICSs) (*Cochrane Database Syst Rev 2011(12):CD004106*).
- **ICSs**
  - The rationale for using ICSs stems from the central role of inflammation in the pathogenesis of COPD.
  - ICSs may increase the FEV_1, reduce the frequency of COPD exacerbations, and improve quality of life. They do not slow the rate of decline of lung function over time (*N Engl J Med 1999;340:1948*; *BMJ 2000;320:1297*; *Eur Respir J 2003;21:68*).
- **Combination therapy:** Compared to single-agent therapy, a combination of medications may yield superior efficacy while reducing the potential for toxicity. Some examples follow:
  - The combination of an ICS and an LABA is effective in reducing the rate of COPD exacerbations, but this benefit must be balanced against an increased risk of pneumonia (*N Engl J Med 2007;356:775*).

TABLE 9-7 Inhalational Pharmacotherapy for Stable Chronic Obstructive Pulmonary Disease[a]

Short-Acting β-Agonists

Name	Dose	Side Effects[b]
Albuterol	MDI: two puffs q4-6h Nebulizer: 2.5 mg q6-8h	Palpitations, tremor, anxiety, nausea/vomiting, throat irritation, dyspepsia, tachycardia, arrhythmia, hypertension Cardiovascular effects may be less common with levalbuterol
Levalbuterol *(Xopenex)*	MDI: two puffs q4-6h Nebulizer: 0.63-1.25 mg q6-8h	
	Long-Acting β-Agonists	
Salmeterol *(Serevent Diskus)*	DPI: one inhalation (50 µg) bid	Headache, upper respiratory tract infection, cough, palpitations, fatigue, diarrhea
Formoterol *(Foradil)*	DPI: one capsule (12 µg) bid	
Arformoterol *(Brovana)*	Nebulizer: 15 µg bid	
Indacaterol[c] *(Arcapta)*	DPI: one capsule (75 µg) daily	
	Anticholinergics[d]	
Ipratropium *(Atrovent)*	MDI: two puffs q4-6h Nebulizer: 0.5 mg q6-8h	Xerostomia, cough, nausea/vomiting, diarrhea, urinary retention
Tiotropium *(Spiriva)*	DPI: one puff (18 µg) daily	
Aclidinium *(Tudorza)*	DPI: one puff (400 µg) bid	
	Fixed Combination Medications	
Albuterol/Ipratropium *(Combivent Respimat, DuoNeb)*	Inhalational spray: one spray qid Nebulizer: one 3-mL vial qid (each vial contains 2.5 mg albuterol and 0.5 mg ipratropium)	As above for each individual medication class (anticholinergic, β-agonist)
Fluticasone/Salmeterol *(Advair)*	DPI: one puff bid Recommended dose is 250 µg fluticasone/50 µg salmeterol	As above, plus lower respiratory tract infection (pneumonia) and oral candidiasis

	Reduced exacerbations seen with 500 µg/50 µg dose	
Budesonide/Formoterol *(Symbicort)*	DPI: two puffs bid 160 µg budesonide/4 µg formoterol	
Umeclidinium/Vilanterol *(Anoro)*	DPI: one puff daily 62.5 µg umeclidinium/25 µg vilanterol	As above for each individual medication class

DPI, dry powder inhaler; MDI, metered-dose inhaler.

[a]Commonly used medications are listed. This table is not exhaustive.

[b]Only the most common side effects are listed.

[c]Indacaterol dosage approved in United States is lower than in other countries including Canada.

[d]Short-acting anticholinergic therapy (e.g., ipratropium) is usually discontinued with initiation of long-acting anticholinergic therapy (e.g., tiotropium), because minimal additional benefit is expected, side effects may increase, and use of two inhaled anticholinergic agents has had limited evaluation.

- Combination therapy with a LABA and a long-acting anticholinergic agent sustains improved lung function compared to either agent alone (*Eur Respir J 2005;26:214*).
- Fixed-dose, long-acting combination therapies improve lung function better than either preparation alone, but data on symptom and exacerbation reduction are limited (*Lancet Respir Med 2013;1:199*).
- Questions remain regarding the value of the incremental gains of adding long-acting anticholinergic therapy to LABA/ICS combinations, suggesting a stepwise approach with individualized therapy based on symptoms, side effects, and exacerbation frequency (*Cochrane Database Syst Rev 2014(3):CD010844*).

- **Macrolide antibiotics** (e.g., azithromycin 250 mg daily)
  - May function as an anti-infective or direct anti-inflammatory in COPD.
  - In patients with previous exacerbations, the frequency of subsequent exacerbations decreased by 19%; however, improvement in clinical symptoms was modest (*N Engl J Med 2011;365:689*).
  - The benefit may be absent in current smokers and greater in older individuals (>65 years) and milder disease (FEV_1 >50%).
  - Hearing loss in the absence of tinnitus was reported, suggesting routine monitoring with audiometry should be considered with chronic therapy.
- **Phosphodiesterase-4 (PDE4) inhibitors** (e.g., roflumilast 500 µg daily)

- U.S. Food and Drug Administration (FDA) approved for a relatively narrow indication of severe COPD (FEV_1 <50%) and chronic bronchitis with frequent exacerbations, demonstrating a 17% reduction in exacerbations (*Lancet 2009;374:685*).
- Appears to be safe when used as additional therapy to chronic bronchodilators.
- Did not result in improvements in clinical symptoms possibly due to a higher frequency of side effects, particularly gastrointestinal, that limit the dose tolerated.
- Limited long-term data and the possibility of weight loss and increased psychiatric symptoms suggest close monitoring is indicated.

- **Theophylline**
  - Theophylline is a xanthine derivative with bronchodilator properties. Patients not responding adequately to inhaled bronchodilator therapy may benefit from the addition

    of theophylline, but potential toxicities and lack of data regarding efficacy in patients already on long-acting inhaled combination therapies limit its use.
  - Sustained-release theophylline is dosed once or twice a day. Serum levels should be maintained between 8 and 12 µg/mL to avoid toxicity.
  - Side effects include anxiety, tremor, headache, insomnia, nausea, vomiting, dyspepsia, tachycardia, tachyarrhythmia, and seizure.
  - In the event of suspected toxicity, theophylline should be stopped and a serum level measured.
  - Patients with severe COPD may experience clinical deterioration with discontinuation of theophylline.
  - Theophylline clearance is increased in current smokers and reduced in the elderly and patients with liver disease or congestive heart failure.
- **Systemic corticosteroids** are not recommended for the long-term management of COPD due to an unfavorable side effect profile and limited efficacy. However, they are sometimes used in patients with severe disease who are not responding to other therapies. If used, chronic oral steroid therapy should be administered at the minimum effective dose and discontinued as soon as is feasible. Routine bone mineral density assessment to prevent complications of osteoporosis should be incorporated.
- **IV α_1-antitrypsin (A1AT)** augmentation therapy may benefit select patients with severe A1AT deficiency and COPD (*Am J Respir Crit Care Med 2012;185:246*). Weekly infusion of 60 mg/kg is the standard treatment.
- For the treatment of stable COPD, antibiotics, mucolytics, antioxidants, immunoregulators, antitussives, vasodilators, respiratory stimulants, narcotics, and leukotriene inhibitors have not shown significant benefit.

Other Nonpharmacologic Therapies

- **Supplemental oxygen** decreases mortality and improves physical and mental functioning in hypoxemic patients with COPD.
  - A room-air resting ABG is the gold standard test for determining the need for supplemental oxygen. Pulse oximetry may be useful for routine checks after a baseline oxyhemoglobin saturation is assessed and compared for accuracy with the measured arterial oxyhemoglobin saturation (SaO_2).
  - Oxygen therapy is indicated for patients with an arterial partial pressure of oxygen (PaO_2) ≤55 mm Hg or an SaO_2 ≤88%, or if a patient has a PaO_2 <60 mm Hg or an SaO_2 <90% and evidence of PH, polycythemia (hematocrit >55%), or heart failure.

- Supplemental oxygen requirements are typically greatest during exertion and least at rest while awake. Patients who require supplemental oxygen during exertion often need it during sleep as well. Although the exact amount of supplemental oxygen required during sleep can be measured with pulse oximetry, it is reasonable to initially estimate the amount needed by setting the oxygen flow rate at 1 L/min greater than that required during rest while awake.
- The oxygen prescription should include the delivery system (compressed gas, liquid, or concentrator) and the required oxygen flow rates (liters per minute) for rest, sleep, and exercise.
- Patients receiving long-term oxygen therapy should undergo reevaluation to assess oxygen requirements at least once a year.

- **Pulmonary rehabilitation** is a multidisciplinary intervention that improves symptoms and quality of life and reduces the frequency of exacerbations in patients with COPD (*Am J Respir Crit Care Med 2006;173:1390*). Components of a rehabilitation program include exercise training, nutritional counseling, and psychosocial support. Pulmonary rehabilitation should be considered for all patients with moderate to severe COPD (*N Engl J Med 2009;360:1329*).

- **Vaccinations**
  - Annual influenza vaccination reduces the incidence of influenza-related acute respiratory illnesses in COPD patients (*Chest 2004;125:2011*).
  - Although pneumococcal vaccination has not been shown to significantly reduce morbidity and mortality in COPD patients, it is still reasonable to give this vaccination (*Cochrane Database Syst Rev 2006;(4):CD001390*).

Surgical Therapy

- **Lung transplantation** for severe COPD can improve quality of life and functional capacity. The data are conflicting regarding survival, and a consistent survival benefit has not been demonstrated.

  Selection criteria for transplantation for COPD patients include a BODE score (Table 9-8) (see Outcome/Prognosis section) of 7 to 10 or at least one of the following: history of hospitalization for a COPD exacerbation associated with acute hypercapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] >50 mm Hg); PH, right heart failure, or both, despite supplemental oxygen therapy; FEV_1 <20%; and either a DLCO <20% or homogeneous distribution of emphysema (*J Heart Lung Transplant 2006;25:745*).
- **LVRS** may provide quality of life and survival benefits in a specific subset of patients with upper lobe-predominant emphysema and significantly reduced exercise capacity (*Am J Respir Crit Care Med 2011;184(7):763*).

SPECIAL CONSIDERATIONS

Acute Exacerbation of COPD

- A COPD exacerbation is defined as increased dyspnea, often accompanied by increased cough, sputum production, sputum purulence, wheezing, chest tightness, or other symptoms (and signs) of acutely worsened respiratory status, in the absence of an alternative explanation.
- Respiratory infections (viral and bacterial) and air pollution cause most exacerbations (*Thorax 2006;61:250*).

- The differential diagnosis includes pneumothorax, pneumonia, pleural effusion, congestive heart failure, cardiac ischemia, and pulmonary embolism.

TABLE 9-8 BODE Index

	Points on BODE Index[a]			
Variable	0	1	2	3
FEV_1 (% of predicted)	≥65	50-64	36-49	≤35
Distance walked in 6 min (meters)	≥350	250-349	150-249	≤149
mMRC dyspnea scale	0-1	2	3	4
Body mass index	>21	≤21		

FEV_1, forced expiratory volume in 1 second; mMRC, Modified British Medical Research Council Questionnaire (see Table 9-3).

[a]The total possible cumulative values range from 0-10.

From Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350(10):1005-12.

- In addition to the history and physical examination, assessment of a patient with a suspected COPD exacerbation should include oxyhemoglobin saturation, ABG, electrocardiogram, and CXR.
- Criteria for hospital admission include a significant increase in symptom severity, severe underlying COPD, significant comorbidities, failure to respond to initial medical management, diagnostic uncertainty, and insufficient home support (*GOLD Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Update 2014]. Available at www.goldcopd.com*).
- Criteria for admission to an intensive care unit include the need for invasive mechanical ventilation, hemodynamic instability, severe dyspnea that does not adequately respond to therapy, mental status changes, and persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis despite supplemental oxygen and noninvasive ventilation (*GOLD Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Update 2014]. Available at www.goldcopd.com*).
- **Pharmacotherapy** (Table 9-9)
  - **Short-acting β-agonists (SABAs) are the first-line therapy for COPD exacerbations**. Short-acting anticholinergic agents can be added in the event of inadequate response to SABAs.

TABLE 9-9 Pharmacotherapy for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Medication Name	Dose	
Albuterol	MDI: two to four puffs q1-4h Nebulizer: 2.5 mg q1-4h	
Ipratropium	MDI: two puffs q4h Nebulizer: 0.5 mg q4h	
Prednisone	40 mg/d × 5 days	
	Antibiotics[a]	
Patient Characteristics	Pathogens to Consider	Antibiotic[b] (One of the Following)
No risk factors for poor outcome or drug-resistant pathogen[c]	*Haemophilus influenzae* *Streptococcus pneumoniae* *Moraxella catarrhalis*	Macrolide, second- or third-generation cephalosporin, doxycycline, trimethoprim/sulfamethoxazole
Risk factors present	As above, plus gramnegative rods, including *Pseudomonas*	Antipseudomonal fluoroquinolone or β-lactam

MDI, metered-dose inhaler.

[a]Indicated for all inpatients and most outpatients. Dosing recommendation from the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

[b]Treat for 3-7 days. If recent antibiotic exposure, select an agent from an alternative class. Take local resistance patterns into account.

[c]Risk factors: age >65 years, comorbid conditions (especially cardiac disease), forced expiratory volume in 1 second (FEV_1) <50%, more than three exacerbations/year, antibiotic therapy within the past 3 months (*Thorax 2006;61:337*).

- Many patients experiencing an acute exacerbation of COPD have difficulty performing optimal MDI technique. Therefore, numerous clinicians opt to deliver bronchodilators via nebulization.
- Due to the risk of serious side effects, clinicians typically avoid using methylxanthines (e.g., theophylline) for acute exacerbations. However, if a patient uses methylxanthines chronically, discontinuation during an exacerbation is discouraged due to the risk of decompensation.
- **Systemic corticosteroids** produce improvement in hospital length of stay, lung function, and the incidence of relapse. They are recommended for all inpatients and most outpatients experiencing an exacerbation of COPD (*N Engl J Med 2003;348:2618*; *N Engl J Med 1999;340:1941*; *Lancet 1999;354:456*). A prednisone dose of 40 mg for 5 days is recommended over longer regimens (*JAMA 2013;309:2223*).
- **Antibiotic therapy** is routinely administered but most often benefits patients with sputum purulence as well as patients with a need for mechanical ventilation (*Ann Intern Med 1987;106:196*; *Chest 2000;117:1638*; *Lancet 2001;358:2020*).

- **Supplemental oxygen** should be administered with a target oxygen saturation of 88-92%.
- **Thromboprophylactic measures** should be used given the increased risk of deep venous thrombosis in patients hospitalized for COPD exacerbation (*Chest 2009;135:786*).
- **Noninvasive ventilation** (Table 9-10) reduces intubation rate, improves respiratory acidosis, decreases respiratory rate, and decreases hospital length of stay (*BMJ 2003;326:185*).
- **Endotracheal intubation** and invasive mechanical ventilation are required in some patients (Table 9-11).
- Discharge criteria for patients with acute exacerbations of COPD include the need for inhaled bronchodilators less frequently than every 4 hours; clinical and ABG stability for at least 12-24 hours; the ability to eat, sleep, and ambulate fairly comfortably; adequate patient understanding of home therapy; and adequate home arrangements.

  Prior to discharge from the hospital, chronic therapy issues should be readdressed, including supplemental oxygen requirements, vaccinations, smoking cessation, assessment of inhaler technique, and pulmonary rehabilitation.

TABLE 9-10 Indications and Contraindications for Noninvasive Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Indications	Contraindications
Moderate-to-severe dyspnea with evidence of increased work of breathing	Respiratory arrest Hemodynamic instability Altered mental status, inability to cooperate
Acute respiratory acidosis with pH ≤7.35 and/or $PaCO_2$ >45 mm Hg (6.0 kPa)	High risk of aspiration Viscous or copious secretions Recent facial or gastroesophageal surgery
Respiratory rate >25	Craniofacial trauma

	Fixed nasopharyngeal abnormalities Burns Extreme obesity

Data from the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

TABLE 9-11 Indications for Invasive Mechanical Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Failure to improve with or not a candidate for noninvasive ventilation (see Table 9-10) Severe dyspnea with evidence of increased work of breathing
Acute respiratory acidosis with pH <7.25 and/or $PaCO_2$ >60 mm Hg (8.0 kPa)
PaO_2 <40 mm Hg (5.3 kPa)
Respiratory rate >35
Coexisting conditions such as cardiovascular disease, metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, pneumothorax, large pleural effusion

Data from the Global Strategy for Diagnosis, Management, and Prevention of COPD, 2015, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from http://www.goldcopd.com.

COMPLICATIONS

- Patients with severe COPD and chronic hypoxemia may develop PH and right-sided heart failure.
- COPD patients are at increased risk for lung cancer, ischemic heart disease, pneumothorax, arrhythmias, osteoporosis, and psychiatric disorders such as anxiety and depression.
  - Annual low-dose CT screening of asymptomatic heavy smokers (age >55 years, >30 pack-year history) provides a 20% reduction in mortality from lung cancer. This must be balanced with the risk of invasive procedures from false-positive tests that were seen in approximately 40% of screened individuals (*N Engl J Med 2011;365:395*). In the largest screening trial, the majority of false-positive results could be resolved with repeat imaging.
  - Many patients with mild and moderate (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage I and II) COPD will die of cardiovascular disease. Therefore, cardioselective β-blockers should be used when indicated.
  - Osteoporosis and vitamin D deficiency are common in COPD and should be monitored and treated.
- Sleep disturbances are estimated to affect 50% of patients with COPD. Newer nonbenzodiazepine medications such as zolpidem appear to be safe in patients with less severe COPD (*Proc Am Thorac Soc 2008;5:536*).

OUTCOME/PROGNOSIS

The BODE index (see Table 9-8) is a composite of body mass index, airflow obstruction, dyspnea, and exercise tolerance that has been validated as a more accurate predictor of COPD mortality than FEV_1 alone (*N Engl J Med 2004;350:1005*).

Asthma

GENERAL PRINCIPLES

Definition

- Asthma is a heterogeneous airway disease characterized by chronic inflammation, hyperresponsiveness with exposure to a wide variety of stimuli, and variable airflow obstruction. As a consequence, patients have paroxysms of cough, dyspnea, chest tightness, and wheezing.
- **Asthma is a chronic disease with episodic acute exacerbations that are interspersed with symptom-free periods.** Exacerbations are characterized by a progressive increase in

asthma symptoms that can last minutes to hours. They are associated with viral infections, allergens, and occupational exposures, and occur when airway reactivity is increased and lung function becomes unstable.

Classification

- Asthma severity should be classified based on both level of impairment (symptoms, lung function, daily activities, and rescue medication use) and risk (exacerbations, lung function decline, and medication side effects).
- At the initial evaluation, this assessment will determine the level of severity in patients not on controller medications (Table 9-12). The level of severity is based on the most severe category in which any feature appears. On subsequent visits, or if the patient is on a controller medication, this assessment is based on the lowest step of therapy to maintain clinical control (Table 9-13). Control of asthma is based on the most severe impairment or risk category.
- During an exacerbation, the acute severity of the attack should be classified based on symptoms, signs, and objective measures of lung function (Table 9-14).
- Patients who have had two or more exacerbations requiring systemic corticosteroids in the past year may be considered in the same category as those who have persistent asthma, regardless of level of impairment.

Epidemiology

In the United States:

- Asthma is the leading chronic illness among children (20-30%) (*NCHS Data Brief 2012;1*).
- The prevalence of asthma and asthma-related mortality had been increasing from 1980 to the mid-1990s, but since the 2000s, a more gradual increase in prevalence and decrease in mortality have occurred. Currently, an estimated 300 million individuals are affected worldwide and 250,000 individuals worldwide die every year due to asthma.

- African Americans are more likely than Caucasians to have emergency department (ED) visits and hospitalizations and have a higher rate of mortality due to asthma.

Etiology

Possible factors for asthma development can be broadly divided into host, genetic, and environmental factors.

- There have been multiple genes, chromosomal regions, and epigenetic changes associated with the development of asthma. Racial and ethnic differences have also been reported in asthma and are likely the result of a complex interaction between genetic, socioeconomic, and environmental factors.
- There are multiple environmental factors that contribute to the development and persistence of asthma. Severe viral infections early in life, particularly respiratory syncytial virus (RSV) and rhinovirus, are associated with the development of asthma in childhood and play a role in its pathogenesis.
- Childhood exposure and sensitization to a variety of allergens and irritants (e.g., cigarette smoke, mold, pet dander, dust mites, cockroaches) may play a role in the development of asthma, but the exact nature of this relationship is not yet fully elucidated. By contrast, early-life exposure to indoor allergens together with certain bacteria (microbiome) may be protective for urban children. The prevalence of asthma in children raised in a rural setting is reduced, although the reason for this is not fully known.

Pathophysiology

Asthma is characterized by airway obstruction, hyperinflation, and airflow limitation resulting from multiple processes:

- Acute and chronic airway inflammation characterized by infiltration of the airway wall, mucosa, and lumen by activated eosinophils, mast cells, macrophages, and T lymphocytes.

P.264

P.265

Components of innate immunity including natural killer T cells, neutrophils, and innate lymphoid lymphocytes are also implicated.

TABLE 9-12 Classification of Asthma Severity on Initial Assessment

	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Daytime symptoms	≤2 d/wk	≥2 d/wk but not daily	Daily	Throughout the day
Nighttime symptoms	≤2×/mo	3-4×/mo	≥1×/wk but not nightly	Nightly
Activity limitations	None	Minor	Some	Extreme
Reliever medicine use	≤2 da/wk	≥2 d/wk but not	Daily	Several times per day

		daily			
FEV_1	≥80%	≥80%	60-80%		<60%
Exacerbations	0-1×/yr	≥2×/yr	≥2×/yr		≥2×/yr
Management	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred		Low-dose ICS	Low-dose ICS	Medium- or high-dose ICS + LABA	Add-on therapy: i.e., omalizumab, bronchial thermoplasty
Alternative	Low-dose ICS		LTRA, cromolyn, theophylline	High-dose ICS + LTRA or theophylline	Consider low-dose OCS

In 2-6 wk, evaluate level of asthma control and adjust therapy accordingly.

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β-adrenergic agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids.

Data from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available from: http://www.ginasthma.org National Asthma Education and Prevention Program. Expert Panel Report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, 2007.

TABLE 9-13 Assessment of Asthma Control

	Well Controlled	Not Well Controlled	Very Poorly Controlled
Daytime symptoms	≤2 d/wk	>2 d/wk	Throughout the day
Nighttime symptoms	None	1-3×/wk	≥4×/wk
Activity limitations	None	Some	Extreme
Reliever medicine use	≤2×/wk	>2×/wk	Frequent

FEV_1 or PEF	≥80%	60-80%	<60%
Validated questionnaire	ACT ≥20 ACQ <0.75	ACT 16-19 ACQ >1.5	ACT ≤15
Exacerbations	0-1/yr	≥2×/yr	≥2×/yr
Management	Maintain at lowest step possible Consider step down if well controlled for ≥3 mo	Step up one step	Step up one to two steps and consider short-course OCS
Follow-up	1-6 mo	2-6 wk	2 wk

ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids PEF, peak expiratory flow.

Data from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014. Available at: http://www.ginasthma.org. National Asthma Education and Prevention Program. Expert Panel Report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

- Bronchial smooth muscle contraction resulting from mediators released by a variety of cell types including inflammatory, local neural, and epithelial cells.
- Epithelial damage manifested by denudation and desquamation of the epithelium leading to mucous plugs that obstruct the airway.
- Airway remodeling characterized by the following findings:
  - Subepithelial fibrosis, specifically thickening of the lamina reticularis from collagen deposition
  - Smooth muscle hypertrophy and hyperplasia
  - Goblet cell and submucosal gland hypertrophy and hyperplasia resulting in mucous hypersecretion
  - Airway angiogenesis
  - Airway wall thickening due to edema and cellular infiltration

Risk Factors

A number of factors increase airway hyperresponsiveness and can cause an acute and chronic increase in the severity of the disease:

- Allergens such as dust mites, cockroaches, pollens, molds, and pet dander in susceptible patients.
- Viral upper respiratory tract infections.

TABLE 9-14 Classification of Asthma Exacerbation Severity

	Moderate	Severe	Impending Respiratory Arrest
FEV_1 or PEF predicted or personal best	40-69%	<40%	<25% or unable to measure
Symptoms	DOE or SOB with talking	SOB at rest	Severe SOB
Exam	Expiratory wheeze	Inspiratory and expiratory wheeze	Wheeze may become absent
	Some accessory muscle use	Increased accessory muscle use Chest retraction Agitation or confusion	Accessory muscle use with paradoxical thoracoabdominal movement Depressed mental status
Vitals	RR <28/min HR <110 bpm O_2sat >91% RA No pulsus paradoxus	RR >28/min HR >110 bpm O_2sat <91% RA Pulsus paradoxus >25 mm Hg	Same as severe but could develop respiratory depression and/or bradycardia
$PaCO_2$	Normal to hypocapnia	>42 mm Hg	Hypercapnia is a late sign

DOE, dyspnea on exertion; FEV_1, forced expiratory volume in 1 second; HR, heart rate; O_2sat, oxygen saturation; PEF, peak expiratory flow; RA, room air; RR, respiratory rate; SOB, shortness of breath.

Data from Global Initiative for Asthma. GINA report, global strategy for asthma management and prevention. http://www.ginasthma.org. 2011; National Asthma Education and Prevention Program. Expert Panel Report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, 2007.

- Many occupational allergens and irritants such as perfumes, cleaners, or detergents, even in small doses.
- Changes in weather (i.e., from warm to cold), strong emotional stimuli, and exercise.
- Indoor and outdoor pollutants, such as nitrogen dioxide (NO_2) and tobacco and wood smoke, can trigger acute

bronchospasm and should be avoided by all patients.

- Obesity is associated with increased asthma severity.
- Medications such as β-blockers (including ophthalmic preparations), aspirin, and NSAIDs can cause the sudden onset of severe airway obstruction.

Prevention

- Strict compliance and appropriate follow-up can help prevent worsening of asthma control.
- Identification and avoidance of risk factors (allergens, irritants) that exacerbate symptoms play a key role in prevention.
- Recognition and management of comorbidities such as obesity, sinonasal diseases, gastroesophageal reflux disease (GERD), and psychiatric disorders are important.
- All patients with asthma should receive a yearly influenza vaccination.

Associated Conditions

- **Rhinosinusitis**, with or without nasal polyps, is frequently present and should be treated with intranasal or oral corticosteroids, saline rinses, and/or antihistamines. Antibiotics should be reserved for superimposed bacterial infections.
- **Vocal cord dysfunction (VCD)** can coexist with or masquerade severe, uncontrolled asthma. Treatment consists of speech and, if needed, behavioral therapy.
- Symptomatic **GERD** can cause cough and wheezing in some patients and may benefit from treatment with H_2 blockers or proton pump inhibitors. Empiric treatment of GERD in asymptomatic patients with uncontrolled asthma is not an effective strategy.
- **Obesity** is increasingly being recognized as a comorbid condition as well as possibly playing a role in worsening asthma control. This may be related to altered lung mechanics, altered respiratory patterns, or an increase in systemic inflammation. Obese patients should be strongly encouraged to focus on weight loss through diet and exercise.
- Smoking prevalence in patients with asthma is the same as the general population. Although no convincing evidence links tobacco use with developing asthma, it may make patients less responsive to ICSs and more difficult to control. Tobacco cessation should be encouraged in all patients.
- **Obstructive sleep apnea (OSA)** may make asthma more difficult to control and should be addressed with an overnight polysomnogram if suspected.

DIAGNOSIS

Clinical Presentation

History

- Recurring episodes of cough, dyspnea, chest tightness, and wheezing are suggestive of asthma. Symptoms are often worse at night or early morning, in the presence of potential triggers, and/or in a seasonal pattern.
- A personal or family history of atopy can increase the likelihood of asthma.

- Patients presenting for the first time over 50 years old, patients with >20 pack-years of smoking, and lack of response to asthma therapy are features that make asthma less likely as the sole cause of respiratory symptoms.

Physical Examination

- Auscultation of wheezing and a prolonged expiratory phase can be present on exam, but a normal chest exam does not exclude asthma.
- Signs of atopy, such as eczema, rhinitis, or nasal polyps, often coexist with asthma.
- During a suspected asthma exacerbation, a rapid assessment should be performed to identify patients who require immediate intervention (see Table 9-14).
  - Respiratory distress and/or peak expiratory flow (PEF) <25% of predicted.
  - The presence or intensity of wheezing is an unreliable indicator of the severity of an attack.
  - SC emphysema should alert the examiner to the presence of a pneumothorax or pneumomediastinum.

Diagnostic Criteria

- In general, the diagnosis is supported by the presence of symptoms consistent with asthma combined with demonstration of variable expiratory airflow obstruction.
- Adequate response to asthma treatment is a valid method to assist with making the diagnosis.

Differential Diagnosis

Other conditions may present with wheezing and must be considered, especially in patients who are not responsive to therapy (Table 9-15).

TABLE 9-15 Conditions that Can Present as Refractory Asthma

Upper airway obstruction
Tumor
Epiglottitis
Vocal cord dysfunction
Obstructive sleep apnea
Lower airway disease
Allergic bronchopulmonary aspergillosis
Chronic obstructive pulmonary disease
Cystic fibrosis
α_1-Antitrypsin deficiency
Bronchiectasis
Bronchiolitis obliterans
Tracheomalacia
Endobronchial lesion
Foreign body
Herpetic tracheobronchitis
Adverse drug reaction
Aspirin
β-Adrenergic antagonist
Angiotensin-converting enzyme inhibitors

Inhaled pentamidine
Congestive heart failure
Gastroesophageal reflux
Sinusitis
Hypersensitivity pneumonitis
Churg-Strauss syndrome
Eosinophilic pneumonia
Hyperventilation with panic attacks
Dysfunctional breathlessness

Diagnostic Testing

Laboratories

- Routine laboratory tests are not indicated for the diagnosis of asthma and should not delay the initiation of treatment.
- During an exacerbation, monitor oxygen saturation. ABG measurement should be considered in patients in severe distress or with an FEV_1 of <40% of predicted values after initial treatment.
  - A PaO_2 <60 mm Hg is a sign of severe bronchoconstriction or of a complicating condition, such as pulmonary edema or pneumonia.
  - Initially, the $PaCO_2$ is low due to an increase in respiratory rate. With a prolonged attack, the $PaCO_2$ may rise as a result of severe airway obstruction, increased dead space ventilation, and respiratory muscle fatigue. **A normal or increased $PaCO_2$ is a sign of impending respiratory failure and necessitates hospitalization.**

Allergy Tests

- Allergy skin tests or immunoassays for allergen-specific IgE are helpful to identify sensitization to specific inhalant allergens when allergen exposure is concerned as a trigger.
- Results of allergy tests must correlate with history and clinical presentation.

Exhaled Nitric Oxide

- Fractional concentration of exhaled nitric oxide (FeNO) may be used as a marker of eosinophilic airway inflammation in asthma.
- An FeNO level >50 parts per billion (ppb) is associated with a good response to ICSs. However, it is generally recommended not to use FeNO to guide asthma therapy.

Imaging

- Obtaining a CXR is not routinely required and is performed only if a complicating pulmonary process, such as pneumonia or pneumothorax, is suspected or to rule out other causes of respiratory symptoms in patients being evaluated for asthma.
- CT of the chest can be considered in patients with severe asthma refractory to treatment to evaluate for alternative diagnosis.

Diagnostic Procedures

- **Pulmonary function tests (PFTs)** are essential to the diagnosis of asthma. In patients with asthma, PFTs demonstrate an obstructive pattern—the hallmark of which is a decrease in expiratory flow rates.
  - A reduction in FEV_1 and a proportionally smaller reduction in the FVC occur. This produces a decreased FEV_1/FVC ratio (generally <0.7 or the lower limit of normal value). With mild obstructive disease that involves only the small airways, the FEV_1/FVC ratio may be normal, with the only abnormality being a decrease in airflow at midlung volumes (forced expiratory flow 25-75%).
  - The clinical diagnosis of asthma is supported by an obstructive pattern that improves after bronchodilator therapy. **Improvement is defined as an increase in FEV_1 of >12% and 200 mL after two to four puffs of a short-acting bronchodilator.** Most patients will not demonstrate reversibility at each assessment.
  - In patients with chronic, severe asthma, the airflow obstruction may no longer be completely reversible. In these patients, the most effective way to establish the maximal degree of airway reversibility is to repeat PFTs after a course of oral corticosteroids (usually 40 mg/d for 10-14 days) and to use the same criteria as above for reversibility. The lack of demonstrable airway obstruction or reactivity does not rule out a diagnosis of asthma.
  - In cases in which spirometry is normal, the diagnosis can be made by showing heightened airway responsiveness to a **methacholine challenge**. A methacholine challenge is considered positive when a provocative concentration of 8 mg/mL or less causes a drop in FEV_1 of 20% (PC_{20}). A PC_{20} >16 mg/mL is considered a negative test.
- An objective measurement of airflow obstruction is essential to the evaluation of an exacerbation. The severity of the exacerbation should be classified as:
  - Mild (PEF or FEV_1 >70% of predicted or personal best)
  - Moderate (PEF or FEV_1 40-69%)
  - Severe (PEF or FEV_1 <40%)
  - Life-threatening/impending respiratory arrest (PEF or FEV_1 <25%)

TREATMENT

- Medical management involves chronic management and a plan for acute exacerbations, otherwise known as the **asthma action plan**. Most often, it includes the daily use of an anti-inflammatory, disease-modifying medication (long-term control medications), and as-needed use of a short-acting bronchodilator (quick-relief medications).
- The goals of daily management are to **avoid impairment** (lack of symptoms while maintaining normal activity and pulmonary function) and to **minimize risk** (preventing exacerbations, loss of lung function, and medication side effects). Successful management requires patient education, objective measurement of airflow obstruction, and a medication plan for daily use and for exacerbations.
- When initiating therapy for a patient not already on controller medicine, one should assess the patient's severity and assign the patient to the highest level in which any one feature has occurred over the

previous 2-4 weeks (see Table 9-12).

- Assessment of control on subsequent visits is used to modify therapy when following patients already on controller medication (see Table 9-13).
- Address the following issues before stepping up the therapy when there is a poor response to controller medicine after 2-3 months of treatment.
  - Nonadherence to medications
  - Incorrect inhaler technique
  - Ongoing exposure to allergens and/or irritants
  - Comorbidities: obesity, sinonasal diseases, GERD, OSA, and depression
  - Alternative diagnoses (see Table 9-15)

	If well-controlled for ≥3 mo, step down ⟷ If not well-controlled, step up after addressing avoidance, adherence, comorbidities, and triggers					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Rapid medication	**As-needed SABA**					
Preferred controller medication	None	Low-dose ICS	Low-dose ICS + LABA or medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA and evaluation for omalizumab	Add OCS to Step 5 medications
Alternate controller medication		LTRA or Cromolyn or sustained-released theophylline	Low-dose ICS with either LTM or sustained-release theophylline	Consider adding LTM and/or sustained-release theophylline		

Figure 9-1. Management algorithm based on level of control. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTM, leukotriene modifier; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist. (From Global Initiative for Asthma. GINA Report, global strategy for asthma management and Prevention. http://www.ginasthma.org, 2011; National Asthma Education and Prevention Program. Expert panel report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, 2007.)

- The goal of the stepwise approach is to gain control of symptoms as quickly as possible. At the same time, level of control varies over time and, consequently, medication requirements as well, so therapy should be reviewed every 3 months to check whether stepwise reduction is possible (Figure 9-1).
- **Management of an exacerbation** requiring hospital-based care should follow a treatment algorithm to triage patients based on response to treatment (Figure 9-2).
  - The response to initial treatment (three treatments with a short-acting bronchodilator every 20 minutes

for 60-90 minutes) can be a better predictor of the need for hospitalization than the severity of an exacerbation.
    - Patients at high risk of asthma-related death (see Outcome/Prognosis section) should be advised to seek medical attention early in the course of an exacerbation.
    - A low threshold for admission is appropriate for patients with recent hospitalization, a failure of aggressive outpatient management (with oral corticosteroids), or a previous life-threatening attack.

Medications

First Line

- **Short-acting bronchodilators**
    - Quick-relief medications used on an as-needed basis for long-term management of all severities of asthma as well as for rapid treatment of exacerbations given via either MDI or nebulization.
    - For long-term management, a **SABA** used on an as-needed basis (e.g., albuterol, two puffs q6h) is appropriate.
    - SABA is considered the drug of choice for preventing exercise-induced bronchoconstriction.

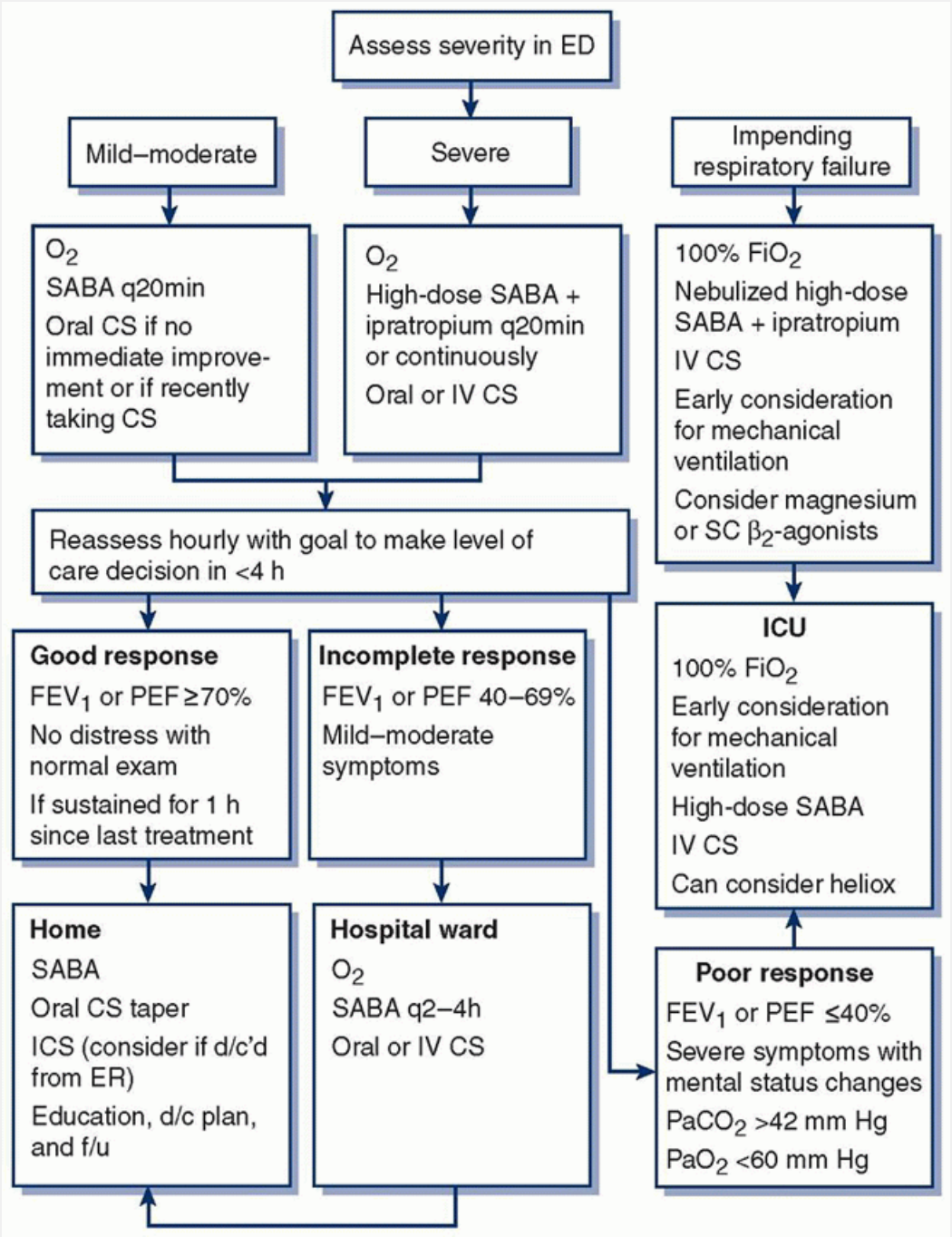


Figure 9-2. Treatment algorithm for asthma exacerbation. CS, corticosteroid; d/c, discharge; ED, emergency department; FEV_1, forced expiratory volume in 1 second; f/u, follow-up; ICS, inhaled corticosteroid; ICU, intensive care unit; PEF, peak expiratory flow; SABA, short-acting β_2-agonist. (From Global Initiative for Asthma. GINA Report, global strategy for asthma management and prevention. http://www.ginasthma.org, 2011; National Asthma Education and Prevention Program. Expert panel report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, 2007.)

- During an exacerbation, reversal of airflow obstruction is achieved most effectively by frequent administration of an inhaled SABA.
  - For a **mild-to-moderate exacerbation**, initial treatment starts with two to six puffs of albuterol via MDI with a spacer or 2.5 mg via nebulizer and is repeated q20min until improvement is obtained or toxicity is noted.
  - For a **severe exacerbation**, albuterol 2.5-5.0 mg q20min with ipratropium bromide 0.5 mg q20min should be administered via nebulizer. Alternatively, albuterol

10.0-15.0 mg, administered continuously over an hour, may be more effective in severely obstructed adults. If used, telemetry monitoring is necessary.
    - Levalbuterol four to eight puffs or nebulized 1.25-2.5 mg q20min can be substituted for albuterol but has not been associated with fewer side effects in adults.
    - The subsequent dosing schedule is adjusted according to the patient's symptoms and clinical presentation. Often, patients require a SABA q2-4h during an acute attack. The use of an MDI with a spacer device under supervision of trained personnel is as effective as aerosolized solution by nebulizer. Cooperation may not be possible in the patient with severe airflow obstruction.
    - SC administration of a β_2-adrenergic agonist is unnecessary if inhaled medications can be administered quickly with an adequate response. In rare settings, aqueous epinephrine (0.3-0.5 mL of a 1:1000 solution SC q20min) or terbutaline (0.25 mg SC q20min) for up to three doses can be used. However, there has been no evidence to suggest their superiority over aerosolized therapy. Their use is contraindicated if the patient has had a myocardial infarction within the last 6 months or is having active angina. If used, ECG monitoring is necessary.
  - All SABAs now use hydrofluoroalkane (HFA) as a propellant. They should be primed with four puffs when first used and again if not used over 2 weeks.
- **ICSs**
  - ICSs are safe and effective for the treatment of persistent asthma. They are generally administered via a dry powder inhaler (DPI), MDI with a spacing device, or nebulized.
  - Dosing depends on assessment of severity and control (Table 9-16).
  - Once-daily dosing of ICS may be as effective as twice-daily dosing in the management of mild persistent asthma and may improve adherence.
  - Systemic corticosteroid absorption can occur in patients who use high doses of ICS. Consequently, prolonged therapy with high-dose ICS should be reserved for patients with severe disease or for those who otherwise require oral corticosteroids.
  - Attempts should be made to decrease the dose of ICS every 2-3 months to the lowest possible dose to maintain control.
- **LABAs**
  - Recommended for moderate and severe persistent asthma in patients not adequately controlled with ICS.
  - Salmeterol or the faster acting formoterol added to ICS has consistently been shown to improve lung function, improve both day and nighttime symptoms, reduce exacerbations, and minimize the required dose of ICS.
  - LABA should only be used in combination with ICS in patients with asthma (salmeterol/fluticasone, budesonide/formoterol, or mometasone/formoterol).
  - The benefits of adding LABAs are more substantial than those achieved by leukotriene modifiers (LTMs), theophylline, or increased doses of ICS.
- **Systemic corticosteroids**
  - May be necessary to gain control of disease quickly via either oral or IV route.
  - If chronic symptoms are severe and accompanied by nighttime awakening or PEF is <70% of predicted values, a short course of oral corticosteroid (prednisone 40-60 mg/d for 5-7 days) might be necessary.
  - Long-term therapy is occasionally necessary and should be started at low dose (≤10 mg/d prednisone

or equivalent), and repeated attempts should be made to reduce the dose while patients are receiving high-dose ICS. Side effects associated with longterm therapy should be closely monitored. Osteoporosis prophylaxis may be necessary.

- **During an exacerbation, systemic corticosteroids speed the resolution of exacerbations of asthma and should be administered promptly to all patients.**
  - The ideal dose of corticosteroid needed to speed recovery and limit symptoms is not well defined. A single or divided daily dose equivalent to prednisone 40-60 mg is

P.273

P.274

usually adequate. Oral corticosteroid administration seems to be as effective as IV administration if given in equivalent doses.

TABLE 9-16 Comparative Daily Adult Dosages for Inhaled Corticosteroids

Drug	Low Dose	Medium Dose	High Dose
Triamcinolone HFA (75 µg/puff)	300-750 µg	>750-1500 µg	>1500 µg
Beclomethasone HFA (40 or 80 µg/puff)	80-240 µg	>240-480 µg	>480 µg
Budesonide DPI (90, 180, or 200 µg/dose)	180-600 µg	>600-1200 µg	>1200 µg
Budesonide nebulized respules (250, 500, or 1000 µg/respules)	250-500 µg	>500-1000 µg	>1000 µg
Ciclesonide HFA (80 or 160 µg/puff)	160-320 µg	>320-640 µg	>640 µg
Flunisolide HFA (80 µg/puff)	320 µg	>320-640 µg	>640 µg
Fluticasone HFA (44, 110, or 220 µg/puff)	88-264 µg	>264-440 µg	>440 µg
Fluticasone DPI (50, 100, or 250 µg/dose)	100-300 µg	>300-500 µg	>500 µg
Mometasone furoate DPI (110 or 220 µg/puff)	220 µg	440 µg	>440 µg
Combination agents			
Budesonide/formoterol (MDI: 80/4.5 or 160/4.5 µg/puff)	Two puffs bid: 80/4.5 µg/puff	Two puffs bid: 80/4.5 to 160/4.5	Two puffs bid: 160/4.5

		µg/puff	µg/puff
Fluticasone/salmeterol (MDI: 45/21, 115/21, or 230/21 µg/puff) (DPI: 100/50, 250/50, or 500/50 µg/dose)	One inhalation bid: 100/50 µg	One inhalation bid: 250/50 µg	One inhalation bid: 500/50 µg
Mometasone/formoterol (MDI: 100/5 or 200/5 µg/puff)	Two inhalations bid: 100/5 µg/puff	Two inhalations bid: 100/5 µg/puff to 200/5 µg/puff	Two inhalations bid: 200/5 µg/puff

DPI, dry powder inhaler; MDI, metered-dose inhaler.

Data from Global Initiative for Asthma. GINA Report, global strategy for asthma management and prevention. http://www.ginasthma.org. 2011; National Asthma Education and Prevention Program. Expert panel report 3. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, 2007.

- IV methylprednisolone, 125 mg, given on initial presentation, decreases the rate of return to the ED for patients who are discharged.
- For maximal therapeutic response, tapering of high-dose corticosteroids should not take place until objective evidence of clinical improvement is observed (usually 36-48 hours or when PEF >70%). Initially, patients are given a daily dose of oral prednisone, which is then reduced slowly.
- A 7- to 14-day tapering dose of prednisone is usually successful in combination with an ICS instituted at the beginning of the tapering schedule. In patients with severe disease or with a history of respiratory failure, a slower reduction in dose is appropriate.
- Patients discharged from the ED should receive oral corticosteroids. A dose of prednisone, 40 mg/d for 5-7 days, can be substituted for a tapering schedule in selected patients. Either regimen should be accompanied by the initiation of an ICS or an increase in the previous dose of ICS.

Second Line

- **LTMs**
  - **Montelukast** (10 mg PO daily) and **zafirlukast** (20 mg PO bid) are oral leukotriene receptor antagonists (LTRAs), and **zileuton** (extended-release 1200 mg bid) is an oral 5-lipoxygenase inhibitor. The LTRAs are recommended as an alternative first-line medication for mild persistent asthma and as an add-on to ICS for more severe forms of asthma.
  - As add-on therapy to ICS, these agents have been shown to improve lung function, lead to improved quality of life, and lead to fewer exacerbations. However, compared with ICS plus LABA, they are not as effective in improving asthma outcomes.
  - **A LTM should be strongly considered for patients with aspirin-sensitive asthma, exercise-induced bronchoconstriction, or concurrent allergic rhinitis, or individuals who cannot master the use of an inhaler.**

- **Anti-IgE therapy**
  - **Omalizumab** is a monoclonal antibody against IgE that is approved for the management of patients with moderate to severe persistent allergic asthma with a demonstrable sensitivity to a perennial aeroallergen and incomplete control with ICS.
  - Omalizumab can decrease airway inflammation through its effects on IgE. Treatment with omalizumab decreases eosinophil counts in sputum and biopsy specimens and attenuates lymphocyte proliferation and cytokine production.
  - Omalizumab is administered 150-375 mg SC q2-4wk and dosed based on the patient's baseline IgE level (if between 30-700 IU/mL) and weight.
  - Addition of omalizumab in adults and children 12 years of age or older has been shown to reduce exacerbation rates and need for corticosteroids in patients on a controller medication regimen. Rescue medication use is often reduced, and asthma-related quality of life is improved. Health care utilization (ED visits, hospital admissions) is decreased with omalizumab use in severe asthmatics. At least 16 weeks of treatment are needed to determine the efficacy of omalizumab.
  - Allergic rhinitis symptoms often improve with omalizumab therapy. In one controlled trial, omalizumab use reduced nasal symptom severity scores and rescue antihistamine use in a dose-dependent manner (*JAMA 2001;286(23):2956*).
- **Long-acting muscarinic antagonists:** Tiotropium bromide as add-on therapy to ICS with or without LABA is associated with improved lung functions, fewer symptoms, and reduced exacerbations in patients with inadequately controlled asthma (*N Engl J Med 2012;367:1198*)
- **Methylxanthines:** Sustained-release theophylline at low doses (300 mg/d) may be useful as adjuvant therapy to an anti-inflammatory agent in persistent asthma, especially for

controlling nighttime symptoms. Clinical use is limited due to the narrow therapeutic window.
- **IV magnesium sulfate:** During a severe exacerbation refractory to standard treatment over 1 hour, one dose of 2 g IV over 20 minutes in the ED should be considered. It has been shown to acutely improve lung function especially in those with severe, life-threatening exacerbations (*Ann Emerg Med 2000;36:181*).
- **Inhaled heliox:** During a severe exacerbation refractory to standard treatment over 1 hour, heliox-driven albuterol nebulization in a mixture with oxygen (70:30) should be considered. It has been shown to acutely improve lung function, especially in those with severe, life-threatening exacerbations (*Acad Emerg Med 2005;12:820*).
- **Antibiotics:** Antibiotic therapy has not been shown to have any benefit when used to treat exacerbations. Antibiotics can only be recommended as needed for treatment of comorbid conditions, such as pneumonia or bacterial sinusitis.
- **Bronchial thermoplasty:** Bronchial thermoplasty is a novel therapy for severe asthma in which a specialized radiofrequency catheter is introduced through a bronchoscope to deliver thermal energy to smaller airways in order to reduce smooth muscle mass surrounding the airways. Although asthma symptoms worsen immediately after the procedure, long-term (at least 5 years) asthma-related quality of life and health care utilization improve with bronchial thermoplasty (*J Allergy Clin Immunol 2013;132:1295*). Bronchial thermoplasty should be performed by experienced bronchoscopists in conjunction with an asthma specialist.

Other Nonpharmacologic Therapies

- **Supplemental oxygen** should be administered to the patient who is awaiting an assessment of arterial

oxygen tension and should be continued to maintain an oxygen saturation >92% (95% in patients with coexisting cardiac disease or pregnancy).

- **Mechanical ventilation** may be required for respiratory failure.
  - General principles include use of a **large endotracheal tube (≥7.5 mm)**, **low tidal volumes**, **prolonged expiratory time with high inspiratory flows**, **low respiratory rate**, **and low positive end-expiratory pressure (PEEP)**, and in some patients, **permissive hypercapnia**, with the goal to avoid dynamic hyperinflation. Patients with asthma who are intubated often have elevated plateau pressures and intrinsic PEEP.
  - Heavy sedation may be needed and should be maximized before the use of paralytics, given their adverse side effects.
  - Evidence is lacking to suggest modes of noninvasive ventilation are beneficial.
- SC **allergen immunotherapy (SCIT)** can be considered in allergic patients with mild to moderate disease with persistent symptoms despite adherence to allergen avoidance and medication. SCIT is relatively contraindicated in patients with severe or unstable asthma (chronic oral corticosteroid use or severe exacerbations requiring hospitalization or intubation in the previous 6 months).

Lifestyle/Risk Modification

Diet

There is no general diet that is known to improve asthma control. However, a small percentage of patients may have reproducible deterioration after exposure to dietary sulfites used to prevent discoloration in foods such as beer, wine, processed potatoes, and dried fruit, and therefore, these foods should be avoided in patients if they have had prior reactions to these foods.

Activity

Patients should be encouraged to lead an active lifestyle. If their asthma is well controlled, they should expect to be as physically active as they desire. If exercise is a trigger, patients

should be advised to continue physical activity after prophylactic use of an LTM (montelukast 10 mg 2 hours before exercise) or an inhaled β_2-adrenergic agonist (two to four puffs 15-20 minutes before exposure).

SPECIAL CONSIDERATIONS

- During pregnancy, patients should have more frequent follow-up because the severity of asthma often changes and requires medication adjustment. **There is more potential risk to the fetus with poorly controlled asthma than with exposure to asthma medications, most of which are generally considered safe.** A recent birth cohort study of ICSs in pregnant women with asthma confirmed their safety (*Am J Resp Crit Care Med 2012;185(5):557*).
- Occupational asthma requires a detailed history of occupational exposure to a sensitizing agent, lack of asthma symptoms prior to exposure, and a documented relationship with symptoms and the workplace. Beyond standard asthma medical treatment, exposure avoidance is crucial.
- Aspirin-exacerbated respiratory disease (AERD): Patients with aspirin sensitivity and chronic rhinosinusitis with nasal polyps typically have onset of asthma in the third or fourth decade of life. A precipitous onset of symptoms should raise the possibility of reaction to acute ingestion of aspirin or an NSAID. Aspirin desensitization may be considered in patients with corticosteroid-dependent asthma or

those requiring daily aspirin/NSAID therapy for other medical conditions.

COMPLICATIONS

Medication Side Effects

- **SABA:** Sympathomimetic symptoms (tremor, anxiety, tachycardia), decrease in serum potassium and magnesium, mild lactic acidosis, prolonged QT_c
- **ICS**
  - Increased risk for systemic effects at high doses (equivalent >1000 µg/d of beclomethasone) including skin bruising, cataracts, elevated intraocular pressure, and accelerated loss of bone mass.
  - Pharyngeal and laryngeal effects are common, such as sore throat, hoarse voice, and oral candidiasis. **Patients should be instructed to rinse their mouth after each administration to reduce the possibility of thrush.** A change in the delivery method and/or use of a valved holding chamber/spacer may alleviate the other side effects.
- **LABA**
  - Fewer sympathomimetic-type side effects.
  - Associated with an increased risk of severe asthma exacerbations and asthma-related death when used without ICS based on the Salmeterol Multicenter Asthma Research Trial (SMART), which showed a very low but significant increase in asthma-related deaths in patients receiving salmeterol (0.01-0.04%) (*Chest 2006;129(1):15*).
  - Should only be used in combination with ICS. FDA recommends discontinuation of LABA once asthma control is achieved and maintained.
- **LTM**
  - Cases of newly diagnosed Churg-Strauss vasculitis after exposure to LTRA have been described, but it is unclear whether they are related to unmasking of a preexisting case with concurrent corticosteroid tapering or whether there is a causal relationship.
  - Zileuton can cause a reversible hepatitis, so it is recommended that hepatic function be monitored at initiation once a month during the first 3 months, every 3 months for the first year, and then periodically.

- **Omalizumab (anti-IgE) therapy:** Anaphylaxis occurs in 1-2 per 1000 patients, usually within 2 hours of the first dose. For this reason, patients should be medically observed 2 hours after the initial dose and then for 30 minutes after subsequent dosing. Patients should possess self-administered epinephrine to be used as needed for anaphylaxis. No association between omalizumab therapy and increased risks of malignancy and thromboembolic events has been identified.
- **Methylxanthines**
  - Theophylline has a narrow therapeutic range with significant toxicities, such as arrhythmias and seizures, as well as many potential drug interactions, especially with antibiotics.
  - Serum concentrations of theophylline should be monitored on a regular basis, aiming for a peak level of 5-10 µg/mL; however, at the lower doses used for asthma, toxicity is much less likely.

REFERRAL

Referral to a specialist should be considered in the following situations:

- Patients who require step 4 (see Figure 9-1) or higher treatment, or patients who have had a life-threatening asthma exacerbation
- Patients being considered for anti-IgE therapy, bronchial thermoplasty, or other alternative treatments
- Patients with atypical signs or symptoms that make the diagnosis uncertain
- Patients with comorbidities such as chronic sinusitis, nasal polyposis, allergic bronchopulmonary aspergillosis, VCD, severe GERD, severe rhinitis, or significant psychiatric or psychosocial difficulties interfering with treatment
- Patients requiring additional diagnostic testing, such as rhinoscopy or bronchoscopy, bronchoprovocation testing, or allergy skin testing
- Patients who need to be evaluated for allergen immunotherapy

PATIENT EDUCATION

- Patient education should focus on the chronic and inflammatory nature of asthma, with identification of factors that contribute to increased inflammation.
  - The consequences of ongoing exposure to chronic irritants or allergens and the rationale for therapy should be explained. Patients should be instructed to avoid factors that aggravate their disease, on how to manage their daily medications, and on how to recognize and deal with acute exacerbations (known as an asthma action plan).
  - Review the principles of asthma medications and skills of inhaler technique.
  - The use of a **written daily management plan** as part of the education strategy is recommended for all patients with persistent asthma.
- It is important for patients to recognize signs of poorly controlled disease.
  - These signs include an increased or daily need for bronchodilators, limitation of activity, waking at night because of asthma symptoms, and variability in the PEF.
  - Specific instructions about handling these symptoms, including criteria for seeking emergency care, should be provided.

MONITORING/FOLLOW-UP

- PEF monitoring provides an objective measurement of airflow obstruction and can be considered in patients with moderate to severe persistent asthma. However, symptom-based asthma action plans are equivalent to PEF-based plans in terms of overall self-management and control (*Respirology 2001;6(4):297*).

The patient must be able to demonstrate correct use of the peak flow meter. The personal best PEF (the highest PEF obtained when the disease is under control) is identified, and the PEF is checked when symptoms escalate or in the setting of an asthma trigger. This should be incorporated into an asthma action plan, setting 80-100% of personal best PEF as the “green” zone, 50-80% as the “yellow” zone, and <50% as the “red” zone.

- Patients should learn to anticipate situations that cause increased symptoms. For most individuals, monitoring

symptoms instead of PEF is sufficient (symptom-based asthma action plan).

- Questionnaires can also provide objective monitoring of asthma control. The Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) are useful instruments to rapidly assess patient-reported asthma control.

OUTCOME/PROGNOSIS

- Most patients with asthma can be effectively treated and achieve good control of their disease when following the stepwise treatment approach. Goals should include minimal use of reliever medication, freedom from troublesome symptoms, near-normal lung function, absence of serious attacks, and ability to lead a physically active life.
- Previous exacerbations that have required the use of oral corticosteroids or led to respiratory failure, as well as the use of more than two canisters per month of inhaled short-acting bronchodilator and seizures with asthma attacks, have been associated with severe and potentially fatal asthma.

10
Pulmonary Diseases

Murali Chakinala
Tonya D. Russell
Patrick Aguilar
Adrian Shifren
Andrea Loiselle
Alexander Chen
Ali Sadoughi
Allen Burks
Praveen Chenna
Brad Bemiss
Daniel B. Rosenbluth

Pulmonary Hypertension

GENERAL PRINCIPLES

Definition

Pulmonary hypertension (PH) is the sustained elevation of the mean pulmonary artery pressure (mPAP) (≥25 mm Hg at rest).

Classification

- PH is subcategorized into five major groups (Table 10-1):
  - Group I—**Pulmonary arterial hypertension (PAH)**
  - Group II—**PH due to left heart disease**
  - Group III—**PH due to lung diseases and/or hypoxemia**
  - Group IV—**Chronic thromboembolic pulmonary hypertension (CTEPH)**
  - Group V—**PH with unclear multifactorial mechanisms**
- **PAH** represents a specific group of disorders with similar pathologies and clinical presentation, with a propensity for right heart failure in the absence of elevated left-sided pressures.

Epidemiology

- PH is most often due to left heart disease (Group II) or parenchymal lung disease (Group III).
- **Idiopathic PAH (IPAH)** (Group I) is a rare disorder with an estimated prevalence of 6-9 cases per million compared to an overall PAH prevalence of 15-26 cases per million (*Am J Respir Crit Care Med 2006*;*173:1023*; *Eur Respir J 2007;30:104*). The average age of PAH patients in modern registries is approximately 50 years (*Am J Respir Crit Care Med 2006;173:1023*; *Eur Respir J 2007;30:1103*). IPAH patients tend to be even younger, with a mean age of approximately 35 years (*Ann Intern Med 1987;107:216*).
- Despite increased awareness, PAH continues to be diagnosed late in its course, with a reported delay of 27

months from symptom onset and the majority of patients in advanced World Health Organization (WHO) functional class III or IV (*Am J Respir Crit Care Med 2006;173:1023*).

- IPAH and PAH associated with systemic sclerosis are the most common subtypes of PAH (*Eur Respir J 2007;30:1103*).
- Incidence of **CTEPH** (Group IV) may be as high as 4% among survivors of acute pulmonary embolism (*N Engl J Med 2004;350:2257*).

Pathophysiology

- Complex origins of PAH include infectious/environmental insults or comorbid conditions that "trigger" the condition in individuals susceptible due to a genetic predisposition.
  - Mutations in the bone morphogenetic protein receptor II (*BMPR-II*) gene are the overwhelming cause of heritable PAH. Other susceptibility factors are speculated to exist but have not been identified.
  - A total of 70% of familial PAH and 10-40% of sporadic or anorexigen-associated cases are found to have mutations in *BMPR-II* (*Circulation 2010;122:156*).

TABLE 10-1 Clinical Classification of Pulmonary Hypertension: Dana Point (2008) Classification System of Pulmonary Hypertension

I. Pulmonary arterial hypertension (PAH)

Idiopathic PAH
Heritable:

BMPR-II, ALK-1 (ACVR1), ENG, SMAD9, CAV1, KCNK3
Unknown

Drug and toxin induced
Associated with:

Connective tissue diseases
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis

Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn

II. Pulmonary hypertension due to left heart disease

Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

III. Pulmonary hypertension due to lung diseases and/or hypoxemia

Chronic obstructive lung disease
Interstitial lung disease
Other pulmonary diseases with mixed obstructive and restrictive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases

IV. Chronic thromboembolic pulmonary hypertension (CTEPH)
V. Pulmonary hypertension with unclear multifactorial mechanisms

Hematologic disorders: *chronic hemolytic anemia, myeloproliferative disorders, splenectomy*
Systemic diseases: *sarcoidosis, pulmonary Langerhans cell histiocytosis, neurofibromatosis, lymphangioleiomyomatosis*
Metabolic disorders: *glycogen storage disease, Gaucher disease, thyroid disorders*
Others: *tumoral obstruction, fibrosing mediastinitis, chronic renal failure on hemodialysis*

ALK1 (ACVR1), activin-like receptor kinase-1; *BMPR-II*, bone morphogenetic protein receptor II; *CAV1*, caveolin-1; *ENG*, endoglin; *KCNK3*, potassium channel super family K member-3.
From Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34-41.

- PAH involves a complex interplay of factors resulting in progressive vascular remodeling with endothelial cell and smooth muscle proliferation, vasoconstriction, and in situ thrombosis at an arteriolar level. Vessel wall changes and luminal narrowing restrict the flow of blood and lead to higher than normal pressure as blood flows through the vessels, which is quantifiable by an elevated pulmonary vascular resistance (PVR) (*Circulation 2009;119:2252*).
  - Elevated PVR results in increased afterload to the right ventricle (RV), which over time increases RV wall tension and work, ultimately impacting RV contractility.

  - Initially, cardiac output diminishes during strenuous exercise. As PH severity worsens, maximal cardiac output is achieved at progressively lower workloads; ultimately, resting cardiac output is reduced.
  - Unlike the left ventricle (LV), the RV has limited ability to hypertrophy and tolerates high afterload poorly, causing “vascular-ventricular uncoupling” and eventual RV failure, the most common cause of death.
  - In very advanced stages, pulmonary artery pressures decline as the failing RV cannot generate enough blood flow to maintain high pressures.
- Mechanisms of PH in Groups II-V vary and include high postcapillary pressures, hypoxemia-mediated vasoconstriction and remodeling, parenchymal destruction, thromboembolic narrowing or occlusion of large arteries, and compression of proximal vasculature.

Prevention

Yearly screening transthoracic echocardiogram (TTE) is indicated for high-risk groups including individuals with known *BMPR-II* mutation, scleroderma spectrum of disease, portal hypertension undergoing liver

transplantation evaluation, and congenital systemicto-pulmonary shunts (e.g., ventricular septal defects, patent ductus arteriosus).

DIAGNOSIS

Clinical Presentation

- **Symptoms** include **dyspnea** (most common), exercise intolerance, fatigue, palpitations, exertional dizziness, **syncope**, chest pain, lower extremity swelling, increased abdominal girth (ascites), and hoarseness (impingement of recurrent laryngeal nerve by enlarging pulmonary artery).
- Explore for underlying risk factors (i.e., anorectic drugs, methamphetamines) or associated conditions (e.g., connective tissue diseases, LV heart failure [congestive heart failure (CHF)], obstructive sleep apnea syndrome [OSAS], and venous thromboembolism [VTE]).
- Auscultatory signs of PH include **prominent second heart sound** (loud S_2) with loud P_2 component, RV S_3, tricuspid regurgitation, and pulmonary insufficiency murmurs.
- **Signs of right heart failure**
  - Elevated jugular venous pressure
  - Hepatomegaly
  - Pulsatile liver
  - Pedal edema
  - Ascites
- Physical examination should focus on identifying underlying conditions linked to PH: skin changes of scleroderma, stigmata of liver disease, clubbing (congenital heart disease), and abnormal breath sounds (parenchymal lung disease).

Diagnostic Testing

- **The purpose of diagnostic testing is to confirm clinical suspicion of PH, determine etiology of PH, and gauge severity of condition, which assists with treatment planning.**
- **Acute illnesses** (e.g., pulmonary edema, pulmonary embolism, pneumonia, adult respiratory distress syndrome) can cause **mild PH** (pulmonary artery systolic pressure [PASP] <50 mm Hg) or aggravate preexisting PH.
- Evaluation of **chronic PH** becomes necessary if pulmonary artery pressures remain elevated after resolution of the acute process.
- If chronic PH is considered based on clinical suspicion or during the evaluation of a vulnerable population (see Prevention section), **TTE should be the initial test**.

TTE with Doppler and Agitated Saline Injection

- **Estimate PASP** by Doppler interrogation of tricuspid valve regurgitant jet. The absence of tricuspid regurgitation does not exclude elevated pulmonary artery pressure. Sensitivity for PH is 80-100%, and correlation coefficient with invasive measurement is 0.6-0.9 (*Chest 2004;126:14S*). **Invasive measurement is recommended if suspicion remains despite a normal estimation by echocardiogram.**
- **Assess RV characteristics**, looking for pressure overload and dysfunction (e.g., RV hypertrophy and/or dilation, RV hypokinesis, displaced intraventricular septum, paradoxical septal motion, LV compression, and pericardial effusion from impaired pericardial drainage). Tricuspid annular plane systolic excursion <1.8 cm

is associated with worse survival (*Am J Respir Crit Care Med 2006;174(9):1034*). Absence of any RV abnormalities makes moderate or severe PH unlikely.

- **Identify causes of PH** (e.g., LV systolic or **diastolic dysfunction**, left-sided valvular disease, left atrial structural anomalies, and congenital systemic-to-pulmonary shunts). Left atrial enlargement, elevated LV filling pressures, and diastolic dysfunction are important clues for LV diastolic heart disease that frequently leads to PH, especially in the elderly (*J Am Coll Cardiol 2009;53:1119*).
- Transesophageal echocardiogram is indicated to exclude intracardiac shunts suspected by TTE, although the majority of such shunts are a patent foramen ovale.
- Additional studies, as outlined in the following text and in Figure 10-1, should be completed if PH is unexplained by TTE or if PAH is still a consideration after echocardiography (*Chest 2004;126:14S*).

Laboratories

- Evaluate for causative conditions and gauge degree of cardiac impairment.
  - Complete blood counts (CBCs)
  - Blood urea nitrogen, serum creatinine

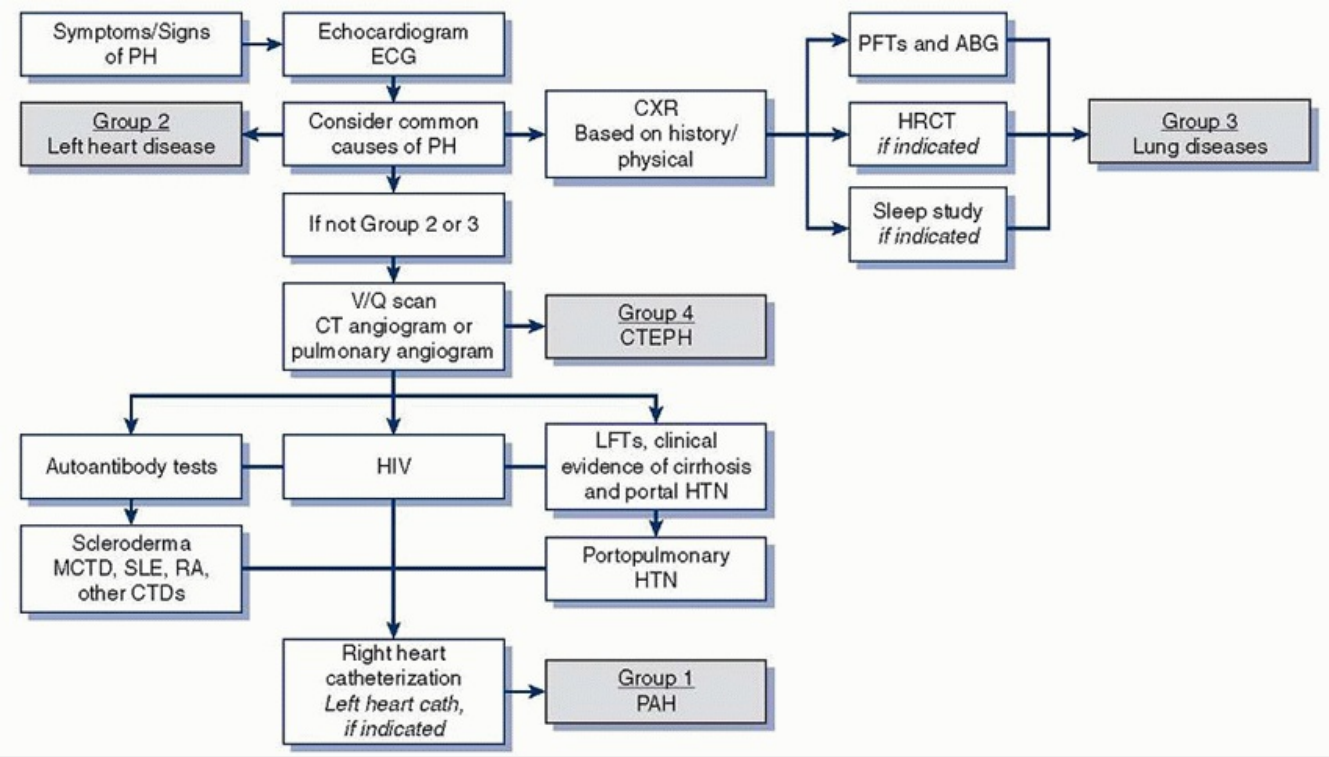


Figure 10-1. Algorithm for diagnostic workup of pulmonary hypertension. ABG, arterial blood gas; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; HRCT, high-resolution CT; HTN, hypertension; LFT, liver function test; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; V/Q, ventilation-perfusion

  - Hepatic function tests
  - Brain natriuretic peptide (BNP)
  - HIV serology
  - Thyroid-stimulating hormone (TSH)
  - Antinuclear antibody (ANA), antitopoisomerase antibodies, anticentromere anti bodies, extractable nuclear antigen antibody, and potentially other serologies of autoimmune disease

- Additional laboratory studies, based on initial findings, include complete thyroid function studies, hepatitis B and C serologies, hemoglobin electrophoresis, antiphospholipid antibody, and lupus anticoagulant.

Electrocardiography

Signs of **right heart enlargement** include RV hypertrophy, right atrial enlargement, right bundle branch block, and RV strain pattern (S wave in lead I with Q wave and inverted T wave in lead III), but these findings have low sensitivity in milder PH.

Pulmonary Function Testing

- **Spirometry and lung volumes** to assess for obstructive (e.g., **chronic obstructive lung disease**) or restrictive (e.g., interstitial lung disease [ILD]) ventilatory abnormalities.
- **Diffusing capacity for carbon monoxide (DLCO)** is usually reduced with parenchymal lung diseases, but isolated mild to moderate reduction is often encountered in PAH.
- **Arterial blood gas (ABG):** Elevated arterial partial pressure of carbon dioxide (PaCO2) is an important clue for a hypoventilation syndrome.
- **Six-minute walk (6MW) or simple exercise test**
  - Unexplained exercise-induced desaturation could indicate PH.
  - Distance walked correlates with WHO functional classification and provides intermediate prognosis (*Am J Respir Crit Care Med 2000;161:487*).
- **Nocturnal oximetry:** Nocturnal desaturations could indicate OSAS. PH patients with symptoms of sleep-disordered breathing should undergo **polysomnography** (PSG). Nocturnal desaturations are common in PAH, even in the absence of OSAS, and should be treated with nocturnal supplemental oxygen (*Chest 2007;131:109*).

Imaging

- General findings include enlarged central pulmonary arteries as well as RV enlargement with opacification of retrosternal space, seen best on lateral view.
- Clues to specific PH diagnosis include:
  - Decreased peripheral vascular markings or pruning (PAH)
  - Very large pulmonary vasculature throughout lung fields (congenital-to-systemic shunt)
  - Regional oligemia of pulmonary vasculature (chronic thromboembolic disease)
  - Interstitial infiltrates (ILD)
  - Hyperinflated lungs (chronic obstructive lung disease)
- **Ventilation-perfusion (V/Q) lung scan**
  - Critical for excluding chronic thromboembolic disease but could also be abnormal in pulmonary veno-occlusive disease and fibrosing mediastinitis.
  - **Heterogeneous perfusion patterns** are associated with PAH.
  - Presence of one or more segmental mismatches raises concern for chronic thromboembolic disease and should be investigated with computed tomography (CT) or pulmonary angiography (*N Engl J Med 2001;345:145*).
- **Chest CT scan**
  - Confirms suspicion of CTEPH, if initial screening V/Q scan suspicious
  - Evaluates lung parenchyma and mediastinum
  - High-resolution images to assess for interstitial or bronchiolar disease

- **Pulmonary angiography** can be done safely in the setting of severe PH.
  - Confirms CTEPH.
  - Determines surgical accessibility of thrombotic material.
  - Inferior vena cava filter can be deployed at the same time.
- **Cardiac MRI**
  - Investigates cardiac anomalies leading to the development of PAH, especially if transesophageal echocardiogram is contraindicated
  - Provides anatomic and functional information about the RV, including ventricular volumes, ejection fraction, and stroke volume index, which have prognostic value

Diagnostic Procedures

- **Lung biopsy**
  - Lung biopsy is rarely performed but useful if lung disease requires histologic confirmation (e.g., pulmonary vasculitis or veno-occlusive disease).
  - The risk of surgery is usually prohibitive in the setting of severe PH or RV dysfunction.
- **Right heart catheterization: Essential investigation if PAH is suspected and treatment is being considered.**
  - **Confirm noninvasive estimate of PASP**, because TTE can under- and overestimate PASP (*Am J Respir Crit Care Med 2009;179:615*).
  - **Measure cardiac output and mean right atrial pressure (RAP) to gauge severity of condition and predict future course.** Increased RAP is an indicator of RV dysfunction and has greatest odds ratio for predicting mortality (*Ann Intern Med 1987;107:216*).
  - **Investigate etiologies of PH**, including left heart disease (by measuring pulmonary artery wedge pressure [PAWP] manually at end-expiration) or missed systemic-topulmonary shunts (by noting “step-ups” in oxygen saturations).
  - Exercise hemodynamics can elicit PH occurring during exercise or also confirm suspicion of diastolic heart failure, but exercise protocols and methods of measurement are not standardized.
- **Acute vasodilator testing** is recommended if PAH is suspected.
  - Performed with a **short-acting vasodilator**, such as IV adenosine, IV epoprostenol, or inhaled nitric oxide. **Long-acting calcium channel blockers (CCBs) should not be used for initial vasodilator testing** due to risk of sustained systemic hypotension (*Chest 2004;26:35S*).
  - **Not recommended for patients in extreme right heart failure** (mean RAP >20 mm Hg).
  - Definition of a **responder** is **decline in mPAP of 10 mm Hg *and* concluding mPAP of 40 mm Hg with stable or improved cardiac output** (*Chest 2004;126:35S*).
  - Responders should undergo a CCB trial with pulmonary artery catheter in place. If vasoresponsiveness is recapitulated, chronic CCB therapy can be prescribed (see Treatment section).
- **Left heart catheterization** should be done to directly measure **LV end-diastolic pressure** if PAWP cannot reliably exclude left heart disease, especially in patients older than 65 years.

TREATMENT

- **Management of PH depends on the specific category of PH.**
  - Patients with PH due to left heart disease should receive appropriate therapy for the underlying causative condition with the goal of minimizing postcapillary pressures.
  - Patients with underlying lung diseases should be treated as appropriate for specific condition. Examples include bronchodilators (e.g., obstructive lung disease), immunomodulators (e.g., ILDs), noninvasive ventilation (e.g., OSAS), and supplemental oxygen.

  - CTEPH is often treated by **pulmonary thromboendarterectomy** at specialized centers and requires careful screening to determine resectability and expected hemodynamic response (*N Engl J Med 2001;345:1465*). Patients with inoperable CTEPH can benefit from riociguat, a soluble guanylate cyclase stimulator (*N Engl J Med 2013;369:319*).
- Regardless of PH diagnosis, normoxemia should be maintained to avoid hypoxic vasoconstriction and further aggravation of pulmonary artery pressures. **Supplemental oxygen** to maintain adequate arterial saturations (>89%) 24 hours a day is recommended. However, normoxemia may not be possible in the presence of a significant right-to-left shunt (e.g., intracardiac right-to-left shunt).
- **In-line filters** should be used to prevent paradoxical air emboli from IV catheters in PH patients with large right-to-left shunts.
- **Pneumovax and influenza vaccination** should be given to avoid respiratory tract infections.
- Patients with severe PH and RV dysfunction should **minimize behaviors** that can acutely decrease RV preload and/or increase RV afterload, which could cause circulatory collapse:
  - **Deep Valsalva** maneuvers can raise intrathoracic pressure and induce syncope through diminished central venous return (e.g., vigorous exercise, severe coughing paroxysm, straining during defecation or micturition).
  - **High altitudes** (>5000 ft) due to low inspired concentration of oxygen.
  - **Cigarette smoking**, because of nicotine's vasoactive effects.
  - **Pregnancy**, due to hemodynamic alterations that further strain the heart.
  - Systemic **sympathomimetic** agents, such as decongestants and cocaine.

Medications

- **PAH patients are candidates for vasomodulator/vasodilator** therapy (Figure 10-2 and Table 10-2).
  - There are four categories of PAH-specific therapies with unique mechanisms of action:
    - **Endothelin receptor antagonists** block the binding of endothelin-1 to its receptors on pulmonary artery smooth muscle cells, which would typically cause vasoconstriction and cellular hypertrophy/growth.
    - **Phosphodiesterase-5 inhibitors** block the enzyme that shuts down nitric oxide-mediated vasodilation and platelet inhibition.
    - **Soluble guanylate cyclase stimulator** activates the downstream signal of nitric oxide through stimulation of its intermediate messenger, soluble guanylate cyclase, and induces vasodilation and platelet inhibition.
    - **Prostanoids** induce vasodilation, inhibit cellular growth, and inhibit platelet aggregation.
  - Initial choice of PAH-specific therapy should be individualized to the severity of one's condition (see Figure 10-2).

- **Predictors of poor prognosis** include (*Chest 2011;141:354*):
  - PAH subtype: scleroderma, portopulmonary hypertension, familial PAH
  - Men older than 60 years
  - Renal insufficiency
  - BNP >180 pg/mL
  - PVR >32 Wood units
  - RAP >20 mm Hg
  - DLCO ≤32%
  - Pericardial effusion
  - Systolic blood pressure <110 mm Hg
  - Resting heart rate >92 bpm

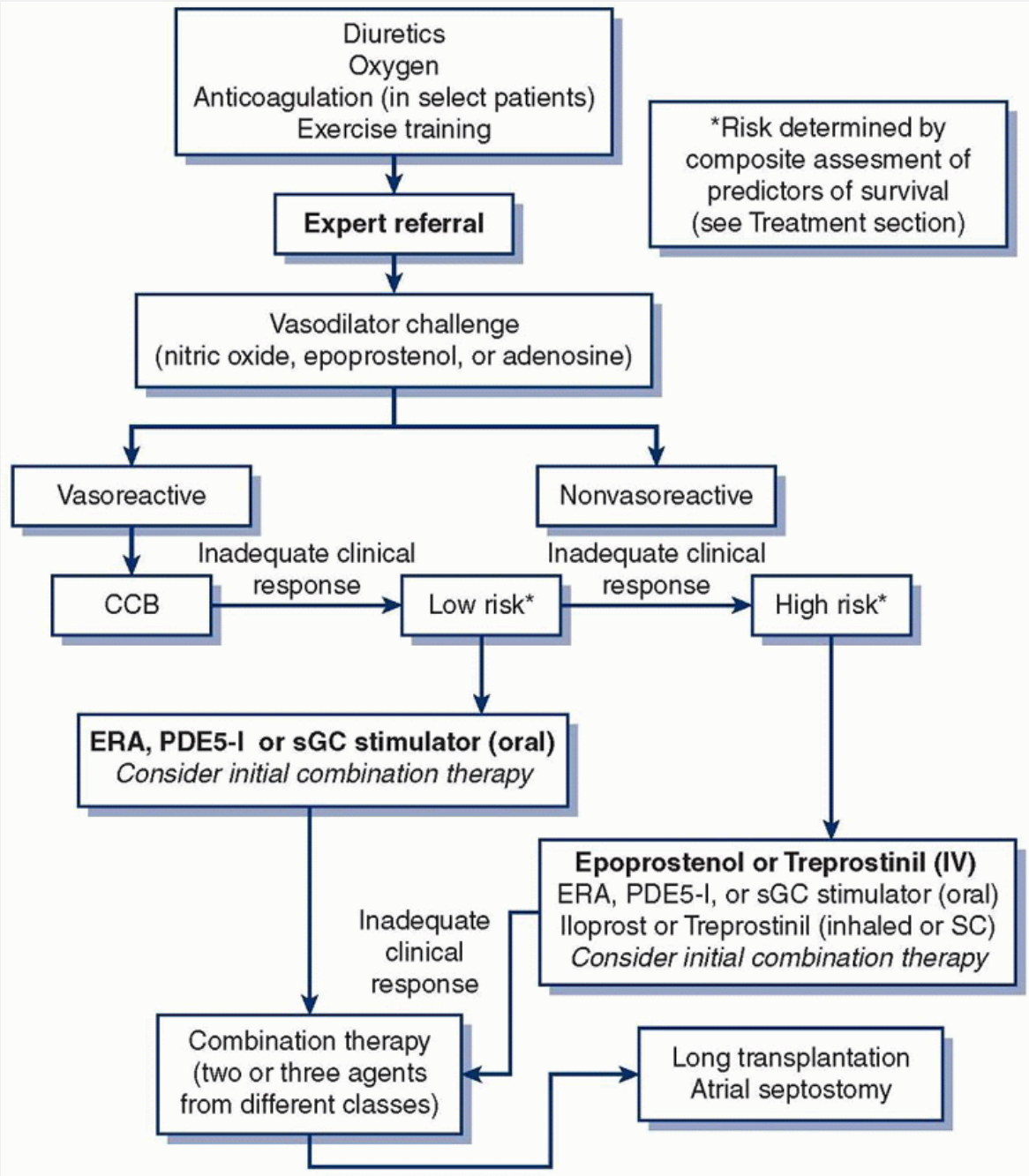


Figure 10-2. Algorithm for management of pulmonary arterial hypertension. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 I, phosphodiesterase-5 inhibitor; sGC, soluble

guanylate cyclase.

- New York Heart Association (NYHA) functional class IV
- 6MW distance <165 m

- Due to the complexity of some therapies, an individual's comorbid conditions, cognitive abilities, and psychosocial makeup must also be heavily factored.
- Combination therapy regimens, which include medications from more than one class of therapy, are quickly becoming common in the management of PAH.
- Because current therapies for PAH are palliative and not curative, patients require close follow-up because deterioration often occurs, requiring alternative/additional medical and possibly surgical intervention (see Figure 10-2). Although there is no consensus on follow-up strategy, periodic functional (e.g., 6MW and WHO functional classification) and cardiac (e.g., TTE, MRI, or right heart catheterization) assessments provide the most sound strategy.

P.287

P.288

TABLE 10-2 Vasomodulator/Vasodilatory Therapy for Pulmonary Arterial Hypertension

Drug	Therapeutic Class	Route of Delivery	Dosing Range	Adverse Effects	Cautions
Nifedipine, amlodipine, diltiazem	Calcium channel blockers	PO	Varies by patient tolerance	Peripheral edema, hypotension, fatigue	Use only in patients who are vasoresponsive during acute vasodilator challenge; avoid if low cardiac output or decompensated right heart failure
Sildenafil, tadalafil	Phosphodiesterase-5 inhibitor	PO	20 mg tid/40 mg/d	Headache, hypotension, dyspepsia, myalgias, visual disturbances	Avoid using with nitrates or protease inhibitors
Riociguat	Soluble guanylate cyclase stimulator	PO	2.5 mg tid	Hypotension	Avoid using with nitrates; approved for PAH and inoperable

					CTEPH or PH persistent after endarterectomy
Bosentan	Endothelin receptor antagonist	PO	125 mg bid	Hepatotoxicity, teratogen, peripheral edema	Monthly liver function monitoring; avoid using with glyburide and glipizide
Ambrisentan	Endothelin receptor antagonist	PO	5-10 mg/d	Teratogen, peripheral edema, nasal congestion	Monthly liver function monitoring; avoid using with glyburide and glipizide.
Macitentan	Endothelin receptor antagonist	PO	10 mg/d	Teratogen, peripheral edema, anemia	Strong interaction with warfarin; monthly liver function monitoring
Iloprost	Prostanoid	IH	2.5-5.0 µg 6-8×/d	Cough, flushing, headache, trismus	Suboptimal adherence due to dosing frequency; overnight drug holiday
Treprostinil	Prostanoid	SC, IV, or PO	Varies by patient tolerance	Headache, jaw pain, diarrhea, extremity pain	With continuous parenteral use, catheter-related complications (IV); site pain/reaction (SC); GI distress with PO use
Epoprostenol	Prostanoid	IV	Varies by patient tolerance	Headache, jaw pain, diarrhea, extremity pain	Continuous parenteral agent; very short half-life; catheter-related complications

	(IV); high-output state at higher doses

CTEPH, chronic thromboembolic pulmonary hypertension; GI, gastrointestinal; IH, inhaled; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

- **Diuretic therapy** (loop diuretic ± aldosterone antagonist ± thiazides)
  - Alleviates **right heart failure** and improves symptoms.
  - Overdiuresis or too rapid of a diuresis can be poorly tolerated due to **preload dependency** of the RV and limited ability of the cardiac output to compensate for systemic hypotension.
- **Anticoagulation**
  - Chronic anticoagulation improves survival, primarily in IPAH (*N Engl J Med 1992;327:76*; *Circulation 1984;70:580*). Use of anticoagulation in other types of PAH is controversial.
  - Warfarin is dosed to **target international normalized ratio (INR) of 1.5-2.5** (*Chest 2004;126:35S*).
  - Anticoagulant therapy is not urgent and can be stopped for invasive procedures or active bleeding.
- **Inotropic agents**
  - Modestly improve right heart function, cardiac output, and symptoms.
  - Dobutamine and milrinone are best suited for **short-term use** in extremely decompensated states.

Surgical Management

- **Lung transplantation or heart-lung transplantation**
  - Reserved for suitable patients with PAH who **remain in advanced functional class III-IV despite maximal medical therapy**.
  - The **Lung Allocation Score** (LAS), derived from multiple clinical variables, takes into consideration PH diagnosis and provides a mechanism for prioritizing PAH patients beyond their imputed LAS. This improves the likelihood for patients with IPAH to receive transplants; however, mortality on the waiting list is high compared to other diagnoses.
  - Because the RV recovers after isolated lung transplantation, heart-lung transplantation is usually reserved for complex congenital heart defects that cannot be repaired.
  - Median survival after lung transplantation is approximately 5 years, and **survival for IPAH patients at 5 years is approximately 50%** (*J Heart Lung Transplant 2005;24:956*).
- **Atrial septostomy**
  - Palliative procedure performed in cases of right heart failure (i.e., syncope, hepatic congestion, prerenal azotemia) refractory to medical therapy.
  - Percutaneous creation of a right-to-left shunt across the interatrial septum in patients whose RAPs are greater than left atrial pressures.
  - Despite arterial oxyhemoglobin desaturation and hypoxemia, oxygen delivery increases from improved LV filling and cardiac output.
- **Septal defect closure**
  - In select cases of intracardiac defects that still have significant left-to-right shunting, closure can be undertaken by **percutaneous or surgical** means.

- Criteria for closure include net left-to-right shunt with flow ratio (pulmonary flow/systemic flow) ≥1.5, resistance ratio (PVR/systemic vascular resistance) ≤0.6 (*Circulation 2008;118:2395*), and PVR <4.6 Wood units (*J Am Coll Cardiol 2013; 62:D34*).

Prognosis

The 1-, 3-, and 5-year survival rates in PAH are 85%, 70%, and 55%, respectively, with median survival of 3.6 years (*Circulation 2010;122:156*; *Eur Respir J 2007; 30:1103*).

Obstructive Sleep Apnea-Hypopnea Syndrome

GENERAL PRINCIPLES

Definition

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a disorder in which patients experience apneas or hypopneas due to upper airway narrowing. It is associated with excessive daytime somnolence (*Sleep 1999;22:667*).

Classification

- **Apneas** represent complete cessation of airflow.
  - Obstructive events are associated with continued respiratory effort.
  - Central events are associated with no respiratory effort.
- **Hypopneas** represent diminished airflow associated with at least a 3-4% oxygen desaturation.
- **Respiratory effort-related arousals (RERAs)** represent changes in airflow that lead to an arousal but do not meet criteria for an apnea or hypopnea.
- All respiratory events must last at least 10 seconds to be counted.
- **Apnea-hypopnea index (AHI)** is the number of apneas and hypopneas per hour of sleep.
- **Respiratory disturbance index (RDI)** is the number of apneas, hypopneas, and RERAs per hour of sleep.

Epidemiology

- The prevalence of OSAHS in the general population is estimated to be about 4%, with men being twice as likely as women to be affected (*Eur Respir J 2009;33:907*; *JAMA 2004;291:2013*; *N Engl J Med 1993;328:1230*).
- Obesity is a significant risk factor for obstructive sleep apnea (OSA) (*N Engl J Med 1993;328:1230*).

Etiology

- **OSA:** Narrowing of the upper airway due to excessive soft tissue or structural abnormalities
- **Central sleep apnea:** Disturbance of central control of respiration during sleep

Pathophysiology

OSA occurs due to narrowing of the upper airway, which results in diminished airflow or cessation of airflow leading to arousals that fragment sleep.

Risk Factors

Risk factors for OSAHS include obesity, nasal obstruction, adenoidal or tonsillar hypertrophy, and mandibular size and positioning (*Otolaryngol Clin North Am 1990;23:727*). Potential risk factors also include family history and smoking (*JAMA 2004;291:2013*).

Prevention

- Weight loss
- Avoiding sedatives such as hypnotic medications or alcohol

Associated Conditions

- **Cardiovascular disease**, including systemic hypertension, heart failure, arrhythmia, myocardial infarction, and stroke (*Circulation 2008;118:1080*). OSA has been established as an independent risk factor for hypertension (*Eur Respir J 2007;29:156*).
- **Increased risk of death**, mainly due to cardiovascular events (*Sleep 2008;31:1071*; *Sleep 2008;31:1079*; *N Engl J Med 2005;353:2034*).

- Increased prevalence of **diabetes** has been noted in patients with OSAHS, independent of the effect of obesity (*Am J Respir Crit Care Med 2005;172:1590*; *J Clin Endocrinol Metab 2000;85:1151*).
- Higher risk of motor vehicle accidents (*Sleep 1997;20:608*).

DIAGNOSIS

Clinical Presentation

History

- **Habitual loud snoring** is the most common symptom of OSAHS, although not all people who snore have this syndrome. Patients with OSA may experience snore arousals along with a sensation of gasping or choking.
- Excessive daytime sleepiness (**hypersomnolence**) is a classic symptom of OSAHS (Table 10-3). Patients may describe falling asleep while driving or having difficulty concentrating at work.
- Patients may also complain of personality changes, intellectual deterioration, morning headaches, nocturnal angina, loss of libido, and chronic fatigue.

Physical Examination

- All patients should have a thorough nose and throat examination to detect sources of upper airway obstruction that are surgically correctable (e.g., septal deviation, enlarged tonsils), especially if continuous positive airway pressure (CPAP) is poorly tolerated.
- Increased severity of OSA has been associated with a higher **Mallampati class** (Table 10-4) (*Eur Respir J 2003;21:248*).

Diagnostic Criteria

A **polysomnogram** demonstrating obstructive events with an RDI >5 is diagnostic of OSA. If the RDI is between 5-15, a patient may qualify for CPAP if there is a comorbid condition such as hypertension, coronary artery disease, depression, or hypersomnolence. If there are no comorbid conditions, then the RDI has to be >15 in order for a patient to qualify for CPAP.

Differential Diagnosis

- In addition to OSAHS and sleep-related hypoventilation, the differential diagnosis for daytime sleepiness includes sleep deprivation, periodic limb movement disorder, narcolepsy, and medication side effects.

TABLE 10-3 Symptoms Associated with Obstructive Sleep Apnea-Hypopnea Syndrome

Excessive daytime sleepiness
Snoring
Nocturnal arousals
Nocturnal apneas
Nocturnal gasping, grunting, and choking
Nocturia
Enuresis
Awakening without feeling refreshed
Morning headaches
Impaired memory and concentration
Irritability and depression
Impotence

TABLE 10-4 Mallampati Airway Classification

Class	Visible Structures with Mouth Maximally Open and Tongue Protruded
I	Hard palate, soft palate, uvula, tonsillar pillars
II	Hard palate, soft palate, uvula
III	Hard palate, soft palate, base of uvula
IV	Hard palate

From Mallampati SR, Gatt SP, Gugino LD, et al. A clinical sign to predict difficult tracheal intubation: A prospective study. *Can Anaesth Soc J* 1985;32(4):429-34. With kind permission from Springer Science Business & Media B.V.

- Patients should also be evaluated for other medical conditions that may cause nighttime awakenings and dyspnea and thus mimic OSAHS, such as chronic lung disease, CHF, and gastroesophageal reflux disease.

Diagnostic Testing

- The gold standard for the diagnosis of OSAHS is **overnight PSG** ("sleep study") with direct observation by a qualified technician (*Am Rev Respir Dis 1989;139:559*). Sleep studies are typically performed in the outpatient setting.
- Typical indications for a sleep study include snoring with excessive daytime sleepiness, titration of optimal positive airway pressure therapy, and assessment of objective response to therapeutic interventions.
- PSG involves determination of sleep stages using electroencephalography, electromyography, and electro-oculography and assessment of respiratory airflow and effort, oxyhemoglobin saturation, cardiac electrical activity (e.g., ECG), and body position.
- Data are analyzed for sleep staging, the frequency of respiratory events, limb movements, and abnormal behaviors. Respiratory events are categorized as obstructive or central.
- Most sleep studies are performed as "split studies," where the first few hours of the study are diagnostic and the latter part of the study is used for CPAP titration if the AHI is consistent with moderate-to-severe OSA.
- Some patients only have significant events when lying in certain positions (usually supine) or during rapid eye movement (REM) sleep. These patients may require a complete overnight study for diagnosis and a second study for initiation of therapy.
- Recognizing the cost, required manpower, and limited availability of PSG, the American Academy of Sleep Medicine supports the use of unattended portable monitoring as an alternative to PSG for patients with a high pretest probability of moderate to severe OSA without significant comorbid medical conditions or other suspected sleep disorders. The portable device must record airflow, respiratory effort, and blood oxygenation, and results should be reviewed by a sleep specialist (*J Clin Sleep Med 2007;3:737*). Portable devices can underestimate the severity of OSA because the number of events per hour is calculated using total recording time rather than total sleep time.

TREATMENT

The therapeutic approach to OSAHS depends on the severity of the disease, comorbid medical conditions, and patient preference and expected compliance. Treatment must be highly individualized, with special attention paid to correcting potentially reversible exacerbating factors.

Medications

- No pharmacologic agent has sufficient efficacy to warrant replacement of positive airway pressure as the primary therapeutic modality for OSAHS.
- **Modafinil** may improve daytime sleepiness in patients with persistent symptoms despite adequate CPAP use (*Sleep 2006;29:31*).
- Medical treatment of conditions that may contribute to muscle hypotonia or weight gain, such as hypothyroidism, are of benefit.

Nonpharmacologic Therapies

- **Positive airway pressure**
  - **CPAP** delivers air via a face mask at a constant pressure level throughout the respiratory cycle with the goal of pneumatically splinting open the upper airway, thus preventing collapse and airflow obstruction.
  - The PSG determines the positive airway pressure (expressed in cm H_2O) required to optimize airflow. The pressure setting is gradually increased until obstructive events, snoring, and oxygen desaturations are minimized.

- The benefits of positive airway pressure include consolidated sleep and decreased daytime sleepiness. Hypertension, nocturia, peripheral edema, polycythemia, and PH may also improve. Additionally, CPAP is a highly cost-effective intervention (*Can J Physiol Pharmacol 2007;85:179*) that appears to reduce the risk of cardiovascular events (*Am J Respir Crit Care Med 2007;176:1274*) and may also improve the metabolic syndrome associated with OSA (*N Engl J Med 2011;365:2277*).
- **Nasal CPAP (nCPAP) is the current treatment of choice for most patients with OSAHS.**
  - The compliance rate with nCPAP is approximately 50%.
  - Compliance can be improved with education, instruction, follow-up, adjustment of the mask for fit and comfort, humidification of the air to decrease dryness, and treatment of nasal or sinus symptoms.
  - Use of a full face mask (oronasal) has not been shown to improve compliance compared to the use of nCPAP. However, full-face masks are frequently used in patients who "mouth breathe" or patients who require higher CPAP pressures, because they will often experience air leak through the mouth when using nCPAP.
- Autotitrating positive airway pressure machines use flow and pressure transducers to sense airflow patterns and then automatically adjust the pressure setting in response. Small studies have shown that autotitrating CPAP may be as effective as traditional CPAP and appears to be preferred by patients (*Respiration 2007;74:279*; *Chest 2006;129:638*).
- **Bilevel positive airway pressure** is typically used to treat OSA in the following settings: pressures >15-20 cm H_2O are required, intolerance of CPAP, or concern for concomitant hypoventilation.
- All noninvasive positive-pressure ventilation devices may induce dryness of the airway, nasal congestion, rhinorrhea, epistaxis, skin reactions to the mask, nasal bridge abrasions, and aerophagia. Some of these nasal symptoms may be treated with nasal saline, decongestants, and use of a humidifier.
- Some patients, such as those with coexisting chronic obstructive pulmonary disease, require supplemental oxygen to maintain adequate nocturnal oxygen saturations (SaO_2 ≥90%).

- **Oral appliances**
  - Used for mild OSAHS, with aim to increase airway size to improve airflow. These devices, such as the mandibular advancement device, can be fixed or adjustable, and most require customized fitting. Many devices have not been well studied.
  - Contraindications include temporomandibular joint disease, bruxism, full dentures, and inability to protrude the mandible.
- **Nasal expiratory resistance device**
  - Nasal plugs increase resistance with expiration, creating a back pressure to stent open the upper airway.

  - Most effective for milder OSA. Should not be used in patients with significant comorbid conditions such as lung disease.
- **Upper airway stimulation device**
  - The U.S. Food and Drug Administration (FDA) has recently approved an upper airway stimulation device for use in patients with moderate to severe OSA who cannot tolerate CPAP.
  - Although AHI and daytime sleepiness improved with this device, there was residual mild OSA (*N Engl J Med 2014;370:139*).

Surgical Management

- **Tracheostomy**

- Tracheostomy is very effective in treating OSAHS but is rarely used since the advent of positive airway pressure therapy.
- Tracheostomy should be reserved for patients with life-threatening disease (cor pulmonale, arrhythmias, or severe hypoxemia) or significant alveolar hypoventilation that cannot be controlled with other measures.

- **Uvulopalatopharyngoplasty (UPPP)**
  - UPPP is the most common surgical treatment of mild-to-moderate OSAHS in patients who do not respond to medical therapy.
  - UPPP enlarges the airway by removing tissue from the tonsils, tonsillar pillars, uvula, and posterior palate. UPPP may be complicated by change in voice, nasopharyngeal stenosis, foreign body sensation, velopharyngeal insufficiency with associated nasal regurgitation during swallowing, and CPAP tolerance problems.
  - The success rate of UPPP for treatment of OSAHS is only approximately 50%, when defined as a 50% reduction of the AHI, and improvements related to UPPP may diminish over time (*Sleep 1996;19:156*). Thus, UPPP is considered a second-line treatment for patients with mild to moderate OSAHS who cannot successfully use CPAP and who have retropalatal obstruction.
- **Staged procedures**

In experienced centers, other staged procedures for OSA can be performed, including mandibular osteotomy with genioglossus advancement, hyoid myotomy with suspension, and maxillomandibular advancement (MMA) (*Sleep Breath 2000;4:137*). Significant reductions in AHI have been reported with MMA, but more research is needed (*Sleep 2010;33:1396*).

Lifestyle/Risk Modification

- Weight reduction for the obese is recommended (*Chest 1987;92:631*).
- Weight loss, both surgical and through reduced caloric intake, has been shown to reduce the severity of OSA by reduction in AHI (*Am J Respir Crit Care Med 2009;179:320*; *Am J Med 2009;122:535*).
- OSAHS patients should avoid use of alcohol, tobacco, and sedatives.
- Clinicians should counsel patients with OSAHS regarding the increased risk of driving and operating dangerous equipment.

SPECIAL CONSIDERATIONS

Patients with a body mass index >40 kg/m^2 are at increased risk for concomitant sleeprelated hypoventilation due to morbid obesity.

COMPLICATIONS

- When OSAHS is associated with disorders such as obesity and chronic lung disease, patients may develop hypoxemia, hypercapnia, polycythemia, PH, and cor pulmonale (*Mayo Clin Proc 1990;65:1087*).

- Patients with OSAHS are at greater risk for perioperative complications due to intubation difficulty and/or impaired arousal secondary to the effects of anesthetics, narcotics, and sedatives (*Otolaryngol Clin North Am 2007;40:877*).
- The risk of death, hypertension, and poor neuropsychological functioning rises with increasing severity of

OSA.

REFERRAL

Patients with risk factors and symptoms or sequelae of OSAHS should be referred to a sleep specialist and sleep laboratory for further evaluation.

Interstitial Lung Disease

GENERAL PRINCIPLES

Definition

ILDs are a heterogeneous group of disorders, pathologically characterized by infiltration of the lung interstitium with cells, fluid, and/or connective tissue.

Classification

- ILD of known etiology
  - Medication (e.g., bleomycin, amiodarone, nitrofurantoin, methotrexate)
  - Connective tissue disease (e.g., rheumatoid arthritis, scleroderma, polymyositis/dermatomyositis)
  - Pneumoconiosis (e.g., coal worker's pneumoconiosis, silicosis, asbestosis)
  - Radiation
  - Lymphangitic carcinomatosis
- Idiopathic interstitial pneumonias
  - Usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Desquamative interstitial pneumonia (DIP)
  - Respiratory bronchiolitis interstitial lung disease (RB-ILD)
  - Cryptogenic organizing pneumonia (COP)
  - Lymphocytic interstitial pneumonia
  - Acute interstitial pneumonia
- Granulomatous ILD
  - Sarcoidosis
  - Hypersensitivity pneumonitis (HP)
- Cystic lung disease
  - Lymphangioleiomyomatosis
  - Pulmonary Langerhans cell histiocytosis (LCH)
  - Genetic diseases (Birt-Hogg-Dubé, tuberous sclerosis)
  - Light chain deposition disease

DIAGNOSIS

Clinical Presentation

History

- Patients typically present with indolently progressive dyspnea and dry cough. History often reveals years of gradually worsening symptoms, although a subset (acute interstitial pneumonia, acute eosinophilic pneumonia) may present acutely.

- Careful questioning should focus on exposures (pharmacologic agents, asbestos exposure, exposure to industrial fumes or dusts, bird antigens, and mold) as well as symptoms of connective tissue disease.
- Clinical features of common ILDs are described in Table 10-5.

Physical Examination

Findings may include inspiratory crackles and digital clubbing. Close attention should be paid to extrapulmonary findings that point toward connective tissue diseases. Examples include sclerodactyly, mechanic's hands, Raynaud phenomenon, dry mucous membranes, and dermatologic findings such as telangiectasias, rash, or facial erythema.

Diagnostic Approach

Imaging

- Plain radiographs of the chest have variable appearance, with lung volume loss, interstitial thickening, and cystic changes being most common in ILD.
- If initial radiograph or clinical scenario is consistent with ILD, the patient should be referred for high-resolution CT (HRCT), which is the radiographic test of choice for patients with suspected ILD.
- The pattern of radiographic infiltrate is important in the differential diagnosis of ILD. Imaging patterns of common ILDs are described in Table 10-5. Notably, published guidelines exist for the definitive radiologic diagnosis of certain ILDs, specifically idiopathic pulmonary fibrosis (IPF)/UIP (*Am J Respir Crit Care Med 2011;183:788*).

Pulmonary Function Testing

- Spirometry typically demonstrates a restrictive ventilatory defect characterized by a symmetric reduction in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Definitive diagnosis of a restrictive ventilatory defect requires documentation of a reduction in total lung capacity to <80% predicted.
- In certain ILDs (e.g., sarcoidosis, LCH, HP), bronchiolar involvement may result in airflow obstruction, causing the FEV_1 to decrease disproportionately to the FVC. In this circumstance, a mixed obstructive and restrictive defect may be seen. This circumstance may also exist in cases of comorbid emphysema.
- DLCO is often significantly decreased in patients with ILD.

Laboratory Analysis

- Patients with a diagnosis of ILD should be evaluated for evidence of a connective tissue disease as a potential target for therapy. Some connective tissue diseases may manifest primarily with pulmonary symptoms. As an example, approximately 10-20% of patients with rheumatoid arthritis may have lung disease as their initial clinical presentation (*Proc Am Thorac Soc 2007;4(5):443*).
- ANA and rheumatoid factor (RF) should be tested in most patients, even patients with UIP on thoracic imaging. Cyclic citrullinated peptide should also be tested to evaluate for rheumatoid arthritis because the RF may be insufficiently sensitive and has a low positive predictive value.
- Aldolase and creatinine kinase should be tested to evaluate for evidence of myositis. In cases where

suspicion is high for myositis, panels of muscle-specific antibodies should also be obtained.

- In any patient with evidence of scleroderma such as telangiectasis, esophageal dysmotility, or sclerodactyly, antibodies against topoisomerase I (anti-Scl-70) should be obtained.

Diagnostic Procedures

- Bronchoalveolar lavage has little role in ILD outside of evaluating for infection.
- Lung biopsy should be undertaken with the input of pulmonologists and thoracic surgeons with expertise in ILD.
  - Generally, biopsy should be reserved for circumstances where the diagnosis is uncertain and clarification would result in a significantly altered approach to management.

P.297

P.298

TABLE 10-5 Clinical and Radiologic Features of Interstitial Lung Diseases

	Clinical Features	HRCT findings
UIP	■ Forms the radiologic basis for diagnosing IPF in the absence of underlying cause ■ Insidious onset and progressive dyspnea ■ Dry cough ■ Poorly responsive to treatment, poor long-term survival ■ Variable course punctuated by intermittent exacerbations ■ Pattern can be associated with connective tissue disease	■ Subpleural, basal predominant ■ Reticular interstitial thickening ■ Honeycombing with/without traction bronchiectasis ■ Limited ground glass ■ May have atypical distribution in familial cases
NSIP	■ Associated with younger patients and more common in females ■ Commonly associated with collagen vascular diseases, including scleroderma and myositis ■ Response to therapy is variable depending on etiology	■ Interstitial thickening, often with a rim of peripheral subpleural sparing ■ Ground-glass infiltrates ■ Traction bronchiectasis more common than UIP ■ In end-stage disease, may develop fibrotic changes and “bronchiolectasis” that resembles UIP
RB-ILD	■ May be asymptomatic ■ Associated with cigarette smoking ■ Generally responsive to smoking cessation	■ Ground-glass micronodules with an upper lobe predominance

DIP	▪ Associated with cigarette smoking and occupational exposures ▪ Generally responsive to smoking cessation ▪ May be treated with corticosteroids	▪ Peripheral ground-glass opacities or consolidation ▪ May have small, welldefined cysts
AIP	▪ Rapidly progressive ILD with progressive hypoxemia and high mortality ▪ Clinically (and histologically) behaves similarly to “idiopathic ARDS”	▪ Ground-glass opacities admixed with consolidation in geographic pattern ▪ Eventually progresses to fibrosis with architectural distortion and traction bronchiectasis
COP	▪ Subacute course, often presents as multiple treatment failures of bronchitis/pneumonia ▪ Often associated with infections, drug exposures ▪ Responsive to prolonged courses of corticosteroids ▪ Often recurs if steroids are rapidly withdrawn	▪ Multifocal groundglass opacities and consolidations ▪ Usually lower lobe predominant ▪ Infiltrates may be migratory ▪ May have “reverse halo” or atoll sign
CEP	▪ Presents as progressive dyspnea and cough ▪ Patients may have a history of underlying asthma ▪ Peripheral blood and BAL eosinophil counts usually highly elevated	▪ Peripheral consolidations described as the “reverse image of pulmonary edema” ▪ Infiltrates may be migratory
Sarcoidosis	▪ Dyspnea, cough, and chest pain are common presenting symptoms ▪ Systemic symptoms may be prominent ▪ Approximately 1 in 20 cases are asymptomatic and incidentally detected on CXR ▪ Almost any organ system may be affected	▪ Perilymphatic nodules ▪ Patchy ground-glass opacities ▪ Reticular infiltrates ▪ Traction bronchiectasis ▪ Progressive massive fibrosis ▪ Hilar or mediastinal lymphadenopathy
Chronic HP	▪ Presents in a similar fashion to UIP/IPF ▪ There may be a history of systemic symptoms (fever,	▪ Reticular abnormality with an upper or mid-lung predominance ▪ Micronodules ▪ Mosaic attenuation/air trapping

	myalgias)	▪ Peribronchovascular predominance

AIP, acute interstitial pneumonia; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; HRCT, highresolution CT; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis interstitial lung disease; UIP, usual interstitial pneumonia.
Data from: *Curr Probl Diagn* Radiol 2015;44:15; *Am J Respir Crit Care Med* 2011;183:788; Webb RW. *Thoracic Imaging: Pulmonary and Cardiovascular Radiology.* 2005.

- Transbronchial lung biopsy has the highest yield in bronchocentric ILDs, such as sarcoidosis, in which small biopsy samples may suffice for diagnosis (*Thorax 2008;63(Suppl 5):v1*).
- Surgical lung biopsy can be performed by video-assisted thoracoscopic surgery (VATS) or open thoracotomy. HRCT is used to target areas of active disease and avoid lung regions with end-stage fibrosis.
- Although many patients tolerate lung biopsy well, certain subgroups of patients are predisposed to complications, including decompensation of their ILD following lung biopsy (*Chest 2005;127:1600*). Patients with IPF in particular may develop disease exacerbations following lung biopsy, resulting in disease progression and even death.

SPECIFIC INTERSTITIAL LUNG DISEASES

Idiopathic Pulmonary Fibrosis (IPF)

- The incidence of IPF is estimated to be 4.6-16.3 cases per 100,000 population.
- Males are more frequently affected than females.
- Mutations in telomerase RNA component (*TERC*), telomerase reverse transcriptase (*TERT*), pulmonary surfactant protein C (*SFTPC*), surfactant protein A2 (*SFTPA2*), and mucin 5B (*MUC5B*) have been identified in individuals and families with IPF (*Am J Med Sci 2011;341:439*).
- Although the pathophysiology is incompletely understood, pulmonary epithelial cell injury and aberrant wound healing are thought to play a central role.
- Diagnosis is made by either a definite radiographic pattern for UIP on HRCT or UIP pattern on surgical lung biopsy in the absence of other known cause after thorough workup has been completed (*Am J Respir Crit Care Med 2011;183:788*).
- In the setting of a familial fibrotic lung disease, the CT pattern may be atypical, often lacking a basal predominance. Even histologically, strictly defined UIP is identified in less than half of familial fibrotic lung disease cases (*Arch Pathol Lab Med 2012;136:1366*).
- Disease-modifying treatment options are limited in IPF. Increased risks of death and hospitalization have been associated with combined use of *N*-acetylcysteine, azathioprine, and chronic prednisone (*N Engl J Med 2012;366:1968*).

- Pirfenidone, an oral antifibrotic agent, and nintedanib, an oral tyrosine kinase inhibitor, have both been shown to slow the rate of decline in lung function in patients with IPF (*N Engl J Med 2014;370:2083*; *N Engl J Med 2014;370:2071*).
- Pulmonary rehabilitation has been associated with improvements in 6MW distance and quality of life in IPF (*Cochrane Database Syst Rev 2014;10:CD006322*).
- Patients have a widely variable course, but those diagnosed with spirometrically mild, moderate, and severe disease have been reported to have median survivals of 55.6, 38.7, and 27.4 months, respectively (*Chest 2011;140:221*).
- Poor prognostic factors for IPF include a decline in FVC >10% over 6 months, a decrease in 6MW distance >150 m over 12 months, and a decrease in DLCO >15% over 6 months.
- Acute exacerbations of IPF are characterized by acute worsening of dyspnea or oxygenation with no evidence of infection, pulmonary embolus, or heart failure (*Am J Respir Crit Care Med 2011;183:788*). Exacerbations are typically treated with highdose corticosteroids, although their benefit has not been systematically proven. Patients often do not return to their pre-exacerbation baseline after IPF exacerbations (*Chest 2007;132:1652*).
- Lung transplantation remains the ultimate therapy in patients with advanced IPF. Criteria for lung transplantation are listed in Table 10-6. Without lung transplantation, outcomes in IPF remain relatively poor. Patients should be referred for consideration of lung transplantation at time of diagnosis of IPF.

Nonspecific Interstitial Pneumonia (NSIP)

- NSIP is rarely idiopathic; there is typically an identifiable etiology. Idiopathic NSIP is a diagnosis of exclusion. Careful history and physical exam should be performed to guide laboratory testing in the search for an underlying etiology.
- Imaging demonstrates ground-glass opacities with reticular infiltrates in a peripheral distribution. There is often sparing of the immediate subpleural space from infiltration. Traction bronchiectasis can also be seen and may progress to “bronchiolectasis” in advanced disease. This can appear radiographically similar to UIP.
- Except in cases of advanced fibrosis, patients with NSIP fare better than those with IPF (*Am J Respir Crit Care Med 2008;177:1338*).

TABLE 10-6 Criteria for Lung Transplantation in Idiopathic Pulmonary Fibrosis and Sarcoidosis

IPF
Histologic or radiographic evidence of UIP and any of the following: ◦ DLCO <39% predicted ◦ ≥10% decrement in FVC during 6 months of follow-up ◦ SpO_2 <88% during a 6-minute walk test ◦ Honeycombing on HRCT
Sarcoidosis
NYHA functional class III or IV and any of the following: ◦ Hypoxemia at rest

- Pulmonary hypertension
- Right atrial pressure >15 mm Hg

DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; NYHA, New York Heart Association; SpO_2, oxyhemoglobin saturation by pulse oximetry; UIP, usual interstitial pneumonia. Modified from *J Heart Lung Transplant* 2006;25:745-55.

- Treatment of NSIP secondary to connective tissue diseases usually involves immunosuppression with steroids, in combination with agents such as mycophenolate, azathioprine, cyclophosphamide, or rituximab.
- Management of patients with connective tissue disease-related ILD should be undertaken in a multidisciplinary fashion with input from providers who are familiar and experienced with these conditions.
- The effects of treating idiopathic NSIP are not well known but are an area of active investigation. Treatment with mycophenolate mofetil in particular seems promising and has been associated with stable or improved pulmonary physiology (*J Rheumatol 2013;40:640*).

Hypersensitivity Pneumonitis (HP)

- HP is a complex syndrome caused by poorly understood immunologic processes resulting in symptoms of dyspnea and cough that may manifest acutely or progress indolently over time.
- Radiographically, HRCT will demonstrate diffuse nodularity with ground-glass opacities and evidence of air trapping. Findings will generally preferentially affect the upper lobes. In advanced disease, pulmonary fibrosis with architectural distortion may occur (*Semin Respir Crit Care Med 2012;33:543*).
- Innumerable antigenic stimuli have been associated with the development of HP. A careful exposure history should be taken and should include inquiry about exposure to birds or bird feathers (including down feather pillows and blankets), hot tubs (associated with mycobacterial exposure), air humidifiers, molds, animal furs, epoxies, plant matter, industrial dusts, and chemicals. Specific antibody measurements can be sent to specialized labs when indicated.
- HP is characterized by acute, subacute, and chronic phases, with most patients presenting in the chronic phase.
- Corticosteroid therapy has been the classic mainstay of treatment for HP. However, careful attention should be paid toward identification of the offending antigen because antigenic avoidance has been associated with significantly improved mortality (*Chest 2013;144(5):1644*).

Sarcoidosis

- Sarcoidosis is diagnosed by the presence of noncaseating granulomas on biopsy. Verifying absence of infectious etiology is of particular importance in patients with exposure to endemic fungi/mycobacteria.
- The incidence rate in the United States is 35.5/100,000 for blacks and 10.9/100,000 for whites (*Am J Respir Crit Care Med 1999;160:736*).
- The cause of sarcoidosis has not been identified, although there are likely environmental and genetic factors (*Am J Respir Crit Care Med 2011;183:573*).
- Patients frequently present for evaluation of progressive dyspnea and cough. Löfgren syndrome is defined as an acute presentation of sarcoidosis characterized by arthritis, erythema nodosum, and bilateral hilar lymphadenopathy (*Am J Respir Crit Care Med 2011;183:573*).

- CXR imaging varies from hilar adenopathy to diffuse pulmonary fibrosis and is used to stage the disease. Staging is reviewed in Table 10-7.
- On CT scan, air trapping may be present, and parenchymal nodules appear in at least 80% of patients, typically following a bronchovascular distribution with intermittent coalescence into larger opacities (*Eur Radiol 2014;24:807*).
- A granulomatous vasculitis may occur and dispose patients to the development of PH.
- Extrapulmonary manifestations are typical and most commonly include uveitis and skin manifestations such as erythema nodosum (raised, red, tender bumps or nodules on anterior legs) and lupus pernio (indurated plaques with associated discoloration of the nose, cheeks, lips, and ears).
- Central nervous system involvement can manifest as central lesions, mononeuritis multiplex, or a host of other neurologic anomalies. Patients with these findings should be referred to neurology specialists with experience in the treatment of this disorder.
- Myocardial involvement may result in cardiomyopathy, arrhythmia, and sudden cardiac death (*Am Heart J 2009;157:9*).
- Endocrine involvement can manifest as hypercalcemia and hypercalciuria secondary to dysregulated production of calcitriol (*Am J Respir Crit Care Med 1999;160:736*).
- Annual ophthalmology evaluation should be considered a standard part of sarcoidosis care to monitor for ocular involvement. Referral to other specialists may be necessary as other visceral symptoms develop.
- For early stage disease, symptoms and radiographic changes may remit in the absence of treatment. In the setting of symptomatic disease or disease progression, corticosteroid therapy is typically first line. Many patients can be treated with intermittent steroid therapy alone, although those with advanced disease may be transitioned to nonsteroid immunosuppression (*Respir Med 2010;104:717*).
- Prognosis is highly variable, ranging from indolent self-remitting disease to progressive fibrosis necessitating transplantation. Indications for transplantation are reviewed in Table 10-6.

TABLE 10-7 Staging of Sarcoidosis

CXR Findings
Stage 0: Normal
Stage 1: Hilar or mediastinal lymphadenopathy
Stage 2: Hilar or mediastinal lymphadenopathy with pulmonary infiltrates
Stage 3: Pulmonary infiltrates
Stage 4: End-stage fibrosis

Organizing Pneumonia

- Organizing pneumonia is radiographically represented by decreased lung volumes and multifocal patchy consolidation and ground-glass opacities.
- Pathologically, organizing pneumonia represents a response to a proinflammatory stimulus. This is often infectious in nature, although a wide variety of pharmacologic agents and environmental exposures have been

http://internalmedicinebook.com

implicated as well. Idiopathic cases known as COP do occur.

- The typical clinical scenario is a patient with multiple episodes of "pneumonia" treated with antibiotics with absence of complete recovery.
- COP is a diagnosis of exclusion, and a comprehensive search for infectious etiology should be undertaken. In the absence of infectious etiology, disease is typically responsive to steroid therapy. Recurrence, however, is common after steroid withdrawal, and longterm therapy (>6 months) is frequently necessary.

"Smoking-Related" ILD

- The risk of IPF is increased in smokers.
- RB-ILD presents in patients in the third to fifth decades of life with dyspnea, cough, and radiographic evidence of subtle upper lobe ground-glass nodules on HRCT. Prognosis is good with smoking cessation.
- DIP may represent a spectrum of disease along with RB-ILD. The predominant HRCT finding in DIP is ground-glass opacities, which may be peripheral, patchy, or diffuse in distribution. Small cystic spaces occasionally develop within the ground-glass opacities. Response to smoking cessation is generally good, although some patients require corticosteroid therapy. The disease occasionally persists despite therapy (*Eur Respir J 2001;17:122*). A more severe form of DIP may also be observed in occupational exposures, and a congenital form may be seen in children.
- LCH is a parenchymal cystic lung disease characterized by irregular cysts associated with parenchymal nodules, often with sparing of the lung bases. Response to smoking cessation and steroids is generally considered good, although some patients have persistent, treatment-unresponsive disease.

Pneumoconioses

- Pneumoconioses are diseases of the lung parenchyma that result from exposure to inorganic dusts.
- Asbestos-induced lung disease arises from exposure to asbestos. Radiographic findings may range from pleural thickening and plaques to changes similar to UIP. Presence of pleural plaques aids in differentiation from other ILDs, but asbestos-related fibrotic disease can exist in the absence of pleural manifestations. Treatment focuses on asbestos avoidance and supportive care. Prognosis is good in mild disease, although the risk of lung cancer is increased in the setting of concomitant cigarette use.
- Silicosis results from exposure to silica crystals, which are found in stone and sand. Foundry workers, construction workers, and glassblowers are at increased risk. CXRs demonstrate small nodules in the upper and mid zones with hilar adenopathy in a manner similar to sarcoidosis. Treatment is supportive, although close monitoring for development of tuberculosis (TB) is warranted because these patients are at increased risk (*Prim Care Respir J 2013;22:249*).
- Berylliosis is caused by exposure to beryllium and beryllium compounds. Exposure occurs in the aerospace industry, atomic industry, beryllium mining, and fluorescent light bulb manufacturing. It is clinically indistinguishable from sarcoidosis.

Cystic Lung Disease

- Lymphangioleiomyomatosis is a progressive cystic disease of the lung seen almost exclusively in young women. Imaging demonstrates diffuse, round, thin-walled cysts. Pneumothorax (from ruptured cyst) is a commonly described initial presentation.

Lymphangioleiomyomatosis is seen more frequently in patients with tuberous sclerosis. Extrapulmonary manifestations may include renal tumors, specifically angiomyolipomas. Sirolimus has been shown to reduce

http://internalmedicinebook.com

disease progression, but disease recurs once therapy is stopped, and long-term effects are uncertain at this point (*N Engl J Med 2011;364:1595*).

- LCH is described under the "Smoking-Related" ILD section.
- Amyloidosis and light chain deposition disease can be associated with cystic lung disease in the setting of underlying systemic amyloidosis, connective tissue disease, or myeloma. Cysts are variable in size and distribution. Treatment focuses on the underlying condition.
- Lymphocytic interstitial pneumonia is a rare disease, usually associated with connective tissue diseases. Imaging demonstrates irregular cysts, multifocal ground-glass opacities, nodularity, and septal thickening. Treatment and prognosis are variable depending on underlying condition.
- Birt-Hogg-Dubé syndrome is a rare cause of cystic disease associated with skin and renal neoplasms. Cysts are irregularly shaped and localized to the lung bases. Treatment is supportive, and progression is generally slow (*Front Med 2013;7:316*).

MANAGEMENT CONSIDERATIONS

- The medical management of selected ILDs is briefly reviewed in Table 10-8.
- All ILD patients should be monitored for the development of exertional hypoxemia. Supplemental oxygenation should be provided to maintain oxyhemoglobin saturation by pulse oximetry (SpO_2) ≥89% both with rest and exertion.

TABLE 10-8 Medical Treatment of Selected Interstitial Lung Diseases

ILD	Potential Therapeutic Interventions[a]
Medication-induced ILD	○ Discontinue culprit medication ○ Corticosteroids
Connective tissue disease-associated ILD (UIP, NSIP, COP)	○ Corticosteroids ○ Immunosuppressive therapy (e.g., cyclophosphamide, azathioprine, mycophenolate)
IPF	○ Pirfenidone ○ Nintedanib ○ Consideration for participation in a clinical trial
DIP, RB-ILD	○ Smoking cessation ○ Corticosteroids (likely of limited benefit)
Sarcoidosis	○ Corticosteroids ○ Immunosuppressive therapy (e.g., methotrexate, azathioprine, hydroxychloroquine, TNF-α inhibitors)
Chronic HP	○ Avoid offending antigens ○ Corticosteroids (likely of limited benefit)

	○ Immunosuppressive therapy

COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-interstitial lung disease; TNF, tumor necrosis factor; UIP, usual interstitial pneumonia.

[a]Lung transplantation is a consideration for select patients with end-stage interstitial lung disease.

- Smoking cessation/avoidance should be strongly encouraged, and patients should avoid occupational/environmental triggers of their ILD, if identified.
- Pulmonary rehabilitation therapy should be prescribed for all patients if they meet eligibility criteria.
- Bone density assessment is recommended for patients receiving chronic systemic corticosteroid therapy, and periodic reassessment (e.g., every 1-2 years) should be performed.
- *Pneumocystis jirovecii* pneumonia prophylaxis should be considered in patients receiving chronic immunosuppressive therapy (*Mayo Clin Proc 1996;71:5*).
- Patients should receive vaccinations against pneumococcus and influenza.
- Those with advanced or idiopathic ILDs should be considered for referral to centers with expertise in the diagnosis and treatment of these conditions, with particular consideration for participation in ongoing clinical trials.
- ILD increases the risk of PH (*Am J Respir Crit Care Med 2011;45:1*). Patients with dyspnea out of proportion to their parenchymal lung disease or those with symptoms of right heart failure should be screened with TTE. Although the use of pulmonary vasodilators in this population remains controversial, other therapies targeted at maintenance of euvolemia and optimization of RV function can be helpful in controlling symptoms.
- Several of the ILDs are associated with an increased incidence of malignancy. Rapid weight loss or radiographic changes (e.g., new consolidation) should raise suspicion and prompt further workup.
- Goals of care should be made clear, particularly in patients who have advanced fibrotic lung diseases and are not candidates for transplantation. Open discussions of these issues in the clinical arena may prompt family discussions, which can be helpful during acute exacerbations or disease progression (*BMJ Support Palliat Care 2013;3:84*).

Solitary Pulmonary Nodule

GENERAL PRINCIPLES

- The goal of a careful evaluation of the solitary pulmonary nodule (SPN) is to determine if the lesion is more likely **malignant or benign**.
- **A lesion >3 cm has a high likelihood of malignancy and should be treated as such, whereas lesions <3 cm need more careful assessment.**
- Nodules with benign characteristics should be closely followed so that invasive procedures with associated risks can be avoided.
- Identifying early lung cancer is of the utmost importance because there is a >60% survival rate of patients who have a malignant SPN removed (*Chest 2013;145(5):e278S*).

Definition

An SPN is defined as a rounded lesion <3 cm in diameter. It is completely surrounded by lung parenchyma, unaccompanied by atelectasis, intrathoracic adenopathy, or pleural effusion. Pulmonary nodules <8 mm remain within this definition; however, there is evidence to suggest that these nodules have a lower overall malignancy risk (*Chest 2013;145(5):e278S*).

Epidemiology

- Approximately 150,000 SPNs are identified each year in the United States.
- It has been estimated that such a nodule is noted on 0.09-0.20% of all chest radiographs.

Etiology

- Although underlying etiologies for pulmonary nodules are varied, the most important designation clinically is deciphering between a malignant and a nonmalignant process.

- **Malignancy accounts for approximately 40% of SPNs, although this may vary geographically depending on the prevalence of nonmalignant processes such as histoplasmosis.**
- **Granulomas** (both infectious and noninfectious) account for 50% of undiagnosed SPNs.
- The remaining 10% are composed of **benign neoplasms**, such as **hamartomas** (5%) and a multitude of other causes.

Risk Factors

- **Smoking** is the most important associated risk factor for almost all malignant SPNs.
- For infectious etiologies, an immunocompromised state promotes an increased risk.

Lung Cancer Screening

Screening high-risk patients using low-dose chest CT resulted in a 20% relative reduction in mortality from lung cancer compared to screening with CXR (*N Engl J Med 2011;365:395*).

DIAGNOSIS

- Diagnosis of the SPN is made radiographically, usually via CXR or CT scan.
- Most frequently, the nodule is noted incidentally on a study performed for other reasons (e.g., chronic cough, chest pain).

Clinical Presentation

- As stated previously, the majority of SPNs are diagnosed incidentally by radiographic tests done for other reasons, so there may not be overt symptoms.
- There are instances when a nodule may precipitate cough, chest pain, hemoptysis, or sputum production depending on the etiology and location of the SPN.

History

- Ask typical screening questions for malignancy including **weight loss and night sweats**.
- **Hemoptysis** may indicate malignancy but may also prompt investigations for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, TB, and hereditary hemorrhagic telangiectasia (HHT).
- Ask about arthritis and arthralgias for possible undiagnosed rheumatoid arthritis or sarcoidosis.

- Take an exposure history including recent travel history related to endemic mycoses (histoplasmosis, coccidioidomycosis, etc.) as well as possible TB exposures.
- A history of previous malignancies increases the risk of metastatic disease of the lung.
- Patients who are immunosuppressed from HIV, organ transplant, or chronic steroids have increased risk of infectious causes.
- Smoking is linked to 85% of lung cancers. A patient's risk of lung cancer decreases significantly 5 years after smoking cessation, but it never truly returns to normal.
- An occupational history is important including possible exposure to asbestosis (associated with not only mesothelioma, but also non-small-cell lung cancer), silica, beryllium, radon, and ionizing radiation, among others.

Physical Examination

- Although there are no specific physical exam findings related to SPNs, evidence for underlying etiologies may be discovered with a thorough exam.
- Note signs of weight loss or cachexia, suggestive of malignancy.
- Do a thorough lymph node exam. **A cervical lymph node might provide an easy diagnostic target to determine the etiology of an SPN.**

- Perform a breast exam in women and testicular exam in young men.
- A careful skin examination may reveal telangiectasias, erythema nodosum, rheumatoid nodules, or other findings that might suggest a cause.

Diagnostic Criteria

- As mentioned previously, an SPN is identified as a rounded lesion <3 cm in circumference. It is completely surrounded by lung parenchyma, unaccompanied by atelectasis, intrathoracic adenopathy, or pleural effusion.
- The first step in managing an SPN is to stratify the patient in terms of malignancy risk: low-, intermediate-, or high-risk categories (Table 10-9). Risk stratification can be accomplished either qualitatively via clinical judgment or quantitatively using validated risk assessment tools. These approaches appear to be complementary (*Ann Am Thorac Soc 2013;10(6):629*).
- Once the risk of malignancy has been established, further management can proceed, as outlined in Figure 10-3.

Differential Diagnosis

Pulmonary nodules are divided primarily into malignant or benign etiologies, with benign processes further divided into infectious or noninfectious causes (Table 10-10).

Diagnostic Testing

Laboratories

- Routine laboratory testing is seldom helpful unless the history and physical exam strongly suggest an etiology.
- If connective tissue diseases or vasculitides are suspected, perform appropriate testing.
- Hyponatremia may suggest syndrome of inappropriate antidiuretic hormone (SIADH) associated with primary lung cancer, as well as other pulmonary processes.

- Hypercalcemia might suggest lung cancer as well as sarcoidosis.
- Anemia may indicate chronic pulmonary hemorrhage (e.g., HHT) or a chronic inflammatory disease.
- Microbiologic studies, particularly sputum culture, may aid in the diagnosis of an infectious SPN.
- Sputum cytology has limited use, because yield is low for peripherally located, small lesions.

TABLE 10-9 Risk Stratification of a Solitary Pulmonary Nodule

Variable	Low Risk	Intermediate Risk	High Risk
Lesion diameter (cm)	<1.5	1.5-2.2	>2.2
Patient age (years)	<45	45-60	>60
Smoking status	Never smoked or quit >7 yr ago	Current smoker of <20 cigarettes/d or quit <7 yr ago	Current smoker of >20 cigarettes/d
Lesion margin characteristics	Smooth and rounded	Scalloped	Spiculated or corona radiata
Densitometry in Hounsfield units (HU)	<15 HU	>15 HU	>15 HU

http://internalmedicinebook.com

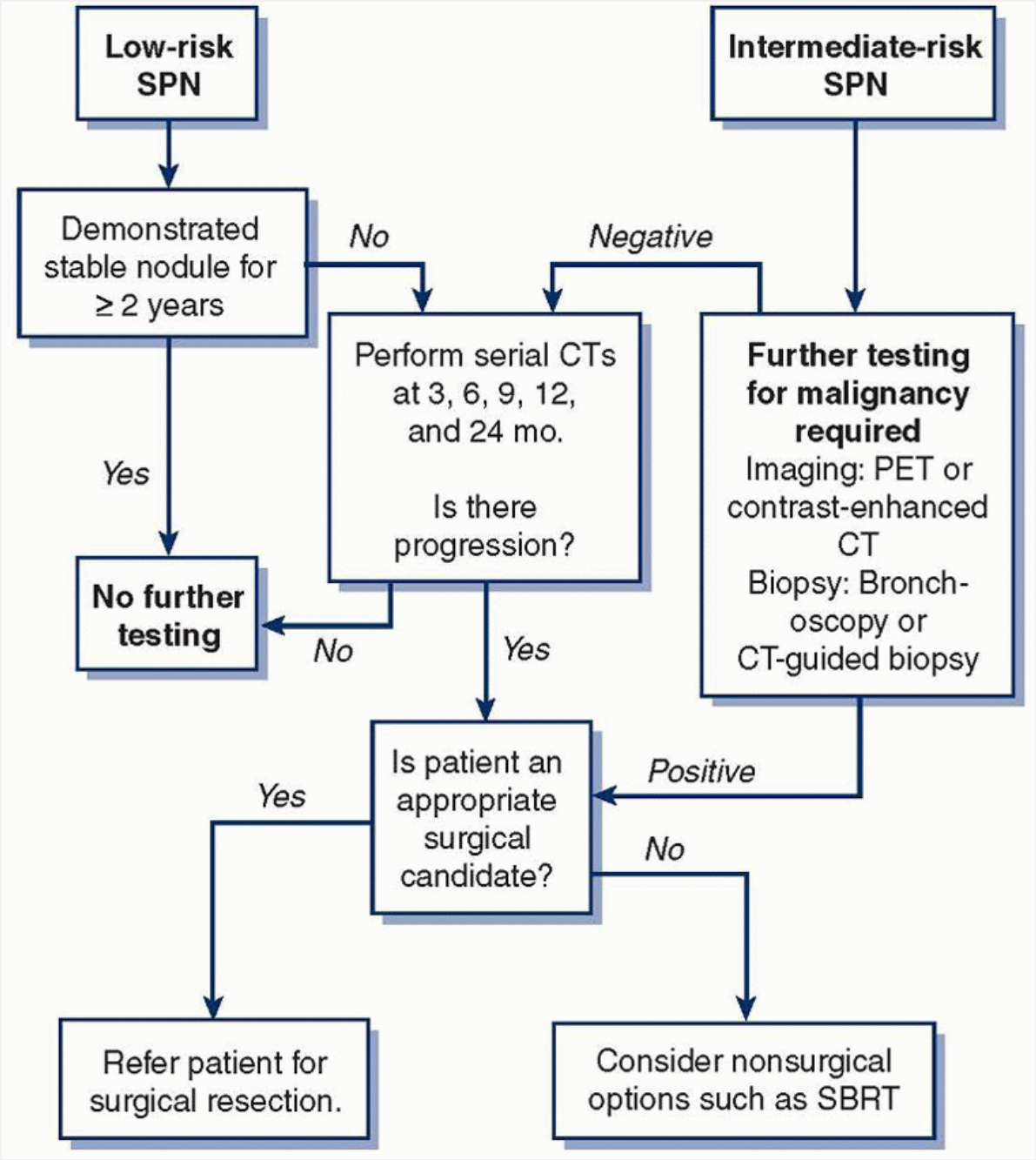


Figure 10-3. Diagnostic and therapeutic management of low- and intermediaterisk pulmonary nodules. PET, positron emission tomography; SBRT, stereotactic body radiation therapy; SPN, solitary pulmonary nodule.

Imaging

The mainstay of diagnostic evaluation of an SPN is via radiographic studies, primarily **CXR, chest CT, and positron emission tomography (PET) scan**.

- **CXR**
  - A previous CXR is an important tool in the initial evaluation of an SPN.
  - If an SPN has been present and unchanged on CXR for >2 years, then further evaluation may not be warranted. Ground-glass lesions may be followed for longer periods of time because the volume-doubling time may be extended in certain types of non-smallcell lung cancers.
  - If an SPN appears on a new radiograph in <30 days, it is likely not malignant and most likely infectious or inflammatory.
  - There are radiographic findings that make it more likely that a lesion is **benign (calcifications, a laminated appearance)**; or more likely **malignant (spiculated, irregular border)** (see Table 10-9).

- The CXR is easy to obtain and delivers a low dose of radiation; however, it has limitations in the initial characterization, and careful comparisons over time are required for SPN evaluation.

TABLE 10-10 Differential Diagnosis of the Solitary Pulmonary Nodule (SPN)

Malignant (40% of SPNs)	◦ Primary pulmonary carcinoma (80% of all malignant SPNs) ◦ Primary pulmonary lymphoma ◦ Primary pulmonary carcinoid ◦ Solitary pulmonary metastasis ◦ Melanoma, osteosarcoma, testicular, breast, prostate, colon, and renal cell carcinoma
Benign neoplasms (5% of SPNs)	◦ Hamartoma (accounts for most benign neoplastic SPNs) ◦ Arteriovenous malformations (consider HHT) ◦ Others, including neural tumors (schwannoma, neurofibroma), fibroma, and sclerosing hemangioma
Granulomas (50% of SPNs)	Infectious ◦ Mycobacterial disease (most commonly tuberculosis) and fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, aspergillosis) Noninfectious granulomas associated with vasculitis ◦ Granulomatosis with polyangiitis (Wegener granulomatosis), Churg-Strauss syndrome ◦ Noninfectious granulomas not associated with vasculitis ◦ Sarcoid granulomatosis, hypersensitivity pneumonitis, and berylliosis
Other etiologies (5% of SPNs)	Infectious ◦ Bacterial (nocardiosis, actinomycosis, round pneumonia), measles, abscess, septic embolus Noninfectious ◦ Lipoid pneumonia, amyloidosis, subpleural lymph node, rheumatoid nodule, pulmonary scar or infarct, congenital malformations (bronchogenic cyst, sequestration), skin nodule, rib fracture, pleural thickening from mass or fluid

HHT, hereditary hemorrhagic telangiectasia.

- **Chest CT**
  - Chest CT is now considered the most important radiologic exam for SPN evaluation. With few exceptions, an SPN requires assessment by CT.
  - Accurate volumetric measurement of lesion size allows precise comparison to determine stability or growth.
  - Imaging allows a careful examination of mediastinal lymph nodes.
  - Thin cuts through the lesion are more sensitive than CXR for characterizing calcifications and lamination

as well as the margins of the lesion.

- **PET scan**
  - 18-Fluorodeoxyglucose (FDG)-PET can help distinguish malignant and benign lesions because cancers are metabolically active and take up FDG avidly.
  - PET has a sensitivity of 80-100% and specificity of 79-100% for detecting malignancy.
  - **False negatives** can occur in bronchoalveolar carcinoma, carcinoid, and mucinous neoplasms, whereas **false positives** are common in nonmalignant "inflammatory" conditions (infectious and autoimmune processes).

  - Higher incidence of both false-positive and false-negative results occurs in nodules <10 mm, thus discouraging the use of PET scan in this situation (*Lung Cancer 2004;45:19*).
  - PET scan is most commonly used in the evaluation of low- to moderate-risk indeterminate nodules for further risk stratification (see Figure 10-3).
- **Contrast-enhanced CT**
  - Technique using contrast enhancement and measurement of Hounsfield units to risk stratify an SPN for malignancy.
  - A multicenter analysis demonstrated high sensitivity but relatively low specificity for identifying malignant nodules (*Radiology 2000;214:73*).
  - This method may be an important tool for risk assessment of an indeterminate SPN in centers that have experience with the technique.

Diagnostic Procedures

- **If a nodule is considered high risk and the patient is an appropriate surgical candidate, then the best approach is to forego biopsy and pursue resection.**
- Any change of an SPN on serial imaging warrants resection or invasive biopsy.
- If a lesion has low-risk characteristics, there is no indication to pursue biopsy and subjecting a patient to unneeded risk.
- **Biopsy** is most often pursued when there is discordance between clinical risk stratification and imaging tests. For example, when pretest suspicion for malignancy is significant but PET imaging is negative, biopsy may be indicated.
- Also, for patients in whom surgery represents significant risk secondary to comorbidities, using a less invasive biopsy strategy to determine the presence of malignancy is appropriate.
- There are primarily two options for biopsy of an SPN: transthoracic needle aspiration (TTNA) and fiber-optic flexible bronchoscopy.
  - **TTNA**
    - This technique is usually performed under the guidance of fluoroscopy, ultrasound, or CT (more common).
    - This approach is most commonly used for nodules with a peripheral location and without anatomic impediment to a biopsy needle.
    - Sensitivity of TTNA for the diagnosis of lung cancer is 80-90% in selected patients.
    - Specificity for identifying malignancy is high with TTNA; however, there is a significant rate of nondiagnostic biopsies, and sensitivity depends on many factors, including nodule size and distance from the pleura.

- A nondiagnostic biopsy does not rule out malignancy.
- The main complication of TTNA is pneumothorax with 25% incidence of minor pneumothorax and 5% incidence of major pneumothorax requiring chest tube drainage.

- **Bronchoscopy**
  - Conventional flexible bronchoscopy is best suited for central airway lesions and has a sensitivity of 88% in malignancy. Advanced bronchoscopic techniques are recommended in the diagnosis of peripheral lesions where their diagnostic yield is superior to that of conventional bronchoscopy.
  - Advanced bronchoscopic modalities include radial probe endobronchial ultrasound and electromagnetic navigation, with sensitivities of 73% and 71%, respectively, for the detection of malignancy in peripheral nodules.
  - These techniques are currently recommended as potential alternatives to CT-guided TTNA by the American College of Chest Physicians for the diagnosis of pulmonary nodules.

TREATMENT

- Management of low- and intermediate-risk SPNs is outlined in Figure 10-3.
- Overall treatment strategy is to identify lesions with significant malignancy risk and pursue surgical resection when possible.

- If a nodule has low-risk characteristics and has demonstrated stability over a period of 2 years, then no further treatment is warranted. Further follow-up of subsolid and purely groundglass lesions may be necessary, because their volume-doubling times may be prolonged.
- If a specific etiology for the SPN is diagnosed (e.g., a connective tissue disease or infection), then treatment is targeted toward the underlying process.

Other Nonpharmacologic Therapies

- Although **surgical resection is preferable in patients with either a high-risk lesion or biopsy-proven malignancy**, if surgical resection is not an option, there are other less effective therapies.
- **Stereotactic radiation** is currently the most widely used therapy in this clinical situation. This mode of external-beam therapy aims to decrease collateral radiation-induced damage to adjacent lung tissue.
- There are more experimental approaches, including brachytherapy and radiofrequency ablation, that are currently under development.

Surgical Management

- Surgical resection of an indeterminate SPN is indicated in the following situations:
  - The clinical probability of malignancy is moderate to high (>60%).
  - The nodule is hypermetabolic by PET imaging.
  - The nodule has been proven malignant by biopsy.
- A combination of surgical techniques, including VATS, mediastinoscopy, and thoracotomy, can lead to diagnosis (via intraoperative frozen section), staging, and potential cure during a single induction of anesthesia.

MONITORING/FOLLOW-UP

- For a low- or intermediate-risk pulmonary nodule for which resection is not warranted (see Figure 10-3), desired, or possible, routine follow-up with chest CT is standard practice.
- The typical practice for following an SPN is with serial chest CT performed at intervals of **3, 6, 12, 18, and 24 months** from initial detection, assessing for any evidence of growth.

Pleural Effusion

GENERAL PRINCIPLES

Definition

The accumulation of fluid in the pleural space.

Classification

Diagnosis and management are based on classifying a pleural effusion as either a **transudate or exudate**.

Etiology (*Thorax 2010;65(Suppl 2):ii4-ii17*)

- **Causes of transudative pleural effusions**
  - Common causes
    - LV failure
    - Liver cirrhosis
  - Less common causes
    - Hypoalbuminemia
    - Peritoneal dialysis
    - Hypothyroidism

    - Nephrotic syndrome
    - Mitral stenosis
  - Rare causes
    - Constrictive pericarditis
    - Urinothorax
    - Meigs syndrome
- **Causes of exudative pleural effusions**
  - Common causes
    - Malignancy
    - Parapneumonic effusions
    - TB
  - Less common causes

http://internalmedicinebook.com

- Pulmonary embolism
- Rheumatoid arthritis and other autoimmune pleuritis
- Benign asbestos effusion
- Pancreatitis
- Post-myocardial infarction
- Post-coronary artery bypass graft

- Rare causes
  - Yellow nail syndrome (and other lymphatic disorders [e.g., lymphangioleiomyomatosis])
  - Drugs
  - Fungal infections

Pathophysiology

- **Normal pleural physiology**
  - Each pleural space produces and reabsorbs up to 15 mL of fluid per day and **contains about 10 mL of fluid at any one time** not apparent on imaging.
  - **Normal pleural fluid chemistries:** lactate dehydrogenase (LDH) <0.6 of serum, protein <0.5 of serum, glucose 0.6-0.8 of serum, pH 7.60.
- **Transudative effusion: alteration of hydrostatic and/or oncotic factors** that increase the formation and/or decrease reabsorption of pleural fluid.
  - CHF: increased venous pressures and lung edema
  - Hepatic cirrhosis and nephrotic syndrome: hypoalbuminemia
  - Malignancy: infiltration/obstruction of pleural capillaries and/or lymphatics (up to 10% of malignant effusions are transudative)
- **Exudative effusion:** either direct or cytokine-induced disruption of normal pleural membranes and/or vasculature leading to **increased capillary permeability**.
  - Infection/pneumonia
  - Malignancy
  - Inflammatory disease (i.e., systemic lupus erythematosus [SLE] or rheumatoid arthritis)
  - Trauma/surgery
  - Pulmonary embolus
- **Fluid markers of pleural infection, inflammation, and/or obstruction** often coexist.
  - **Low glucose and pH levels**
    - Byproducts of microorganism and/or inflammatory cell metabolism
    - Decreased acid removal due to pleural disruption from inflammation or malignancy
  - **High LDH level**

    Cell turnover and lysis

DIAGNOSIS

The clinical setting, combined with pleural fluid analysis, is crucial to establishing a proper diagnosis.

Clinical Presentation

Symptoms and signs may be directly related to the pleural effusion itself and/or to any underlying disease process.

History

- **Dyspnea** due to abnormal pulmonary mechanics: most common symptom, usually develops with >500-1000 mL of pleural fluid but may not correlate
- **Often asymptomatic**
- Pleurisy or referred chest/back/shoulder pain from pleural inflammation
- Should include survey of potential underlying causes

Physical Examination

- Vital signs: Assess for fever, hemodynamic instability, and hypoxemia.
- Chest exam: **Dullness to percussion, decreased breath sounds, and tactile fremitus.** These signs are more sensitive with larger effusions, but the chest exam is often unreliable and should not be used solely to diagnose and approximate size (*Cleve Clin J Med 2008;75:297*).
- A thorough system-based exam should evaluate for CHF, malignancy, pneumonia, hepatic cirrhosis, venous thrombosis, and other potential causes of pleural effusion.

Diagnostic Criteria

- **Analysis of pleural fluid obtained by thoracentesis** is the mainstay of diagnosing an etiology.
- **Transudate: Presence of *all* of Light's criteria** (*Ann Intern Med 1972;77:507*).
  - Fluid:serum protein ratio <0.5
  - Fluid:serum LDH ratio <0.6
  - Pleural fluid LDH <0.67 of upper limit of normal for serum LDH
- **Exudate: Presence of *any* of Light's criteria** (*Ann Intern Med 1972;77:507*).
  - Fluid:serum protein ratio >0.5
  - Fluid:serum LDH ratio >0.6
  - Pleural fluid LDH >0.67 of upper limit of normal for serum LDH
- **Pseudo-exudate:** An effusion that meets one or more of Light's criteria but is actually a transudate.
  - **Usually due to diuretic-treated CHF**, cirrhosis, or nephrotic kidney disease.
  - **Serum-to-pleural fluid albumin gradient >1.2.**
- **Simple parapneumonic effusion:** A sterile, small (encompassing less than one-half the hemithorax), free-flowing pleural effusion in the setting of pneumonia, with pH >7.20 and glucose >60 mg/dL.
- **Complicated parapneumonic effusion: *Any* one of the following** (*Chest 2000;118:1158*):
  - Large (encompassing more than one-half of the hemithorax), free flowing
  - Effusion of any size with loculations
  - Thickened parietal pleura on chest CT
  - Positive Gram stain or culture

- pH <7.20 or glucose <60 mg/dL

- **Empyema: Gross pus in the pleural space or positive Gram stain.** Positive culture is *not* required for diagnosis (high false-negative rate).

Differential Diagnosis

See Table 10-11.

Diagnostic Testing

- Pleural effusion is detected by chest imaging and characterized through sampling by thoracentesis.
- **All parapneumonic effusions and new, undiagnosed effusions should be sampled.**

TABLE 10-11 Clues to Diagnosing the Cause of a Pleural Effusion Based on Fluid Analysis

Gross appearance

- Clear/serous/light yellow: Transudate of any etiology (cardiac, liver, kidney disease), urinothorax (consider if smells like ammonia)
- Bloody/serosanguineous: Hemothorax (surgery/trauma), PE, malignancy
- Purulent/turbid/brown: Infectious/empyema; esophageal rupture
- Putrid odor: Anaerobic empyema
- Milky: Chylothorax/pseudochylothorax

Nucleated cells

- Total >50,000, neutrophilia: Infectious/empyema
- Total <5000: Transudate of any etiology, chronic malignant, tuberculous
- Lymphocytosis (>85%): Tuberculous, lymphoma, chronic rheumatoid, sarcoidosis, pseudo-exudates
- Eosinophilia (>10%): Pneumothorax, hemothorax, fungal, parasitic, medications, malignancy, benign asbestos effusion
- Mesothelial cells (>5%): Normal, transudate

Chemical analysis

- Elevated protein:
  - >3 g/dL: Most exudates; pseudo-exudates (serum-fluid albumin gradient >1.2 g/dL)
  - >4 g/dL: Tuberculous
  - >7-8 g/dL: Blood cell dyscrasias
- Elevated LDH:
  - >1000 IU/L: Empyema, rheumatoid, paragonimiasis, high burden malignant
  - Fluid:serum ratio >1: Pneumocystis or urinothorax
- Glucose <60 mg/dL: Infectious/empyema, rheumatoid, lupus, tuberculous, esophageal rupture, malignant
- pH <7.3: Infectious/empyema, rheumatoid, lupus, tuberculous, esophageal rupture, high burden malignant
- Elevated amylase (> serum): Pancreatitis, esophageal rupture, malignant
- Adenosine deaminase >50 units/L: Tuberculous (unlikely if level <40)
- Triglycerides >110 mg/dL: Chylothorax

LDH, lactate dehydrogenase; PE, pulmonary embolism.

Laboratories

- **Pleural fluid** (see Table 10-11):
  - Note color and consistency
  - Chemistries: Protein, albumin, LDH, glucose, pH
  - Cell count with differential
  - Hematocrit if suspicion for hemothorax (>0.5 of serum is diagnostic)
  - Microbiologic stains and culture per suspicion
  - Cytology (yield approximately 60%)
  - Consider triglyceride, amylase, adenosine deaminase as indicated
- Serum: CBC, comprehensive metabolic panel, LDH, urinalysis, coagulation studies, BNP
- Additional labs guided by suggestion of underlying illness

Electrocardiography

Assess for structural heart disease. Otherwise usually nonspecific and noncontributory.

Imaging

- Standard upright **posteroanterior/lateral CXR**:
  - Diagnostic for a suspected pleural effusion and approximates size (*Radiology: Diagnosis, Imaging, Intervention. Philadelphia: Lippincott, 2000:1*)
    - 75 mL obscures the posterior costophrenic sulcus.
    - 175 mL obscures the lateral costophrenic sulcus.
    - 500 mL obscures the entire diaphragmatic contour.
    - 1000 mL reaches the level of the anterior fourth rib.
  - Helps suggest associated conditions (CHF, pneumonia)
- **Lateral decubitus radiograph**
  - **Demonstrates fluidity**
  - Usually amenable for thoracentesis if fluid layers to >1 cm
- **Thoracic ultrasonography**
  - Accurate and practical in **detecting loculations**
  - Provides **real-time guidance for thoracentesis or thoracostomy tube placement**, reducing complication rates
- **Chest CT with contrast**
  - Helpful in distinguishing fluid from lung mass, atelectasis, pneumonia, or suggesting hemothorax
  - Defines and characterizes pleural loculations, thickening, nodularity, or other abnormalities

Diagnostic Procedures

- **Thoracentesis:** Can be performed safely at the bedside on effusions layering >1 cm on lateral decubitus CXR

- **Complicated/organized effusions should be accessed using real-time ultrasound or CT guidance.**
- **Optimize hemostasis:** prothrombin time/partial thromboplastin time <2× normal, platelets >25 × 10^3/microliter, creatinine <6.0 mg/dL (*Transfusion 1991;31:164*).
- **Microbiologic studies** of a parapneumonic effusion may be falsely negative after antibiotic administration.
- **Cytology is positive for malignancy in up to 60% of cases**, and the sensitivity for diagnosis of pleural malignancy is dependent on the pleural fluid volume extracted during thoracentesis (*Chest 2010;137(1):68-73*). However, previous studies have shown that sending volumes >50 mL did not improve the diagnostic yield (*Chest 2009;135(4):999-1001*).
- The yield from sending more than two specimens (taken on different occasions) is very low and should be avoided.
- **Acid-fast bacteria (AFB) stain and culture sensitivity <30%** (*Chest 2007;131:880*).

- **Closed pleural biopsy:** Performed by transthoracic needle approach
  - **Indicated for the undiagnosed, suspected tuberculous or rheumatoid effusion. Sensitivity >80% when combined with pleural fluid AFB stain and culture** because tuberculous pleuritis is usually diffuse (*Chest 1997;112:702*).
  - This procedure is no longer commonly performed due to increasing evidence that "blind" pleural biopsy is less sensitive in the diagnosis of malignant pleural disease than CT-guided pleural biopsy or local anesthetic thoracoscopy (*Thorax 2010;65:ii54-ii60*).
- **Thoracoscopic pleural biopsy:** Performed under direct pleural visualization. **Semirigid thoracoscopy** is an efficacious and safe procedure in diagnosis of exudative pleural effusions. It has a diagnostic sensitivity and specificity of 91% and 100%, respectively, and is associated with negligible complications (*Chest 2013; 144(6):1857-67*).

TREATMENT

- **Transudates: Usually resolve with treatment of the underlying cause** (heart failure, hepatic disease, nephrotic syndrome)
  - Therapeutic thoracentesis as indicated for persistent larger effusions.
  - Uncommonly, more aggressive measures including pleurodesis, shunts, or placement of a chronic indwelling pleural catheter are indicated for comfort or palliation.
- **Simple/uncomplicated parapneumonic effusion:** Antibiotics and close observation
- **Complicated parapneumonic effusion and empyema** (Figure 10-4): Antibiotics and **early thoracostomy tube drainage** to avoid inflammatory adhesion and organization (*Chest 2000;118:1158*)
  - **Antibiotics should also target anaerobic organisms** because they often complicate empyema (*Lancet 1974;1:338*; *Chest 1993;103:1502*).
  - **Intrapleural tissue plasminogen activator (tPA)-DNase therapy** improves fluid drainage for loculated effusions in patients with pleural infection and reduces the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or tPA alone was shown to be ineffective (*N Engl J Med 2011;365:518-26*).

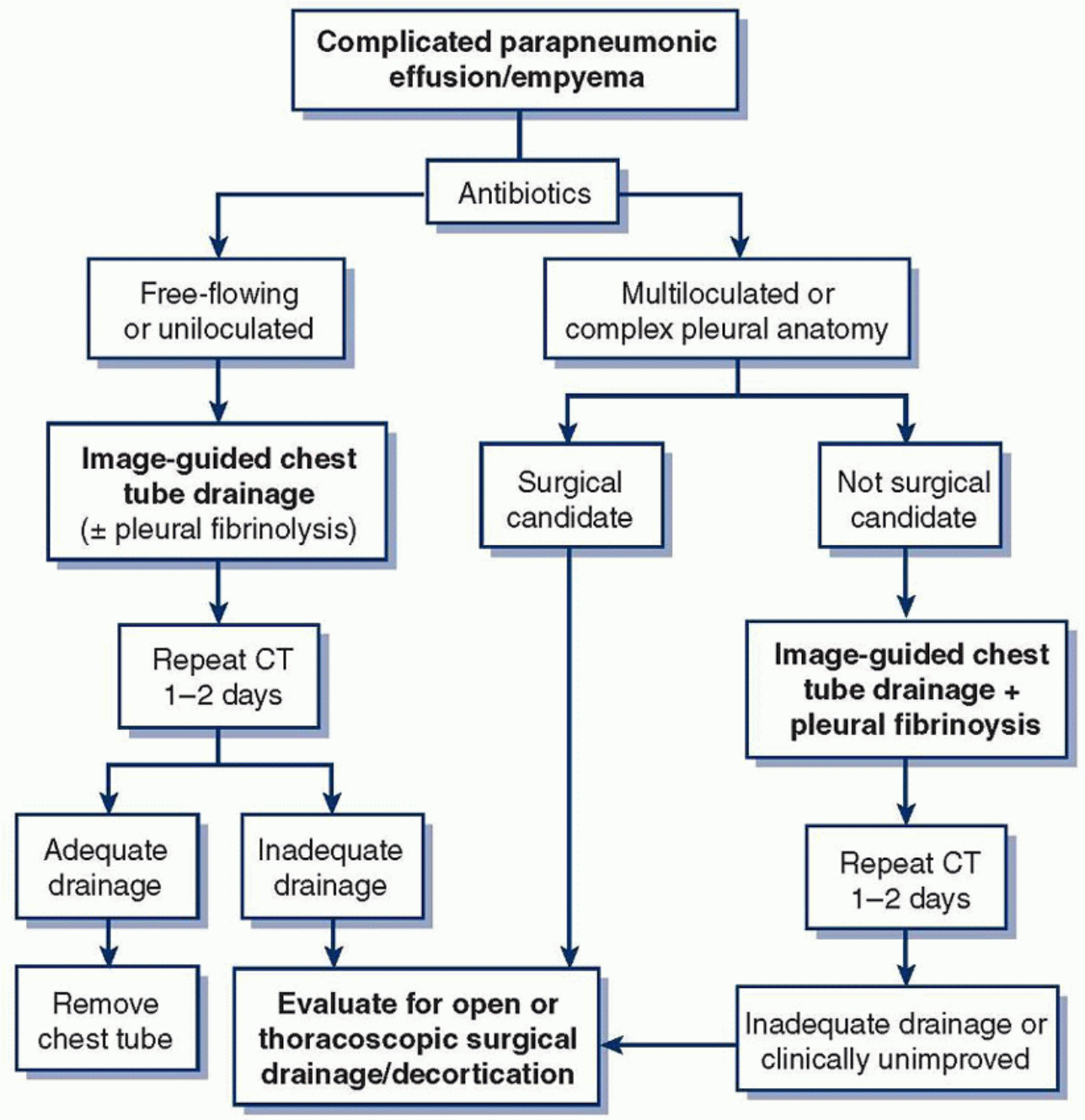


Figure 10-4. Suggested general approach to managing complicated parapneumonic effusions and empyema.

- Chest tube can be removed when adequate drainage is accomplished (<50-100 mL output per day *and* resolution documented on follow-up imaging).
- **Surgical decortication (thoracoscopic vs. open) may be required for effusions exhibiting complex anatomy** (extensive pleural thickening, fibrous organization, and/or multiple loculations) when unresponsive to chest tube drainage and/or intrapleural tPA-DNase therapy.

- **Malignant pleural effusion** (Figure 10-5): recurs in approximately 95% of cases, usually within a week
  - Observation is appropriate in cases of small, asymptomatic, stable effusions.
  - **Therapeutic (large-volume) thoracentesis** (LVT) for comfort.
    - Repeat thoracentesis is reasonable if effusion reaccumulates slowly.
    - **Reexpansion pulmonary edema is very rare** and is unlikely related to rate or volume of fluid removed (*Ann Thorac Surg 2007;84:1656*).

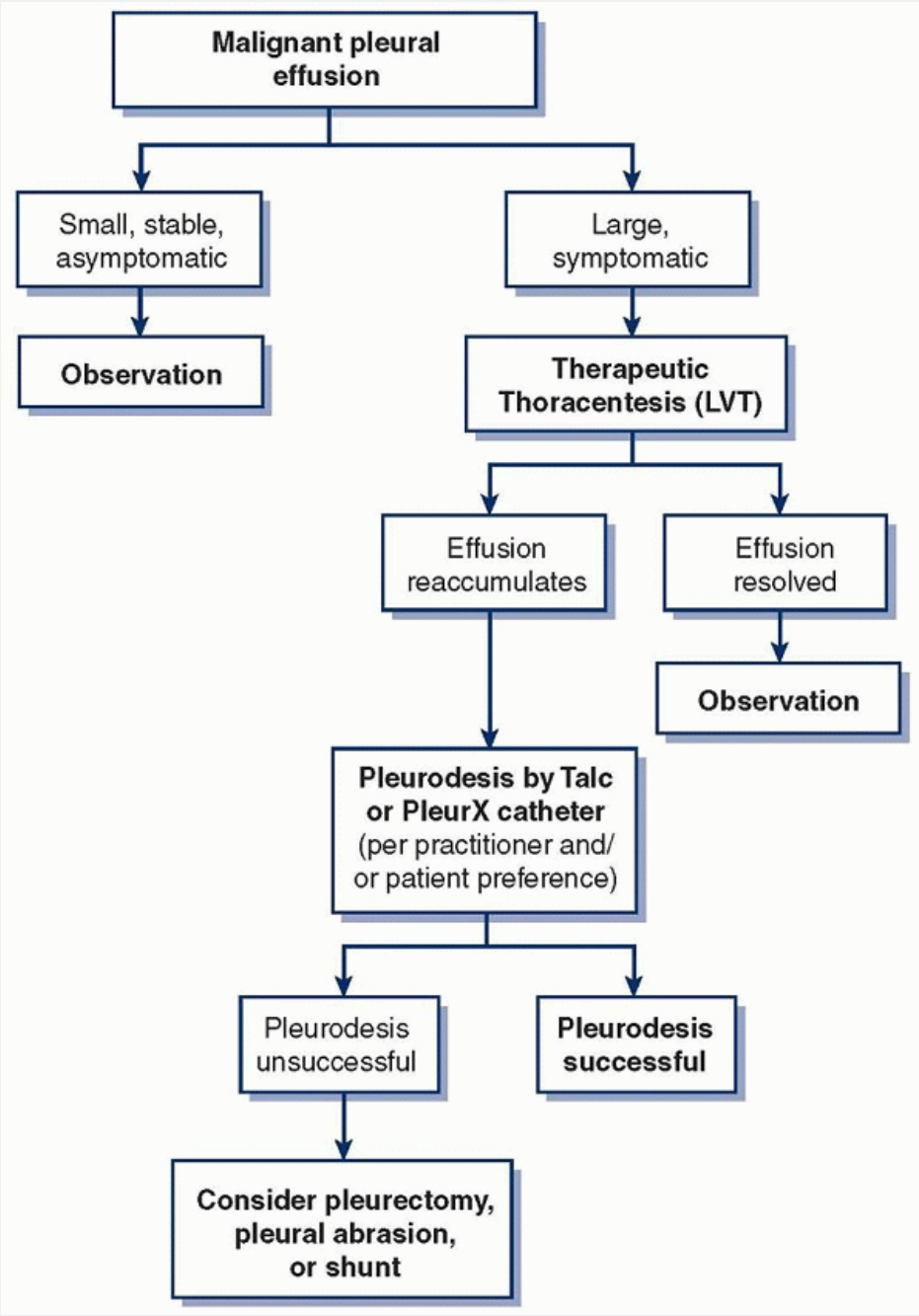


Figure 10-5. Suggested general approach to managing malignant pleural effusions. LVT, large-volume thoracentesis.

- **Removal of at least 1.5 L at a time is safe.** However, **LVT should be discontinued with development of chest discomfort**, which may be a surrogate marker for unsafe drop in pleural pressures (*Chest 2006;129:1556*).
- The correct treatment depends on several factors such as performance status, expected survival, presence of lung reexpansion following pleural drainage, and comorbidities. Among patients with malignant pleural effusion and no previous pleurodesis, there is no significant difference between indwelling pleural catheters and talc pleurodesis at relieving patient-reported dyspnea (*JAMA 2012;307(22):2383-89*).

- **Chemical pleurodesis:** instillation of a pleural sclerosing agent such as talc or doxycycline (*Ann Intern Med 1994;120:56*).
  - Recommended when there is **rapid reaccumulation of fluid**.
  - **Talc**, instilled either as **"slurry"** through a thoracostomy tube or through insufflation during

thoracoscopy (**"poudrage"**), is very effective and more comfortable than doxycycline (*Chest 2005;127:909*).
    - Less effective if lung reexpansion is incomplete after drainage ("trapped lung").
    - Often requires hospitalization for approximately 3-5 days.
  - **Chronic indwelling pleural catheter:** Practically, can be performed in the outpatient setting and maintained easily by the patient and caregiver.
    - A long-term indwelling pleural catheter could be a valid alternative to talc pleurodesis in selected patients with trapped lung syndrome (a lung that fails to reexpand after drainage of pleural effusion) and short life expectancy (*Am J Clin Oncol 2010;33:420*).
    - Spontaneous pleurodesis has been reported in 30-50% of patients with indwelling pleural catheters with repeated drainage, allowing for removal.
    - More successful at palliation than doxycycline pleurodesis (*Cancer 1999;86:1992*).
  - Pleurectomy, pleuroperitoneal shunt, chemotherapy/radiation therapy.

Surgical Management

- **Thoracic decortication:** in cases of complicated parapneumonic effusions that have complex pleural anatomy due to fibrous organization and/or are not amenable or responsive to pleural drainage
- **Pleurectomy or pleural abrasion:** for recurring malignant pleural effusion unresponsive to pleurodesis or chronic catheter drainage

REFERRAL

- Pulmonary (interventional, if available)
- Thoracic surgery as needed

OUTCOME/PROGNOSIS

Depends on etiology of the effusion and the extent of pleural disruption.

- **Transudate:** Depends on management and prognosis of the underlying cause but **generally a good outcome**.
- **Simple parapneumonic effusion: Low morbidity and mortality** if treated appropriately with antibiotics and close observation.
- **Complicated parapneumonic effusion and empyema: With delayed treatment, there is a significantly elevated risk for pleuropulmonary sequelae**, including need for intensive surgical decortication and possibly death.
- **Malignant pleural effusions** all indicate advanced malignant spread. The therapeutic options offered for these patients are usually successful in achieving desired palliation and add very little, if any, morbidity or mortality risk.

Hemoptysis

GENERAL PRINCIPLES

Hemoptysis should be considered a sign of an underlying pathologic process. It can be life threatening and, as such, requires rapid identification, workup, and treatment.

Definition

- **True hemoptysis** is expectoration of blood from the lower respiratory tree, below the glottis.
- **Massive hemoptysis/life-threatening hemoptysis:**
  - By volume: defined in the literature as from >100 mL in 16 hours to >1000 mL in 24 hours.
  - Most commonly defined as **>600 mL of blood expectorated per 24 hours** (*Arch Intern Med 1968;121:495*; *Ann Thorac Surg 1974;18:52*; *Ann Thorac Surg 1978;25:12*; *Am J Med Sci 1987;294,301*; *Flexible Bronchoscopy. 2nd ed. Hoboken: Wiley-Blackwell, 2004*).
  - Clinically: >100 mL in 24 hours is associated with gas exchange abnormality, airway obstruction, or hemodynamic instability.

Classification

The most clinically useful classification of hemoptysis is **massive/life threatening or not**, followed by the **anatomic location** of the bleeding.

- Massive/life threatening: >600 mL/24 h *or* >100 mL/24 h with gas exchange abnormality, airway obstruction, or hemodynamic instability.
- Anatomic location
  - Airway
  - Parenchyma
  - Vascular
  - Combination
- There are various other classifications in the literature based on characteristics (appearance, frequency, rate, volume, and potential for clinical consequences) that often suggest an underlying etiology and may predict outcome and thus help guide diagnostics and management. However, there is considerable overlap in clinical presentation within and among etiologies.

Epidemiology

The incidence of hemoptysis is dependent on the underlying diagnosis. Listed are the incidences of some of the most common causes of hemoptysis (*Arch Intern Med 1969;149:1667*; *Arch Intern Med 1991;151:2449; Chest 1997;112:2*).

- Bronchiectasis: 1-37%
- Bronchitis: 2-37%
- Malignancy: 2-24%
- TB/cavitary lung disease: 2-69% (incidence is much lower in the modern, Western world)
- Pneumonia: 1-16%
- Idiopathic: 2-22%

Etiology

It is generally most clinically useful to identify etiology according to anatomic location, because the more proximal the etiology, the more likely it is to require urgent intervention.

- Airway: **bronchitis/bronchiectasis**, **malignancy**, foreign body, trauma, pulmonary endometriosis, broncholithiasis

- Parenchyma/alveoli: **pneumonia, rheumatologic vasculitides, and pulmonary hemorrhage syndromes** (ANCA-positive vasculitis, Goodpasture syndrome, SLE, diffuse alveolar hemorrhage, acute respiratory distress syndrome)
- Vascular: **elevated pulmonary venous pressure** (LV failure, mitral stenosis), pulmonary embolism, arteriovenous malformation (AVM), pulmonary arterial trauma (i.e., pulmonary

arterial catheter balloon overinflation), varices/aneurysms, rheumatologic vasculitides, and pulmonary hemorrhage syndromes
- Etiologies potentially involving multiple anatomic locations: **cavitary lung disease** (TB, aspergilloma, lung abscess), thrombocytopenia, disseminated intravascular coagulation, anticoagulants, antiplatelets, cocaine, inhalants, lung biopsy, bronchovascular fistula, bronchopulmonary sequestration, Dieulafoy disease
- **Idiopathic/undiagnosed up to 25%:** prognosis usually favorable (*Ann Intern Med 1985;102:829*)

Pathophysiology

The pathogenesis of hemoptysis depends on the etiology and location of the underlying pathologic process.

- Hemoptysis due to bronchitis or bronchiectasis results from **inflammation/irritation of airway mucosa and its associated hyperplastic or otherwise abnormal vascular supply**.
- **The bronchial arterial circulation** (branching from the aorta) supplies high-pressure blood to the airways and, when disrupted (by a foreign body, tumor invasion, fungal invasion, or denuded airway mucosa), can result in massive, life-threatening hemoptysis.
- **The pulmonary arterial circulation** supplies the lung parenchyma (participates in gas exchange) and is under low pressure, but receives all of the cardiac output. Disruption can result in minor hemoptysis (via infections) or more life-threatening hemoptysis due to processes such as vasculitis, diffuse alveolar hemorrhage, pulmonary embolism, acute respiratory distress syndrome, AVM rupture, pulmonary artery catheter trauma, severe mitral stenosis, LV failure, or Rasmussen aneurysm (pulmonary artery aneurysm associated with TB).

DIAGNOSIS

Identifying and correcting the underlying disease is the basis of diagnosis and management of hemoptysis (Figure 10-6).

Clinical Presentation

Hemoptysis may be the only presenting sign or may accompany other manifestations of an underlying disorder (Table 10-12). The appearance, timing, and volume can provide important clues to narrowing the differential diagnosis.

- Appearance: grossly bloody, blood-tinged sputum, streaky, foamy
- Timing: first episode, recurrent episodes, chronic small amounts, acute large amounts
- Volume: submassive, massive

History

- Most important: amount of hemoptysis, age, smoking history, prior lung disease, previous malignancy, risk for coagulopathy, and prior episodes of hemoptysis.
- Review of systems should focus on symptoms suggesting cardiopulmonary disease, active infection, underlying malignancy, and systemic inflammatory disorders.

Physical Examination

- Most important: vital signs including oxygen saturation, general state of health, lung exam noting focal or diffuse abnormal findings such as bronchial breath sounds, crackles, inspiratory and/or expiratory wheezes.
- A thorough exam should always be performed, noting any manifestations suggesting underlying cardiopulmonary, infectious, immunologic, or malignant disease.

Differential Diagnosis

One must distinguish between **true hemoptysis** and **pseudohemoptysis**, which comes from the upper airway (above the glottis) or gastrointestinal tract that is expectorated. See Table 10-12 for most common diagnoses related to hemoptysis.

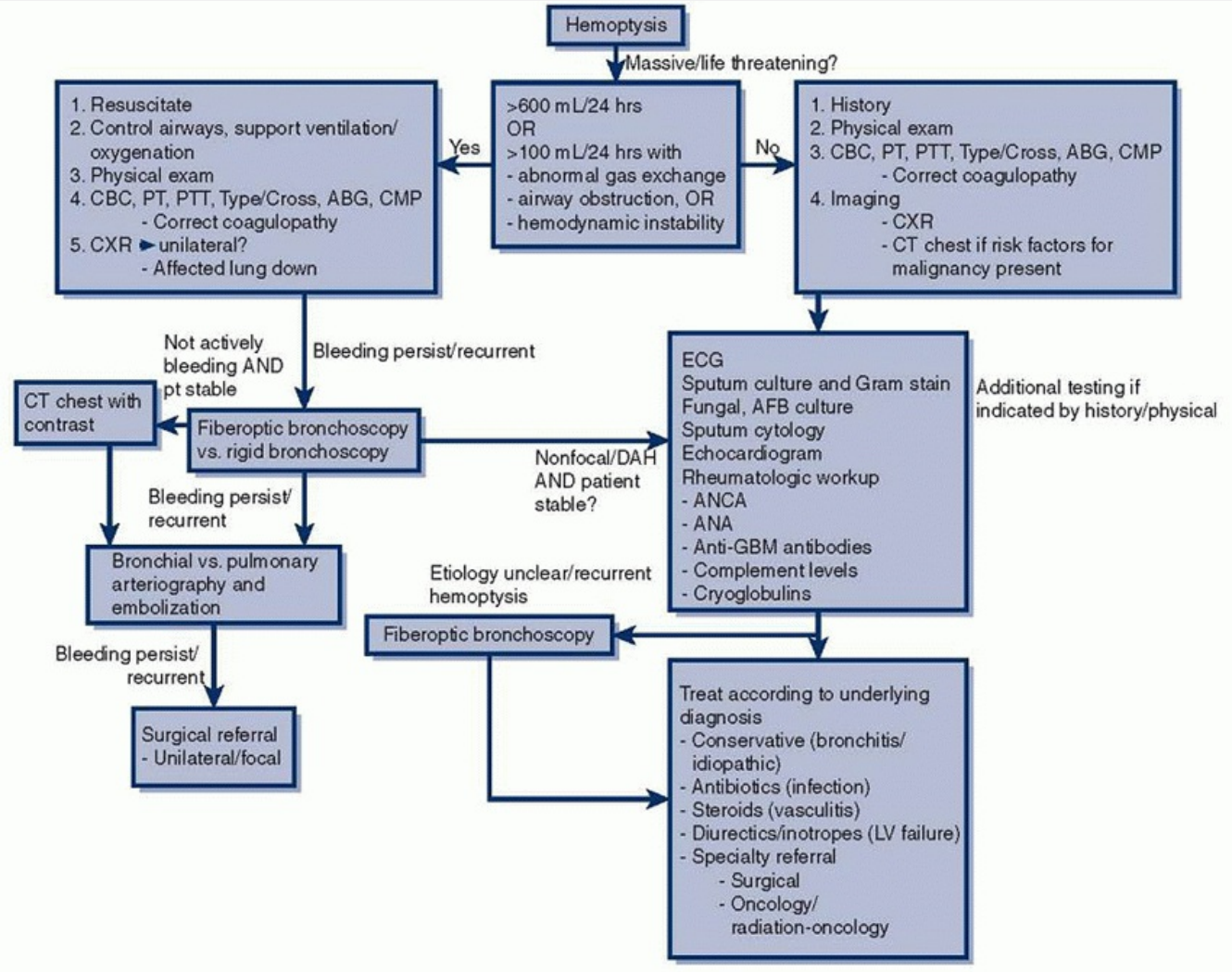


Figure 10-6. Algorithm for evaluation and management of hemoptysis. ABG, arterial blood gas; AFB, acid-fast bacteria; ANA, antinuclear antibody; ANCA, antineu trophil cytoplasmic antibody; CBC, complete blood count; CMP, comprehensive metabolic panel; DAH, diffuse alveolar hemorrhage; GBM, glomerular basement membrane; LV, left ventricle; PT, prothrombin time; PTT, partial thromboplastin time.

Diagnostic Testing

- A thorough **history and physical exam** is important to provide clues and guidance in additional testing.
- Additional testing is aimed at determining clinical stability, localizing the source, and identifying the underlying etiology.

Laboratories and Electrocardiography

- ECG to assess for underlying structural cardiac disease
- CBC, comprehensive metabolic panel, coagulation studies, urinalysis with microscopy
- Type and cross-match blood if hemoptysis massive
- ABG if indicated
- Sputum studies: routine Gram stain and culture, fungal, AFB, and cytology studies as indicated
- Specialized studies as suggested by clinical suspicion
  - CHF: BNP
  - Immunologic disease: ANA/ANCA screen, anti-glomerular basement membrane antibodies, complement levels, cryoglobulins, etc.

Imaging

- **Posteroanterior/lateral CXR** should be performed in all cases of hemoptysis.
  - **Normal or nonlocalizing in up to 50% of all cases** (*Chest 1988;92:70*; *Clin Radiol 1996;51:391*).
  - **Normal in up to 10% of cases caused by bronchogenic carcinoma** (*Chest 1988;92:70*).

TABLE 10-12 Clues to Diagnosing the Cause of Hemoptysis from the History and Physical Exam

Cause of Hemoptysis	Historical Clue	Physical Exam Finding
Bronchogenic carcinoma	Smoker, age >40 yr; recurrent nonmassive hemoptysis, weight loss	Local chest wheezing
Chronic bronchitis/bronchiectasis	Frequent, copious sputum production; frequent "pneumonias"	Scattered, bilateral, coarse chest crackles, wheezes; clubbing
TB, fungal lung disease, lung abscess	Subacute constitutional symptoms; travel and exposure history	Fever, focal coarse chest crackles, cachexia
Acute pneumonia	Acute fever, productive cough, pleurisy, rusty brown hemoptysis	Fever, focal coarse chest crackles, bronchial breath sounds
Vasculitis, hemorrhage syndrome	Subacute constitutional symptoms, hematuria, rash, arthralgias	Diffuse chest crackles, mucosal ulcers, rash
Heart failure	Orthopnea, lower extremity edema, history of valvular disease	Murmurs, diastolic rumble, S_3, loud S_1 or P_2, lower extremity edema

AVM/hereditary hemorrhagic telangiectasia	Platypnea, epistaxis, family history of similar signs and symptoms	Mucosal telangiectasias, orthodeoxia
Pulmonary embolus	Acute dyspnea, pleurisy	Hypoxemia, pleural rub, unilateral lower extremity edema

AVM, arteriovenous malformation; TB, tuberculosis.

- **Chest CT:** Indication often depends on clinical suspicion but should be performed if the diagnosis remains in doubt after initial clinical evaluation or if bronchoscopy is unrevealing (see Figure 10-6).
  - Advantages:
    - Can visualize parenchyma, vasculature, and airways to varying extent.
    - **Especially useful for bronchiectasis, cavitary lung disease, masses, and vascular malformations** (*Chest 1994;105:1155*).
    - HRCT may visualize tumors with efficacy comparable to bronchoscopy (*Radiology 1993;189:677*).
  - Disadvantages:
    - Less efficacious in recognizing subtle bronchial and mucosal lesions (*Chest 1994; 105:1155*)
    - Nonspecific in cases of parenchymal/alveolar hemorrhage
    - Delay in treatment is high risk in an unstable patient
- **Echocardiography** if suspect structural or valvular cardiac disease.

Diagnostic Procedures

- **Fiber-optic (flexible) bronchoscopy:** generally **localizes/lateralizes bleeding source** in over two-thirds of cases, depending on the setting (*Ann Thorac Surg 1989;48:272*)
  - **Indications**
    - If the source is unclear after initial evaluation and imaging or if hemoptysis persists/recurs
    - To rule out infection
    - If the clinical presentation suggests an airway abnormality
    - To obtain brushings/biopsy if CXR/imaging suggests malignancy or is nonlocalizing with the **presence of at least two risk factors for bronchogenic carcinoma:**

      Male sex

      Age >40 years

      >40 pack-year smoking

      Duration of hemoptysis >1 week

      Volume expectorated >30 mL (*Chest 1985;87:142*; *Chest 1988;92:70*; *Ann Intern Med 1991;151:171*)
    - To identify potential anatomic area for arterial embolization
    - To rule out alveolar hemorrhage
  - Timing: Controversial, although increased yield when performed during or within 48 hours of

bleeding (*Am Rev Respir Dis 1981;124:221*)

- **Bronchial and pulmonary arteriography:** perform in **persistent or recurring massive hemoptysis**
  - Advantage: Can be diagnostic and therapeutic via simultaneous **embolization** of the culprit vessel if localized
  - Disadvantages:
    - **Variable and inexact localization** of bleeding depending on clinical setting (*Ann Thorac Surg 1989;48:272*).
    - Anatomic variability.
    - Bleeding usually insufficient for contrast extravasation.
    - Diffuse lung diseases often have associated diffuse vascular abnormalities, making localization difficult (i.e., bronchiectasis).

TREATMENT

The general approach is primarily aimed at **distinguishing massive/life-threatening hemoptysis from nonmassive hemoptysis**. Three main goals: (1) stabilize, (2) diagnose and localize, and (3) decide on need and type of therapy.

- **Nonmassive hemoptysis:** usually treated conservatively and based on underlying disorder (see Figure 10-6).
  - Reverse coagulopathy
  - Antitussives and mild sedatives
  - Bronchoscopy if recurrent
  - Steroids for rheumatologic conditions
  - Antibiotics for infection (fungal, TB, pneumonia, etc.)
  - Diuretics and/or inotropes for heart disease (LV failure, mitral stenosis)
- **Massive hemoptysis:** requires urgent action, intensive monitoring, and an early multidisciplinary approach including an interventional pulmonologist and/or thoracic surgeon and an interventional radiologist (see Figure 10-6).
  - **Initial stabilization:**
    - **Airway management:** very low threshold for intubation, with a large (>8 French) endotracheal tube (*Chest 2000;118;5*)

      Single-lumen main stem intubation for selective ventilation of unaffected lung.

      Double-lumen endotracheal intubation for selective ventilation of unaffected lung. Should be performed and managed only under appropriately skilled supervision.

    - **Lateral decubitus positioning** (affected lung down) to minimize aspiration into unaffected lung
  - **Bronchoscopy** with directed airway therapy:

    Rigid bronchoscopy is favored if available because it provides optimal airway access and ventilatory control, plus easier suctioning and manipulation of instruments.

    - **Direct tamponade with the distal end of the bronchoscope.**
    - **Balloon tamponade**: left in place for 1-2 days. Watch for ischemic mucosal injury or postobstructive pneumonitis (*Thorax 2003;58:814*).
    - Fogarty balloon, bronchial blocker, and pulmonary artery catheter balloons have all been described.
    - **Endobronchial electrocautery** (*Chest 2001;119:781*).
    - **Argon-plasma coagulation** (*Can Respir J 2004;11:305*; *Chest 2001;119:781*).
    - **Topical hemostatic agents:** cold saline, epinephrine, vasopressin, and thrombin (*Am Rev Respir Dis 1987;135:A108*; *Chest 1989;96:473*; *Thorax 1980; 35:901*).
- **Bronchial arteriography and embolization should be performed early** in massive or recurrent hemoptysis.
    - **Successful embolization** **(>85%)** with careful localization (*Chest 2002;121:789*; *Radiology 2004;233:741*).
    - Particularly useful in cystic fibrosis patients (*Am J Respir Crit Care Med 1998;157:1951*; *Chest 2002;121:796*).
    - **Early failure usually due to inadequate or incomplete source vessel identification.** Postembolization arteriography may identify additional systemic culprit vessels, most commonly from the intercostal and phrenic arteries (*Am J Roentgenol 2003; 180:1577*).
    - **Rebleeding common** (up to 20%) over 1 year (*Chest 1999;115:912*; *Respiration 2000;67:412*).
    - **Risks** include bronchial or partial pulmonary infarct/necrosis and, rarely, ischemic myelopathy due to inadvertent embolization of a spinal artery.

Medications

Systemic procoagulants: Use only in unstable massive hemoptysis as a temporizing measure or when conventional bronchoscopic, interventional, or surgical therapies are contraindicated and/or unavailable. Some examples are factor VII, vasopressin, and aminocaproic acid.

Surgical Management

Emergent surgery has high morbidity and mortality compared to elective surgery after stabilization (*Am J Med Sci 1987;294:301-9*).

- **Lobectomy/pneumonectomy offers definitive cure.**
- **Indications: persistent focal/unilateral massive hemoptysis despite other therapy**; particularly useful for stable patients with hemoptysis due to cavitary lung disease, localized bronchogenic carcinoma, AVM, or traumatic injuries (*Crit Care Med 2000;28:1642*).
- **Contraindications:** poor pulmonary reserve, advanced malignancy, active TB, diffuse lung disease, or diffuse alveolar hemorrhage.

REFERRAL

- Pulmonary (interventional for massive hemoptysis, if available)
- Thoracic surgery
- Interventional radiology

OUTCOME/PROGNOSIS

http://internalmedicinebook.com

Mortality depends on etiology and amount (*Arch Intern Med 1983;143:1343*; *Am J Med Sci 1987;294:301*).

- Up to 80% with massive hemoptysis due to malignancy
- <10% with nonmassive hemoptysis
- <1% in bronchiectasis and lung infections

Cystic Fibrosis

GENERAL PRINCIPLES

Definition

Cystic fibrosis (CF) is an **autosomal recessive disorder** caused by mutations of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), located on chromosome 7, which results in multisystem exocrine organ dysfunction.

Epidemiology

- In the United States, approximately 30,000 people are affected by CF, with an incidence of 1 in 3500 live births (*Clin Chest Med 2007;28:279*).
- CF is the most common lethal genetic disease in Caucasians; however, the diagnosis should be considered in patients of diverse ethnic backgrounds as well.
- Patients are typically diagnosed via newborn screening or during childhood, but there is increasing recognition of milder variants that may not present until later in life.
- In 2013, approximately 50% of patients with CF were ≥18 years old.

Etiology

- CF is caused by **mutations in the *CFTR* gene**, a cyclic adenosine monophosphate (cAMP)-regulated chloride channel (*Science 1989;245:1073*).
- The most common mutation in the *CFTR* gene is F508del, the lack of a phenylalanine (F) amino acid at position 508. However, >1900 mutations have been identified.
- CFTR normally maintains hydration of exocrine organ secretions.
- Abnormal CFTR causes decreased chloride secretion and increased sodium absorption on the surface of epithelial cells with resulting thickened secretions in the airways, sinuses, pancreatic ducts, biliary tree, intestines, and reproductive tract.

Pathophysiology

- CFTR normally regulates transport of chloride ions across the epithelium (*Curr Opin Pulm Med 2003;9:486*).
- The primary pulmonary manifestations of disease are related to the malfunction of chloride transport across the airway epithelium, resulting in diminished airway surface liquid and impaired mucociliary clearance.
- Poor mucociliary clearance results in an impaired ability to clear infection. Recurrent infection begets an inflammatory cascade that results in bronchiectasis, chronic infection, and ultimately, premature death (*N Engl J Med 2005;352:1992*).
- Similarly, thickened secretions in the pancreatic and biliary ducts lead to maldigestion, malabsorption, and

occasionally, liver disease and diabetes.

DIAGNOSIS

- The diagnosis of CF is typically made during childhood, but approximately 10% of patients are diagnosed after age 10 (*Cystic Fibrosis Foundation National Patient Registry Annual Data Report 2013. Bethesda, MD: Cystic Fibrosis Foundation, 2014*).

- Newborn screening has increased the frequency of early diagnosis (*J Pediatr 2002;141:804*). In 2013, 62% of new diagnoses were the result of newborn screening (*Cystic Fibrosis Foundation National Patient Registry Annual Data Report 2013. Bethesda, MD: Cystic Fibrosis Foundation, 2014*).
- **At least one criterion** from each set of features must be met to diagnose CF (*J Pediatr 2008;153:S1*):
  - Compatible clinical features of CF (see clinical features), or
  - A positive family history of CF, or
  - A positive newborn screening test

    AND
  - Elevated sweat chloride >60 mmol/L on two occasions, or
  - Presence of two disease-causing mutations in *CFTR*, or
  - Abnormal nasal transepithelial potential difference
- Atypical patients may lack classic symptoms and signs or have normal sweat tests (*Curr Opin Pulm Med 2003;9:498*).
- Although genotyping may assist in the diagnosis, it alone cannot establish or rule out the diagnosis of CF, and the initial test of choice remains the sweat test.

Clinical Presentation

- **Pulmonary manifestations**

  Cough with purulent sputum production, wheezing, hemoptysis, dyspnea, progressive airflow obstruction, bronchiectasis, and pneumothorax
- **Extrapulmonary manifestations**

  Chronic sinusitis, nasal polyposis, pancreatic insufficiency (vitamins A, D, E, and K deficiency), malnutrition, meconium ileus, distal intestinal obstruction syndrome, volvulus, intussusception, rectal prolapse, diabetes mellitus, liver cirrhosis, portal hypertension, cholelithiasis, cholecystitis, nephrolithiasis, male infertility (bilateral absence of the vas deferens), epididymitis, growth retardation, hypertrophic pulmonary osteoarthropathy, and osteopenia

History

Presenting symptoms may include (*J Pediatr 1993;122:1*):

- Cough with purulent sputum production (40%)
- Failure to thrive (29%)
- Malnutrition
- Steatorrhea
- Meconium ileus

Physical Examination

- Underweight

- Inspiratory crackles on lung exam typically anterior and in the apices
- Digital clubbing

Differential Diagnosis

- **Primary ciliary dyskinesia:** bronchiectasis, sinusitis, and infertility, but limited gastrointestinal symptoms and normal sweat chloride levels, occasionally seen with dextrocardia or situs inversus totalis (Kartagener syndrome)
- **Immunodeficiency (e.g., severe combined immunodeficiency, common variable immunodeficiency):** recurrent sinus and pulmonary infections but typically no gastrointestinal symptoms and normal sweat chloride levels
- **Shwachman-Diamond syndrome:** pancreatic insufficiency, cyclic neutropenia, and short stature, which may lead to lung disease, but normal sweat chloride levels (*Hematol Oncol Clin North Am 2009;23:233*)

- **Young syndrome:** bronchiectasis, sinusitis, and azoospermia, but mild respiratory symptoms, lack of gastrointestinal symptoms, and normal sweat chloride levels (*Thorax 1987;42:815*)
- **Idiopathic bronchiectasis**

Diagnostic Testing

- **Skin sweat testing** with a standardized quantitative pilocarpine iontophoresis method remains the **gold standard for the diagnosis of CF** (*Am J Respir Crit Care Med 2006;173:475*).
  - A sweat chloride concentration of ≥60 mmol/L on two separate occasions is consistent with the diagnosis of CF.
  - Borderline sweat test results (40-59 mmol/L sweat chloride) or nondiagnostic results in the setting of high clinical suspicion should lead to repeat sweat testing, nasal potential difference testing, genetic testing, or additional clinical evaluation.
  - Sweat testing should be performed at a CF care center to ensure reliability of results.
  - Abnormal sweat chloride concentrations are rarely detected in non-CF patients.
- **Genetic tests** have detected >1900 putative CF mutations.
  - Two recessive mutations on different alleles must be present to cause CF.
  - The most commonly encountered CF mutation is a deletion of the three nucleotides that code for phenylalanine (F) at amino acid 508 (F508del or **δF508**) of the CFTR protein. In the most recent Cystic Fibrosis Foundation Patient Registry, 86.4% of patients with CF carry this mutation (*Cystic Fibrosis Foundation National Patient Registry Annual Data Report 2013. Bethesda, MD: Cystic Fibrosis Foundation, 2014*).
  - Commercially available CF screens identify >90% of the abnormal genes in a Caucasian Northern European population, although they test for only a minority of the known CF genes. Full gene sequencing is commercially available, but interpretation may be complex. Information about specific mutations and reported clinical phenotype may be found at *http://www.cftr2.org/*.
- **Transepithelial nasal potential difference**
  - A test in which the voltage across the epithelial lining of the nose is measured at baseline, after inhibiting sodium channels with amiloride and after stimulating CFTR with a cAMP agonist (*J Pediatr 1986;108:517*; *Chest 2010;138:919*).

- The test should be repeated on two separate days to confirm diagnosis and should be performed at specialized centers.
- Results may be affected by nasal polyposis or mucosal inflammation.

Laboratories

- Sputum cultures typically identify multiple organisms, including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*. Isolation of mucoid variants of *P. aeruginosa* from the respiratory tract occurs frequently. Use of special culture media to fastidious organisms is recommended.
- Nontuberculous mycobacteria are frequently isolated from the airways of persons with CF and may be pathogenic in some.
- **Testing for malabsorption** due to pancreatic exocrine insufficiency is often not formally performed because clinical evidence (the presence of foul-smelling, bulky, and loose stools; low fat-soluble vitamin levels [vitamins A, D, and E]; and a prolonged prothrombin time [vitamin K dependent]) and a clear response to pancreatic enzyme treatment are usually considered sufficient for the diagnosis. In atypical cases, low fecal elastase level or coefficient of fat absorption <85% on a formal 72-hour fecal fat collection may confirm pancreatic insufficiency.
- Tests that identify chronic sinusitis or infertility, especially obstructive azoospermia in men, also support the diagnosis of CF.

Testing

- CXR shows hyperinflation with cystic lung disease, bronchiectasis, and mucous plugging, especially in the upper lobes.
- HRCT scan may be helpful in evaluating patients with early or mild disease by detecting early changes in the airways.
- Pulmonary function tests demonstrate expiratory airflow obstruction with increased residual volume and total lung capacity.
- Impairment of alveolar gas exchange may be present later in the course of disease, progressing to hypoxemia and hypercapnia.

TREATMENT

- CF therapy aims to improve quality of life and functioning, decrease the number of exacerbations and hospitalizations, avoid complications associated with therapy, reduce the rate of decline in lung function, and decrease mortality.
- A comprehensive program addressing multiple organ system derangements, as provided at CF care centers, is recommended.
- **Pulmonary therapy** (*Am J Respir Crit Care Med 2007;176:957*): primarily focused on clearing pulmonary secretions and controlling infection.
  - **Inhaled bronchodilators:** β-Adrenergic agonists (albuterol metered-dose inhaler, two to four puffs bid-qid; salmeterol or formoterol, one dry powder inhalation bid). Used to treat the reversible components of airflow obstruction and facilitate mucus clearance
  - **Recombinant human deoxyribonuclease:** DNase, dornase-α, Pulmozyme (2.5 mg or one ampule per day inhaled using a jet nebulizer)

- It digests extracellular DNA, decreasing the viscoelasticity of the sputum.
- It improves pulmonary function and decreases the incidence of respiratory tract infections that require parenteral antibiotics (*N Engl J Med 1994;331(10):637-42*).
- Adverse effects may include pharyngitis, laryngitis, rash, chest pain, and conjunctivitis.

- **Hypertonic saline:** (4 mL of inhaled 7% saline twice daily)
  - Due to high osmolality, water is drawn from the airway epithelium and can rehydrate the pericilliary airway surface liquid.
  - Treatment results in fewer exacerbations and improvement in lung function (*N Engl J Med 2006;354:229*).
  - Inhaled bronchodilators should be administered prior to treatments to avoid treatmentinduced bronchospasm.
- **Antibiotics**
  - A combination of an antipseudomonal β-lactam and an aminoglycoside is typically recommended during acute exacerbations (*Am J Respir Crit Care Med 2009;180:802*).
  - Sputum culture and sensitivities should guide therapy. *P. aeruginosa* is the most frequent pulmonary pathogen.
  - The duration of antibiotic therapy is dictated by the clinical response. At least 14 days of antibiotics are typically needed to treat an exacerbation.
  - Home IV antibiotic therapy is common, but hospitalization may allow better access to comprehensive therapy and diagnostic testing. Oral antibiotics are recommended only for mild exacerbations.
  - The use of chronic or intermittent prophylactic antibiotics can be considered, especially in patients with frequent recurrent exacerbations, but antimicrobial resistance may develop.
  - In patients chronically infected with *P. aeruginosa*, the inhaled aerosolized antibiotics tobramycin (300 mg nebulized twice daily) and aztreonam lysinate (75 mg nebulized 3× daily) can be used via alternating 28 days on with 28 days off to

    improve pulmonary function, decrease the density of *P. aeruginosa*, and decrease the risk of hospitalization. Voice alteration (13%) and tinnitus (3%) are potential adverse events associated with long-term inhaled tobramycin (*N Engl J Med 1999;340:23*), and pyrexia and airway irritation have been reported with inhaled aztreonam (*Chest 2009;135:1223*). More recently, continuous alternating inhaled antibiotic therapy has become the standard of care for many patients with chronic *Pseudomonas* infection and pulmonary impairment.
  - Patients with CF have atypical pharmacokinetics and often require higher drug doses at more frequent intervals during an acute exacerbation. In adult patients with CF, for example, cefepime is often dosed at 2 g IV q8h, and tobramycin is often dosed at 8 mg/kg IV daily (aiming for peak levels of 20 μg/mL and trough levels of <2 μg/mL).
  - Once-daily aminoglycoside dosing is preferred and should be guided by pharmacokinetic testing. Monitoring levels (peaks and troughs) of drugs such as aminoglycosides helps to ensure therapeutic levels and to decrease the risk of toxicity.
- **Anti-inflammatory therapy**
  - **Azithromycin** (500 mg oral 3×/week) used chronically shows mild improvement in lung function and reduces days in the hospital for treatment of respiratory exacerbations in patients who are chronically infected with *P. aeruginosa* (*JAMA 2003;290:1749*).

- **Glucocorticoids** used in short courses may be helpful to some patients with asthmalike symptoms, but long-term therapy should be avoided to minimize the side effects, which include glucose intolerance, osteopenia, and growth retardation.
- **Ibuprofen** used in high doses has been used as a chronic anti-inflammatory agent in children age 6-17 with mild impairment of lung function (*Chest 1999;124:689*).

- **Restoration of CFTR function**
  - **Ivacaftor** (150 mg orally twice daily) is a CFTR potentiator that improves lung function and decreases the risk of pulmonary exacerbations in patients with the **missense G551D mutation** (*N Engl J Med 2011;365:1663*). After 144 weeks of use, increases in lung function are maintained (*Lancet Respir Med 2014;2:902*). Only about 4% of the US CF population carries a G551D mutation. Since its initial release, the FDA has approved the use of ivacaftor in patients with the following mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, and R117H. However, this only includes about 7% of the US CF population.
  - **Lumacaftor** (a CFTR "corrector" or chaperone protein) combined with ivacaftor has been shown in two phase III trials to improve lung function and decrease the risk of pulmonary exacerbations in patients who are homozygous for the F508del mutation. This combination therapy is awaiting FDA approval (*Vertex Pharmaceuticals Inc. Two 24-Week Phase 3 Studies of Lumacaftor in Combination with Ivacaftor Met Primary Endpoint with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis who have Two Copies of the F508del Mutation, 2014*).
  - Other CFTR corrector molecules, potentiators, and molecules that suppress *CFTR* nonsense mutations (premature stop codons) are in various phases of clinical development and testing.
- **Mechanical airway clearance devices:** flutter valve, acapella device, high-frequency chest oscillation vests, low- and high-pressure positive expiratory pressure devices
  - Can be used in combination with medical therapy to promote airway clearance.
  - Other alternatives include postural drainage with chest percussion and vibration, and breathing and coughing exercises.
- **Pulmonary rehabilitation**

  When done with exercise rehabilitation may improve functional status and promote clearance of airway secretions

- **Oxygen therapy**
  - May be indicated based on standard recommendations used for the treatment of chronic obstructive pulmonary disease.
  - Rest and exercise oxygen assessments should be performed as clinically indicated.
- **Noninvasive ventilation**
  - Used for chronic respiratory failure due to CF-related bronchiectasis
  - Has not been clearly demonstrated to provide a survival benefit, although it may provide symptomatic relief or may be used as a bridge to transplantation

- **Extrapulmonary therapy**
  - **Pancreatic insufficiency**
    - Primary management involves **pancreatic enzyme supplementation**.
    - Enzyme dose should be titrated to achieve one to two semisolid stools per day and to maintain

adequate growth and nutrition.

- Enzymes are taken immediately before meals and snacks.
- Dosing of pancreatic enzymes should be initiated at 500 units lipase/kg/meal and should not exceed 2500 units lipase/kg/meal.
- **High doses** (6000 units lipase/kg/meal) have been associated with **chronic intestinal strictures** (*N Engl J Med 1997;336:1283*).
- Gastric acid suppression may enhance enzyme activity.

- **Vitamin deficiency**
  - **Vitamins A, D, E, and K** can all be taken orally with meals and enzymes.
  - Iron deficiency anemia requires iron supplementation.
- **CF-related diabetes mellitus**
  - Related to pancreatic insufficiency and managed with **insulin**.
  - Typical diabetic dietary restrictions are liberalized (high-calorie diet with unrestricted fat) to meet the increased energy requirements of patients with CF and to encourage appropriate growth and weight maintenance.
- **Bowel impaction**
  - **Laxatives** such as senna, magnesium citrate, or polyethylene glycol can be tried initially.
  - Refractory cases may require a Hypaque enema with visualization of clearance of the obstruction (*J Cyst Fibros 2011;10:S24*).
  - Can be mistaken for appendicitis or gallbladder disease because the appendix can be enlarged in CF due to mucus inspissation and white blood cell counts and/or alkaline phosphatase elevations, which are common in CF.
  - Narcotic use and/or significant dehydration and/or nonadherence with pancreatic enzyme supplementation can precipitate severe bowel obstruction, so prophylactic laxatives like daily polyethylene glycol (e.g., MiraLAX 17 g in 8 oz water) in postsurgical patients are often indicated.
- **Osteopenia**

  Screening should be routinely performed on patients with CF, and if present, osteopenia may be managed with calcium, vitamin D supplementation, and bisphosphonate therapy as clinically indicated (*Am J Respir Crit Care Med 2004;169:77*).
- **Chronic sinusitis**
  - Many patients will benefit from chronic **nasal steroid** administration.
  - Nasal saline washes may also be helpful.
  - Patients whose symptoms cannot be controlled with medical management may benefit from functional endoscopic sinus surgery and nasal polypectomy.

Surgical Management

- **Massive hemoptysis**

  Treatment includes IV antibiotics and, in refractory cases, may require bronchial artery embolization. Surgical lung resection is rarely needed (*Am J Respir Crit Care Med 2010;182:298*).

- **Pneumothorax**

  Unless small, pneumothoraces are treated with chest tube placement. Surgical pleurodesis should be

http://internalmedicinebook.com

considered in cases of recurrent pneumothorax (*Am J Respir Crit Care Med 2010;182:298*).

- **Lung transplantation**
  - The majority of patients with CF die from pulmonary disease.
  - FEV_1 is a strong predictor of mortality and has been helpful in deciding when to refer patients for lung transplantation (*N Engl J Med 1992;326:1187*).
  - However, other factors such as marked alveolar gas exchange abnormalities (resting hypoxemia or hypercapnia), evidence of PH, or increased frequency or severity of pulmonary exacerbations should also be considered when deciding on referral for transplantation.

Lifestyle/Risk Modification

- **Avoidance of irritating inhaled fumes, dusts, or chemicals**, including second-hand smoke, is recommended.
- **Yearly influenza vaccination** (0.5 mL IM) decreases the incidence of infection and subsequent deterioration (*N Engl J Med 1984;311:1653*).
- **Pneumovax** (0.5 mL IM) may also provide benefit against invasive pneumococcal disease (*Ann Intern Med 1986;104:1*).
- People with CF should avoid contact with others with the disease, unless they are members of the same household, in order to reduce the risk of transmission of infection from one person to another (*Infect Control Hosp Epidemiol 2014;35:S1*).

Diet

A high-calorie diet with vitamin supplementation is typically recommended.

Activity

- CF patients should maintain as much activity as possible.
- Exercise is an excellent form of airway clearance.

SPECIAL CONSIDERATIONS

- When in a health care setting, all personnel should implement contact precautions, whether in the clinic or in the hospital (*Infect Control Hosp Epidemiol 2014;35:S1*).
- Patients with previous isolation of *Burkholderia* should be cared for in a separate area than those without this species.
- Although fertility may be decreased in women with CF secondary to thickened cervical mucus, many women with CF have tolerated pregnancy well (*N Engl J Med 1984;311:1653*).
- Maternal and fetal outcomes are good for women with adequate pulmonary reserve (FEV_1 >50% predicted) and good nutritional status, and pregnancy does not appear to affect their survival (*Chest 2000;118:85*).
- Pregnancies should be planned to optimize patient status and coordinate care with obstetrics. CF genetic screening should be offered to partners of patients with CF.

COMPLICATIONS

Other pulmonary complications of CF may include allergic bronchopulmonary aspergillosis, massive hemoptysis, acquisition of atypical mycobacterium, and pneumothorax.

REFERRAL

- CF patients or suspected CF patients should be referred to a national Cystic Fibrosis Foundation (CFF)-accredited care center.
- Tests such as sweat chloride testing and nasal potential difference are best done at specialized CF care centers.
- A team of CF specialists, including physicians, nutritionists, respiratory therapists, and social workers, aid in the routine care of these patients.

PATIENT EDUCATION

Information can be found at the CFF website (*www.cff.org*).

MONITORING/FOLLOW-UP

All persons with CF should be followed in an accredited CF care center. Patients should follow-up as an outpatient every 3 months with pulmonary function tests and yearly laboratories including vitamin levels and screening for CF-related diabetes.

OUTCOME/PROGNOSIS

- Predictors of increased mortality include age, female gender, low weight, low FEV_1, pancreatic insufficiency, diabetes mellitus, infection with *B. cepacia*, and the number of acute exacerbations (*JAMA 2001;286:2683*).
- With improved therapy, the median survival has been extended to approximately 40 years (*Cystic Fibrosis Foundation National Patient Registry Annual Data Report 2013. Bethesda, MD: Cystic Fibrosis Foundation, 2014*).

11
Allergy and Immunology

Sean Brady

Junfang Jiao

Jennifer M. Monroy

Andrew L. Kau

Adverse Drug Reactions

GENERAL PRINCIPLES

Definition

- An **adverse drug reaction** (ADR) is an undesired or unintended response that occurs when a drug is given for the appropriate purpose.
- The etiology of a drug reaction can be immunologic, toxic, or idiosyncratic in nature.
- An allergic drug reaction is due to an immune response that is mediated by immuno-globulin E (IgE) or T cells.

Classification

- *Type A* reactions are predictable, often dose dependent, and related to the pharmacokinetics of the drug.
- *Type B* reactions are unpredictable and are not related to the dose or the drug's pharma-cokinetics. They account for 10-15% of all ADRs.
  - Immune-mediated adverse reactions can be from a variety of mechanisms. They usually occur upon reexposure to the offending drug.
  - **Pseudoallergic reactions**, formerly called anaphylactoid reactions, are caused by IgE-independent degranulation of mast cells.

Epidemiology

- From 1966-1996, 15.1% of hospitalized US patients experienced an ADR with an inci-dence of 3.1-6.2% of hospital admissions due to ADRs (*JAMA 1998;279:1200*).
- Mortality from ADRs is significant and ranges from 0.14-0.32% (*Curr Opin Allergy Clin Immunol 2005;5(4):309*).

Etiology

- **β-Lactam** antibiotics are most commonly associated with immunologically mediated drug reactions.
  - Anaphylaxis has been reported to occur in 1:100,000, with serious allergic reactions in 4.6 per 10,000 dispenses (*Drug Saf 2007;30(8):705*).
  - Hospitalized patients with a history of penicillin allergy have been shown to have a longer hospital stay with increased incidence of vancomycin-resistant *Enterococcus*, methicillin-resistant *Staphylococcus aureus*, and *Clostridium difficile* infections compared to patients without a reported penicillin allergy (*J Allergy Clin*

Immunol 2014;133(3):790-6).

- Typical reactions include rash, urticaria, fever, and bronchospasm.
- The chemical structure of penicillins results in their high immunogenicity.
  - The core structure is composed of a reactive β-lactam ring that covalently binds with carrier proteins to form a hapten, which stimulates an immune response. The major determinant of immunogenicity of penicillin is the benzylpenicilloyl form seen in 93% of tissue-bound penicillin.
  - The minor antigenic determinants are all remaining penicillin conjugates. They are comprised of benzylpenicillin, benzylpenicilloate, and benzylpenilloate.
  - Most immediate reactions to penicillins are related to the major determinant. In other penicillins such as ampicillin, the side chain is the antigenic determinant.

- Cross-reactivity of β-lactams.

  The cross-reactivity between β-lactam antibiotics is variable and largely determined by their side-chain structure attached to the β-lactam ring.
- Prior to the 1980s, cephalosporins had a higher cross-reactivity to penicillin because they were contaminated with a small amount of penicillin (*J Allergy Clin Immunol 2010;125(2 suppl 2):S126*). Risk of a cross-reaction is 5.0-16.5% with first-generation cephalosporins, 4% with second-generation, and 1-3% with third- or fourth-generation (*J Allergy Clin Immunol 2006;117(2 suppl):S464*).
  - Although many of the reactions to second- and third-generation cephalosporins are directed at the side chains, skin testing to penicillin in these patients can be helpful because most severe anaphylactic reactions are directed against the reactive bicyclic core.
  - Patients with a history of a severe reaction to penicillin should be considered sensitive to cephalosporin unless they are skin test negative. Although patients with a history of a nonanaphylactic reaction to penicillin can often be given a second- or third-generation cephalosporin safely, it is advisable to precede the dose with an oral provocation challenge.
- Skin test cross-reactivity has been documented between carbapenems and penicillins. Patients undergoing a graded carbapenem challenge with a positive penicillin skin test and a negative carbapenem skin test did not have any hypersensitivity reactions (*J Allergy Clin Immunol 2010;125(2 suppl 2):S126*).
- The monobactam aztreonam rarely cross-reacts with penicillins. Ceftazidime does share an identical side chain to aztreonam and is highly cross-reactive (*Ann Pharmacother 2009;43(2):304*).

- **Sulfonamide allergy**
  - There is an increase in allergy to sulfonamides in patients with HIV compared to the general population. Trimethoprim-sulfamethoxazole hypersensitivity occurs in 60% of HIV-positive patients compared to 5% of HIV-negative patients (*Curr Opin Allergy Clin Immunol 2007;7(4):324*).
  - The most frequently seen reaction is a maculopapular rash that develops 7-12 days after initiating the drug. Other reactions include urticaria and, less commonly, anaphylaxis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).
  - Cross-reactivity between antibiotic and nonantibiotic sulfa-containing medications is low.
- **NSAIDs** (including aspirin) can induce pseudoallergic reactions through shunting of prostaglandin production

to leukotriene synthesis in susceptible individuals. When NSAID administration results in respiratory symptoms, it is referred to as aspirin-exacerbated respiratory disease. Samter's triad is the combination of asthma, NSAID sensitivity, and nasal polyposis

Pathophysiology

The immunologic mechanisms for drug hypersensitivity are demonstrated in the Gell and Coombs classification of hypersensitivity (Table 11-1).

Risk Factors

Factors that increase a patient's risk of an ADR include size and structure of drug, route of exposure (cutaneous most immunogenic), dose, duration, frequency, gender (women > men), genetic factors (HLA type, history of atopy), prior drug reaction, coexisting medical illnesses, and concurrent medical therapy.

DIAGNOSIS

Clinical Presentation

- A history is essential for making the diagnosis of an allergic drug reaction. Questions should be directed at establishing the following information: sign and symptoms, timing

of the reaction, purpose of the drug, other medications the patient is receiving, prior exposure to drug or related drug, and history of other allergic drug reactions.

TABLE 11-1 Immunologically Mediated Drug Reactions

Type of Reaction	Representative Examples	Mechanism
Anaphylactic (type 1)	Anaphylaxis Urticaria Angioedema	IgE-mediated degranulation of mast cells with resultant mediator release
Cytotoxic (type 2)	Autoimmune hemolytic anemia Interstitial nephritis	IgG or IgM antibodies against cell antigens and complement activation
Immune complex (type 3)	Serum sickness Vasculitis	Immune complex deposition and subsequent complement activation
Cell mediated (type 4)	Contact dermatitis Photosensitivity dermatitis	Activated T cells against cell surface-bound antigens

- Urticaria, angioedema, wheezing, and anaphylaxis are all characteristics of IgE-mediated (type 1) reactions.

- Symptoms do not typically occur on the first exposure to the medication unless the patient has been exposed to a structurally related medication. On reexposure, however, symptoms tend to manifest acutely (often <1 hour).
- IgE-mediated reactions tend to worsen with repeated exposure to the offending medication.
- Pseudoallergic reactions (non-IgE mediated) can be clinically indistinguishable from IgE-mediated reactions because the final common pathway for their reaction is mast cell degranulation.

- **Maculopapular exanthemas** are the most common cutaneous manifestation of drug allergy.
  - These reactions are mediated by T cells and typically delayed in onset, first occurring between 2-14 days of exposure to culprit medications. Lesions typically begin on the trunk, especially in dependent areas, and spread to the extremities.
  - Rarely, these rashes can progress to DRESS (**d**rug **r**eaction with **e**osinophilia and **s**ystemic **s**ymptoms) or SJS.
- **DRESS** or hypersensitivity syndrome is a serious ADR, often presenting with rash and fever (*Expert Opin Drug Saf 2005;4(3):571*).
  - Systemic involvement can manifest as hepatitis, eosinophilia, pneumonitis, lymphadenopathy, and nephritis.
  - Symptoms tend to present 2-6 weeks after introduction of medication.
  - First described with antiepileptic (carbamazepine) agents but has also been reported to occur with allopurinol, NSAIDs, some antibiotics, and β-blockers.
- **Erythema multiforme (EM), SJS, and TEN** are all serious drug reactions primarily involving the skin.
  - EM is characterized most typically by target lesions.
  - SJS and TEN manifest with varying degrees of sloughing of the skin and mucous membranes (<10% in SJS and >30% in TEN).
- Readministration or future skin testing with the offending drug is absolutely contraindicated.

PREVENTION AND TREATMENT

- **Discontinuation** of the suspected drug is the most important initial approach in managing an allergic drug reaction.

- **HLA testing may be indicated in susceptible populations for prevention of a severe ADR for some drugs such as abacavir and carbamazepine.**
- Other therapeutic maneuvers are directed at limiting further exacerbation of ADRs and may include management of anaphylaxis as well as other supportive measures.
- Future use of the drug in question should **always be avoided** unless there is no therapeutic alternative available.
- If use of the drug must be considered, a careful history of the reaction is helpful in defining the potential risk. Patients may lose their sensitivity to a drug over time, and determining the date of reaction is useful. Symptoms that occur with the start of a drug course are more likely to be IgE-mediated than symptoms that develop several days after the completion of a course.
- The types of symptoms are also important. Toxic reactions (e.g., nausea secondary to macrolide antibiotics or codeine) are not immunologic reactions and do not necessarily predict problems with other

members in their respective class.

- If the patient is taking the drug for a life-threatening illness (e.g., meningitis with penicillin allergy) and the reaction is a mild skin reaction, it may be reasonable to continue the medication and treat the reaction symptomatically. **If the rash is progressive, however, the drug must be discontinued to avoid a desquamative process such as SJS.**

REFERRAL

- If no alternative drug is available and the patient has a history of an IgE-mediated reaction, the patient should be referred to an allergist for further evaluation.
- The allergist may perform one of several procedures if indicated depending on the medication, type of reaction, and availability of testing reagents.
  - **Skin testing** may be performed to assess for the presence of IgE to the medication.
    - Although skin testing may be performed to nearly any medication, sensitivity and specificity of the skin test results have been best established with penicillin. No case of penicillin-induced anaphylaxis has been reported in a patient who is skin test negative.
    - Results of testing to drugs other than penicillin must be interpreted within the clinical context of the case.
  - **Graded dose challenge** assesses how the patient tolerates progressively larger doses of medication (e.g., 1/1000, 1/10, and full dose given 20 minutes apart).
  - **Drug desensitization** is performed when the patient has an identified IgE-mediated reaction but still requires the medication.
    - The exact mechanism by which desensitization prevents anaphylaxis is unclear.
    - The drug must be taken daily at a specified dose to maintain the "desensitized state."
    - If a dose of drug is missed for a period >48 hours following a desensitization procedure, the patient will often need to undergo a repeat desensitization.
  - Successful desensitization or graded challenge does not preclude the development of a non-IgE-mediated, delayed reaction (e.g., rash).

Anaphylaxis

GENERAL PRINCIPLES

Definition

Anaphylaxis is a rapidly developing, life-threatening systemic reaction mediated by the release of mast cell and basophil-derived mediators into the circulation. The peak severity is seen usually within 5-30 minutes.

Classification

- **Immunologic anaphylaxis:**
  - Allergic IgE-mediated anaphylaxis (type 1 hypersensitivity)

http://internalmedicinebook.com

- IgG-mediated anaphylaxis (rare)

- **Nonimmunologic anaphylaxis**

Epidemiology

Incidence of anaphylaxis is approximately 50-2000 episodes per 100,000 person-years with a lifetime prevalence of 0.05-2%. Fatality is estimated at 0.7-2% per case of anaphylaxis.

Etiology

- **Immunologic causes**
  - Foods, especially peanuts, tree nuts, shellfish, finned fish, milk, and eggs
  - Insect stings (bees, wasps, and fire ants)
  - Medications
  - Latex rubber
  - Blood products
- **Nonimmunologic causes**
  - Radiocontrast media
  - Medications (i.e., NSAIDs, opiates, vancomycin, muscle relaxants, rarely ACE-inhibitors, and sulfating agents)
  - Hemodialysis
  - Physical factors (cold temperature or exercise)
  - Idiopathic

Pathophysiology

- Immunologic
  - Anaphylaxis is due to sensitization to an antigen and formation of specific IgE to that antigen. On reexposure, the IgE on mast cells and basophils binds the antigen and cross-links the IgE receptor, which causes activation of the cells with subsequent systemic release of preformed mediators, such as histamine.
  - The release of mediators ultimately causes capillary leakage, cellular edema, and smooth muscle contractions resulting in the constellation of physical symptoms.
- Nonimmunologic

  Non-IgE-mediated anaphylaxis is also mediated by direct degranulation of mast cells and basophils in the absence of immunoglobulins.

Risk Factors

- Immunologic anaphylaxis: IgE-mediated reactions
  - Asthma
  - Previous sensitization and formation of antigen-specific IgE with history of anaphylaxis

- Nonimmunologic anaphylaxis:

  Radiocontrast sensitivity reactions

  - Age >50 years.
  - Preexisting cardiovascular or renal disease.
  - History of allergy.
  - History of previous reaction to radiocontrast media.
  - **Sensitivity to seafood or iodine does not predispose to radiocontrast media reactions.**
- Individuals with **mastocytosis**, a disease characterized by a proliferation of mast cells, are at higher risk for severe anaphylaxis from both IgE- and non-IgE-mediated causes.

Prevention

- **For all types of anaphylaxis, recognition of potential triggers and avoidance are the best prevention.**
- **Self-injectable epinephrine and patient education for all patients with a history of anaphylaxis.**
- Radiocontrast sensitivity reactions
  - Use of low-ionic contrast media is strongly suggested.
  - Premedication before procedure.
    - Prednisone 50 mg PO given 13 hours, 7 hours, and 1 hour prior to procedure
    - Diphenhydramine 50 mg PO given 1 hour before procedure
    - H_2 blocker may also be given 1 hour before procedure
  - **Premedication is not 100% effective, and appropriate precautions for handling a reaction should be taken.**
  - Anaphylaxis can be a presenting sign of underlying mastocytosis.
- Red man's syndrome from vancomycin

  Symptoms can usually be prevented by slowing the rate of infusion and premedicating with diphenhydramine (50 mg PO) 30 minutes prior to start of the infusion.

DIAGNOSIS

Diagnosis is based primarily on history and physical examination and the documentation of the presence of a specific IgE to the suspected allergen (if the trigger is IgE mediated). Confirmation of anaphylaxis can, in some cases, be provided by the laboratory finding of an elevated serum tryptase level. However, the absence of an elevated tryptase level does not exclude anaphylaxis.

Clinical Presentation

- The clinical manifestations of allergic and nonallergic anaphylaxis are the same.
- Most serious reactions occur within minutes after exposure to the antigen, but in some circumstances, the reaction may be delayed for hours.
- Some patients experience a biphasic reaction characterized by a recurrence of symptoms after 4-8 hours.

A few patients have a protracted course that requires several hours of continuous supportive treatment.

- Manifestations include pruritus, urticaria, angioedema, respiratory distress (due to laryngeal edema, laryngospasm, or bronchospasm), hypotension, uterine cramping, abdominal cramping, emesis, and diarrhea.

History

A thorough history is taken to help identify the potential trigger, such as new foods, medications, or other commonly known allergens. Also documenting the time of onset of symptoms—that is, minutes to hours or days after a suspected exposure—can help to classify the type of anaphylaxis.

Physical Examination

- Pay special attention to vital signs: Blood pressure, respiratory rate, and oxygen saturation.
- Airway and pulmonary: Assess for any evidence of laryngeal edema or angioedema. Auscultate lung fields to listen for evidence of wheezing. Continue to assess for need to protect the airway.
- Perform a focused cardiovascular exam.
- Skin: Urticaria or erythema.

Diagnostic Criteria

See Table 11-2 for diagnostic criteria for anaphylaxis.

Severity of anaphylactic reactions can be judged by the following:

- **Mild anaphylactic reactions:** Generalized erythema, urticaria, angioedema, or pruritus
- **Moderate anaphylactic reaction** (features suggesting respiratory, cardiovascular, or gastrointestinal involvement): Dyspnea, stridor, wheezing, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, and abdominal pain in addition to cutaneous symptoms
- **Severe anaphylactic reaction** (hypoxia, hypotension, or neurologic compromise): May have cyanosis or partial pressure of arterial oxygen (PaO_2) ≤92% at any stage, hypotension (systolic blood pressure <90 mm Hg), confusion, loss of consciousness, or neurologic compromise

Differential Diagnosis

- Anaphylaxis due to **preformed IgE and reexposure**: Medications, insect sting, and foods are the most common causes of anaphylaxis. Galactose-α-1,3-galactose allergy is thought to be triggered by tick bites and is a cause of delayed anaphylaxis to red meats including beef, pork, and lamb.
- Causes of **nonallergic anaphylaxis**:
  - **Radiocontrast sensitivity reactions** are thought to be from direct degranulation of mast cells in susceptible patients due to osmotic shifts. Reactions can occur in 5-10% of patients, with fatal reactions occurring in 1 in 40,000 procedures.
  - **Red man's syndrome** from vancomycin consists of pruritus and flushing of the face and neck.

TABLE 11-2 Anaphylaxis

Anaphylaxis is likely when one of the following three criteria occurs:

1. Acute skin and/or mucosal symptoms (e.g., hives, pruritus, flushing, lip/tongue/uvula swelling) and one of the following:

- Respiratory symptoms (e.g., wheezing, stridor, shortness of breath, hypoxia)
- Hypotension or associated end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Exposure to probable allergen for the patient and two or more of the following:
   - Skin/mucosal tissue involvement
   - Respiratory symptoms
   - Hypotension or end-organ dysfunction
   - Persistent gastrointestinal symptoms (e.g., emesis, abdominal pain)
3. Decreased blood pressure after exposure to known allergen for the patient:
   - Adults: Systolic blood pressure <90 mm Hg or >30% decrease in systolic blood pressure
   - Infants and children: Hypotension for age or >30% decrease in systolic blood pressure

---

Adapted from Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

- **Mastocytosis** should be considered in patients with recurrent unexplained anaphylaxis or flushing, especially with previous reactions to nonspecific mast cell degranulators such as opiates and radiocontrast media.
- **Ingestant-related reactions** can mimic anaphylaxis. This is usually due to sulfites or the presence of a histamine-like substance in spoiled fish (scombroidosis).
- **Flushing syndromes** include flushing due to red man's syndrome, carcinoid, vasointestinal peptide (and other vasoactive intestinal peptide-secreting tumors), postmenopausal symptoms, and alcohol use.

- Other forms of shock such as hypoglycemic, cardiogenic, septic, and hemorrhagic.
- Miscellaneous syndromes such as hereditary angioedema (C1 esterase inhibitor [C1 INH] deficiency syndrome), pheochromocytoma, neurologic (seizure, stroke), and capillary leak syndrome.
- Idiopathic.

Diagnostic Testing

- Epicutaneous skin testing and serum specific IgE testing when available to identify trigger allergens.
- Serum tryptase peaks at 1 hour after symptoms begin and may be present for up to 6 hours.

TREATMENT

- Early recognition of signs and symptoms of anaphylaxis is a critical first step in treatment.
- **Epinephrine is the medication of choice for treatment of anaphylaxis.**
- **Maintain recumbent position while assessing and starting therapy.**
- **Airway management is a priority.** Supplemental 100% oxygen therapy should be administered.

Endotracheal intubation may be necessary. If laryngeal edema is not rapidly responsive to epinephrine, cricothyroidotomy or tracheotomy may be required.

- **Volume expansion with IV fluids** may be necessary. An initial bolus of 500-1000 mL normal saline should be followed by an infusion at a rate that is titrated to blood pressure (BP) and urine output.

Medications

- **Epinephrine** should be administered immediately. There are no absolute contraindications for treatment with epinephrine in anaphylaxis.
  - Adult: 0.3-0.5 mg (0.3-0.5 mL of a 1:1000 solution) IM in the lateral thigh, repeated at 10- to 15-minute intervals if necessary.
  - Child: 1:1000 dilution at 0.01 mg/kg or 0.1-0.3 mL administered IM in the lateral thigh, repeated at 10- to 15-minute intervals if necessary.
  - 0.5 mL of 1:1000 solution sublingually in cases of major airway compromise or hypotension.
  - 3-5 mL of 1:10,000 solution via central line.
  - 3-5 mL of 1:10,000 solution diluted with 10 mL of normal saline via endotracheal tube.
  - For protracted symptoms that require multiple doses of epinephrine, an IV epinephrine drip may be useful; the infusion is titrated to maintain adequate BP.
- **Glucagon**, given as a 1-mg (one-ampule) bolus and followed by a drip of up to 1 mg/h can be used to provide inotropic support for patients who are taking β-adrenergic antagonists. β-Adrenergic antagonist therapy increases the risk of anaphylaxis and renders the reaction more difficult to treat (*Ann Intern Med 1991;115:270*).
- **Inhaled β-adrenergic agonists** should be used to treat resistant bronchospasm.
- **Glucocorticoids** have no significant immediate effect but may prevent biphasic reactions. Methylprednisolone 1-2 mg/kg daily for 1-2 days.

- **Antihistamines** relieve skin symptoms but have no immediate effect on the reaction. They may shorten the duration of the reaction.
  - Adult: Diphenhydramine 25-50 mg IM or IV
  - Child: Diphenhydramine 12.5-25.0 mg IM or IV

REFERRAL

Referrals to an allergist for further evaluation should be offered to all patients with a history of anaphylaxis. More importantly, patients with *Hymenoptera* sensitivity should be evaluated to determine eligibility for venom immunotherapy.

Eosinophilia

GENERAL PRINCIPLES

- Eosinophils are a blood granulocyte that can be involved in a variety of infectious, allergic, neoplastic, and idiopathic diseases.
- Eosinophil maturation is promoted by granulocyte-macrophage colony-stimulating hormone (GM-CSF), interleukin (IL)-3, and IL-5.
- Eosinophils are normally seen in peripheral tissue such as mucosal tissues in the gastrointestinal and

respiratory tracts. They are recruited to sites of inflammation.

Definition

- The upper limit of normal varies for blood eosinophilia.
- A value >500 eosinophils/μL is abnormal in most cases.
- The extent of eosinophilia can be categorized as mild (500-1500 cells/μL), moderate (1500-5000 cells/μL), or severe (>5000 cells/μL).
- Degree of eosinophilia is *not* a reliable predictor of eosinophil-mediated organ damage.

Classification

- Peripheral eosinophilia can be divided into primary, secondary, or idiopathic.
  - Primary eosinophilia is seen with hematologic disorders where there may be a clonal expansion of eosinophils (chronic eosinophilic leukemia) or a clonal expansion of cells that stimulate eosinophil production (chronic myeloid or lymphocytic disorders).
  - Secondary eosinophilia has numerous causes such as parasites, allergic diseases, autoimmune disorders, toxins, medications, and endocrine disorders such as Addison disease.
  - Idiopathic eosinophilia is considered when primary and secondary causes are excluded.
- **Eosinophilia associated with atopic disease.**
  - In allergic rhinitis, increased nasal eosinophilia is more common than peripheral blood eosinophilia.
  - Nasal eosinophilia with or without blood eosinophilia may be seen in asthma, nasal polyposis, or nonallergic rhinitis with eosinophilia syndrome (NARES).
  - NARES is a syndrome of marked nasal eosinophilia and nasal polyps. These patients do not have a history of allergies, asthma, or aspirin sensitivity, and have negative skin tests and IgE levels.
  - Sputum eosinophilia is a common feature of asthma and suggests responsiveness to corticosteroid treatment.
- **Eosinophilia associated with pulmonary infiltrates.** This classification is inclusive of the pulmonary infiltrates with eosinophilia syndromes and the eosinophilic pneumonias.
  - **Allergic bronchopulmonary aspergillosis** (ABPA), an IgE-dependent immunologic reaction to *Aspergillus fumigatus* consisting of pulmonary infiltrates, proximal

    bronchiectasis, elevated serum IgE, positive skin testing, presence of precipitins to *Aspergillus*, and peripheral eosinophilia in patients with asthma or cystic fibrosis.
  - Disseminated coccidioidomycosis can lead to marked eosinophilia.
  - **Eosinophilic pneumonias** consist of pulmonary infiltrates with lung eosinophilia and are only occasionally associated with blood eosinophilia.
    - Acute eosinophilic pneumonia is an idiopathic disease that presents with fever, cough, dyspnea, and hypoxemia occurring for days to weeks, typically in males and in individuals who have recently started to smoke tobacco.

- Chronic eosinophilic pneumonia is an idiopathic disease that presents with fever, cough, dyspnea, and significant weight loss occurring for weeks to months, typically in females and nonsmokers. It is associated with peripheral blood eosinophilia. “The photographic negative of pulmonary edema” is a classic radiographic finding (radiographic pattern of predominately peripheral consolidation).
- Löffler syndrome is combination of blood eosinophilia and transient pulmonary infiltrates due to passage of helminthic larvae, usually *Ascaris lumbricoides*, through the lungs.
- Tropical pulmonary eosinophilia is a hypersensitivity response in the lung to lymphatic filariae. Peripheral blood microfilariae are usually not detected.

- **HIV.** Modest to marked eosinophilia of unknown cause can be seen occasionally in patients with HIV. The eosinophilia is usually due to reactions to medications, adrenal insufficiency due to cytomegalovirus with consequent eosinophilia, or eosinophilic folliculitis.
- **Eosinophilia associated with parasitic infection.** Various multicellular parasites or helminths such as *Ascaris*, hookworm, or *Strongyloides* can induce blood eosinophilia, whereas single-celled protozoan parasites such as *Giardia lamblia* do not. The level of eosinophilia reflects the degree of tissue invasion by the parasite. Eosinophilia is usually of the highest grade during the early phase of infection.
  - In cases of blood eosinophilia, ***Strongyloides stercoralis* infection must be excluded** because this helminth can set up a cycle of autoinfection leading to chronic infection with intermittent, sometimes marked, eosinophilia.
  - Tissue eosinophilia may not be accompanied by blood eosinophilia when the organism is sequestered within tissues (e.g., intact echinococcal cysts) or is limited to the intestinal lumen (e.g., *Ascaris* and tapeworms).
  - Among the helminths, the principal parasites that need to be evaluated are *S. stercoralis*, hookworm, and *Toxocara canis*. The diagnostic consideration can also vary according to geographic region.
  - There are some important caveats that need to be considered when evaluating patients for parasitic diseases and eosinophilia: *Strongyloides* can persist for decades without causing major symptoms and can elicit varying degrees of eosinophilia ranging from minimal to marked eosinophilia.
  - *T. canis* (visceral larva migrans) should be considered in children with a propensity to eat dirt contaminated by dog *Ascaris* eggs.
- **Eosinophilia associated with cutaneous disease.**
  - **Atopic dermatitis** is classically associated with blood and skin eosinophilia.
  - **Eosinophilic fasciitis (Shulman syndrome)** is characterized by acute erythema, swelling, and induration of the extremities progressing to symmetric induration of the skin that spares the fingers, feet, and face. It can be precipitated by exercise.
  - **Eosinophilic cellulitis (Wells syndrome)** presents with recurrent swelling of an extremity without tactile warmth and failure with antibiotic therapy.
  - **Eosinophilic pustular folliculitis** is a pruritic skin eruption that can be seen in patients with HIV.
  - **Episodic angioedema with eosinophilia** is a rare disease that leads to recurrent attacks of fever, angioedema, urticaria, weight gain, and blood eosinophilia without other organ damage.

  - **Angiolymphoid hyperplasia with eosinophilia:** Presents with eosinophilia and papules, plaques, and

http://internalmedicinebook.com

nodules on the head and neck.

- **Kimura disease** presents with eosinophilia and large subcutaneous masses on the head or neck of Asian men.

- **Eosinophilia associated with multiorgan involvement.**
  - **Drug-induced eosinophilia.** Numerous drugs, herbal supplements, and cytokine therapies (e.g., GM-CSF and IL-2) can cause blood and/or tissue eosinophilia. Druginduced eosinophilia typically responds to cessation of the culprit medication. Asymptomatic drug-induced eosinophilia does not necessitate cessation of therapy. However, end-organ involvement should always be investigated promptly.
  - **Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome,** is a small- and medium-vessel vasculitis with chronic rhinosinusitis, asthma, and peripheral blood eosinophilia (typically >1500 cells/μL). The onset of asthma and eosinophilia may precede the development of EGPA by several years.
    - Noted to have intravascular and extravascular eosinophilic granuloma formation and lung involvement with transient infiltrates on chest radiograph. Other manifestations include mononeuropathy or polyneuropathy, subcutaneous nodules, rash, gastroenteritis, renal insufficiency, cardiac arrhythmias, and heart failure.
    - Half of patients have antineutrophil cytoplasmic antibodies directed against myeloperoxidase (p-ANCA). Biopsy of affected tissue reveals a necrotizing vasculitis with extravascular granulomas and tissue eosinophilia.
    - Initial treatment involves high-dose glucocorticoids with the addition of cyclophosphamide if necessary. Maintenance therapy with azathioprine is recommended after remission is achieved. Leukotriene modifiers, like all systemic steroid-sparing agents (including inhaled steroids and omalizumab), have been associated with unmasking of EGPA due to a decrease in systemic steroid therapy; however, no evidence exists that these drugs *cause* EGPA (*Chest 2000;117:708*).
  - **Mastocytosis.** Systemic mastocytosis is characterized by infiltration of mast cells into various organs including the skin, liver, lymph nodes, bone marrow, and spleen. Peripheral eosinophilia can be seen in up to 20% of cases of systemic mastocytosis, and bone marrow biopsies often show an excess number of eosinophils.
  - **Endocrine disorders.** Adrenal insufficiency (e.g., Addison disease) in critically ill patients is associated with low-grade eosinophilia.
  - **Hypereosinophilic syndrome** (HES) is a proliferative disorder of eosinophils characterized by sustained eosinophilia >1500 cells/μL for ≥1 month documented on two occasions with eosinophil-mediated damage to organs such as the heart, gastrointestinal tract, kidneys, brain, and lung. All other causes of eosinophilia should be excluded to make the diagnosis (*J Allergy Clin Immunol 2012;130:607*).
    - HES occurs predominantly in men between the ages of 20-50 years and presents with insidious onset of fatigue, cough, and dyspnea.
    - Myeloproliferative variants of HES (M-HES) are characterized by constitutive expression of *FIP1L1/PDGFRA* fusion protein and elevated serum vitamin B12 levels. Unusual IL-5-producing T cells are found in the lymphocytic variant of HES (L-HES).
    - At presentation, patients typically are in the late thrombotic and fibrotic stages of eosinophil-mediated cardiac damage with signs of a restrictive cardiomyopathy and mitral regurgitation. An echocardiogram

may detect intracardiac thrombi, endomyocardial fibrosis, or thickening of the posterior mitral valve leaflet. Neurologic manifestations range from peripheral neuropathy to stroke or encephalopathy. Bone marrow examination reveals increased eosinophil precursors.

- **Acute eosinophilic leukemia** is a rare myeloproliferative disorder that is distinguished from HES by several factors: an increased number of immature eosinophils in the blood

and/or marrow, >10% blast forms in the marrow, and symptoms and signs compatible with an acute leukemia. Treatment is similar to other leukemias.

- **Lymphoma.** Eosinophilia can present in any T- or B-cell lymphoma. As many as 5% of patients with non-Hodgkin lymphoma and up to 15% of patients with Hodgkin lymphoma have modest peripheral blood eosinophilia. Eosinophilia in Hodgkin lymphoma has been correlated with IL-5 messenger RNA expression by Reed-Sternberg cells.
- **Atheroembolic disease.** Cholesterol embolization can lead to eosinophilia, eosinophiluria, renal dysfunction, livedo reticularis, increased erythrocyte sedimentation rate (ESR), and purple toes.
- **Immunodeficiency.** Hyper-IgE syndrome and Omenn syndrome can present with recurrent infections, dermatitis, and eosinophilia.

Epidemiology

In industrialized nations, peripheral blood eosinophilia is most often due to atopic disease, whereas helminthic infections are the most common cause of eosinophilia in the rest of the world.

Pathophysiology

Eosinophilic granules contain basic proteins, which bind to acidic dye. Once activated, eosinophils produce major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase, which are toxic to bacteria, helminths, and normal tissue.

DIAGNOSIS

There are two approaches that are useful for evaluating eosinophilia, either by associated clinical context (Table 11-3) or by degree of eosinophilia (Table 11-4).

Clinical Presentation

History

- A history is important in narrowing the differential diagnosis of eosinophilia. It is important to determine if the patient has symptoms of atopic disease (rhinitis, wheezing, rash) or cancer (weight loss, fatigue, fever, night sweats) and to evaluate for other specific organ involvement such as lung, heart, or nerves. Prior eosinophil count can help determine the duration and magnitude of eosinophilia.
- A complete medication list, including over-the-counter supplements, and a full travel, occupational, and dietary history should be obtained.
- Any pet contact should be ascertained for possible exposure to toxocariasis.

Physical Examination

Physical examination should be guided by the history, with a special focus on the skin, upper and lower respiratory tracts, and cardiovascular and neurologic systems.

Differential Diagnosis

- Various conditions can result in **eosinophilia associated with pulmonary infiltrates** (see Table 11-3). The presence of asthma should lead to consideration of ABPA or EGPA.
- The etiology of **eosinophilia associated with cutaneous lesions** (see Table 11-3) is guided by the appearance of the lesions and results of the skin biopsy. The diagnosis of EGPA cannot be made without a tissue biopsy showing infiltrating eosinophils and granulomas.
- When eosinophilia is marked and all other causes have been ruled out, the diagnosis of **HES** should be considered. Diagnosis requires a blood eosinophilia of >1500/μL on two occasions with associated organ involvement.

TABLE 11-3 Causes of Eosinophilia

Eosinophilia Associated with Atopic Disease
Allergic rhinitis
Asthma
Atopic dermatitis
Eosinophilia Associated with Pulmonary Infiltrates
Passage of larvae through the lung (Löffler syndrome)
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Tropical pulmonary eosinophilia
Allergic bronchopulmonary aspergillosis (ABPA)
Coccidioidomycosis
Eosinophilia Associated with Parasitic Infection
Helminths (*Ascaris lumbricoides*, *Strongyloides stercoralis*, *hookworm*, *Toxocara canis* or *Toxocara cati*, *Trichinella*)
Protozoa (*Dientamoeba fragilis*, *Sarcocystis*, and *Isospora belli*)
Eosinophilia Associated with Primary Cutaneous Disease
Atopic dermatitis
Eosinophilic fasciitis
Eosinophilic cellulitis
Eosinophilic folliculitis
Episodic angioedema with anaphylaxis
Eosinophilia Associated with Multiorgan Involvement
Drug-induced eosinophilia
Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome
Hypereosinophilic syndrome
Eosinophilic leukemia
Systemic mastocytosis
Lymphomas
Miscellaneous Causes
Eosinophilic gastroenteritis
Interstitial nephritis
Retroviral infections (HIV, human T-lymphotropic virus 1)
Eosinophilia myalgia syndrome

Transplant rejection
Atheroembolic disease
Adrenal insufficiency

Diagnostic Testing

Laboratories

- Initial laboratory evaluations generally include complete blood count (CBC) with differential and eosinophil count, liver function tests, serum chemistries and creatinine, markers of inflammation (e.g., ESR and/or C-reactive protein) and urinalysis. Further diagnostic studies are based on clinical presentations and initial findings. Mild **eosinophilia associated with symptoms of rhinitis or asthma** is indicative of underlying atopic disease, which can be confirmed by skin testing.
- Depending on the travel history, **stool examination** for ova and parasites should be done on three separate occasions. Because only small numbers of helminths may pass in the

stool and because tissue- or blood-dwelling helminths will not be found in the stool, **serologic tests** for antiparasite antibodies should also be sent. Such tests are available for strongyloidiasis, toxocariasis, and trichinellosis.

TABLE 11-4 Classification of Eosinophilia Based on the Peripheral Blood Eosinophil Count

Peripheral Blood Eosinophil Count (cells/μL)		
500-2000	2000-5000	>5000
Allergic rhinitis	Intrinsic asthma	Eosinophilia myalgia syndrome
Allergic asthma	Allergic bronchopulmonary aspergillosis	Hypereosinophilic syndrome
Food allergy	Helminthiasis	Episodic angioedema with eosinophilia
Urticaria	Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome	Leukemia
Addison disease	Drug reactions	
Pulmonary infiltrates with eosinophilia syndromes	Vascular neoplasms	

Solid neoplasms	Eosinophilic fasciitis
Nasal polyposis	HIV

- Diagnosis at the time of presentation with Löffler syndrome can be made by detection of *Ascaris* larvae in respiratory secretions or gastric aspirates but not stool.
- Sinus CT, nerve conduction studies, and testing for p-ANCA may be helpful in the diagnosis of EGPA.
- Peripheral blood smear and flow cytometry of lymphocyte subpopulations can aid in the diagnosis of hematologic malignancy. Bone marrow biopsy for pathologic, cytogenetic, and molecular testing on bone marrow and/or peripheral blood (e.g., for *FIP1L1*/*PDGFRA* mutation) may be required. Serum vitamin B_{12} level may be elevated in hematologic causes of HES.
- Evaluation for idiopathic HES should also consist of troponin measurement, echocardiogram, and ECG.
- Immunoglobulin levels are helpful if concerned for an immunodeficiency. Elevated immunoglobulin levels can be found in L-HES.
- A tryptase level is necessary if mastocytosis is considered as a cause of eosinophilia.

Imaging

CXR findings may also help to narrow the differential diagnosis.

- Peripheral infiltrates with central clearing are indicative of chronic eosinophilic pneumonia.
- Diffuse infiltrates in an interstitial, alveolar, or mixed pattern may be seen in acute eosinophilic pneumonia as well as drug-induced eosinophilia with pulmonary involvement.
- Transient infiltrates may be seen in Löffler syndrome, EGPA, or ABPA.
- Central bronchiectasis is a major criterion in the diagnosis of ABPA.
- A diffuse miliary or nodular pattern, consolidation, or cavitation may be found in cases of tropical pulmonary eosinophilia.

Diagnostic Procedures

- If no other cause of pulmonary infiltrates has been identified, a **bronchoscopy** may be necessary for analysis of bronchoalveolar lavage (BAL) fluid and lung tissue. The presence of eosinophils in BAL fluid or sputum with eosinophilic infiltration of the parenchyma is most typical of acute or chronic eosinophilic pneumonia.
- Skin biopsy will aid in diagnosing the cutaneous eosinophilic diseases and EGPA.

TREATMENT

- Mild eosinophilia with no evidence of end-organ damage may not need treatment.
- Oral steroids are indicated when there is evidence of organ involvement. However, strongyloidiasis must be excluded prior to administration of steroids to prevent hyperinfection syndrome.
- When a drug reaction is suspected, discontinuation of the drug is both diagnostic and therapeutic. Other treatment options depend on the exact cause of eosinophilia because, with the exception of HES,

eosinophilia is a manifestation of an underlying disease.

- **HES:** Patients with marked eosinophilia with no organ involvement may have a benign course. In contrast, those with organ involvement and *FIP1L1/PDGFRA*-associated disease may have an extremely aggressive course without treatment.
  - Monitoring and early initiation of high-dose glucocorticoids should be pursued in all patients except those who have the *FIP1L1/PDGFRA* fusion gene.
  - Patients with the *FIP1L1/PDGFRA* fusion mutation should be started on imatinib mesylate (Gleevec), a tyrosine kinase inhibitor. Treatment should be initiated promptly in these patients to prevent progression of cardiac disease and other end-organ damage. Imatinib has been shown to induce disease remission and halt progression (*Blood 2003;101:4714*).
  - Hydroxyurea has been the most frequently used effective second-line agent and/or steroid-sparing agent for HES. Interferon-α2b in combination with glucocorticoids has been used to treat L-HES. Hematopoietic cell transplantation may be considered in refractory HES.
  - Mepolizumab, a humanized anti-IL-5 antibody, has shown promising results in patients who do not have the *FIP1L1/PDGFRA* fusion protein (*N Engl J Med 2008; 358:1215*).
  - Alemtuzumab, an anti-CD52 antibody (CD52 is expressed on the surface of eosinophils), has been shown in a clinical trial to decrease eosinophils counts (*Clin Cancer Res 2009;15:368*).
- Primary eosinophilia disorders should be followed by a specialist; any cases of unresolved or unexplained eosinophilia warrant evaluation by an allergist/immunologist.

Urticaria and Angioedema

GENERAL PRINCIPLES

Definition

- **Urticaria** (hives) are raised, flat-topped, well-demarcated pruritic skin lesions with surrounding erythema. Central clearing can cause an annular lesion and is often seen after antihistamine use. An individual lesion usually lasts minutes to hours.
- **Angioedema** is swelling of the deep dermis and subcutaneous tissue. It is often painful rather than pruritic. It can be found anywhere on the body but most often involves the tongue, lips, eyelids, and/or genitals. When angioedema occurs without urticaria, specific diagnoses must be entertained (see Differential Diagnosis section).

Classification

- **Acute urticaria (with or without angioedema)** is defined as the occurrence of hives and/or angioedema lasting <6 weeks. It can be caused by an allergic reaction to a medication, food, insect sting, or exposure (contact or inhalation) to an allergen. Patients can develop a hypersensitivity to a food, medication, or self-care product that previously had been used without difficulty. In many cases of acute urticaria, no identifiable trigger can be found.
- **Chronic urticaria (with or without angioedema)** is defined as the occurrence of hives and/or angioedema for >6 weeks. There are many possible causes of chronic urticaria and angioedema, including medications, autoimmunity, self-care products, and physical triggers. However, the etiology remains unidentified in >80% of

cases.

Epidemiology

- Urticaria is a common condition that affects 15-24% of the US population at some time in their life. Chronic idiopathic urticaria occurs in 0.1% of the US population, and there does not appear to be an increased risk in persons with atopy.
- Angioedema generally lasts 12-48 hours and occurs in 40-50% of patients with urticaria.

Etiology

- IgE-mediated: Drugs, foods, stinging and biting insects, latex, inhalant, or contact allergen
- Non-IgE-mediated: narcotics, muscle relaxants, radiocontrast, vancomycin, NSAIDs, ACE-inhibitors
- Transfusion reactions
- Infections (i.e., viral, bacterial, parasitic)
- Autoimmune diseases
- Malignancy
- Physical urticaria: Dermographism, cold, cholinergic, pressure, vibratory, solar, and aquagenic
- Mastocytosis
- Hereditary diseases
- Idiopathic

Pathophysiology

Most forms of urticaria and angioedema are caused by the degranulation of mast cells or basophils and the release of inflammatory mediators. Histamine is the primary mediator and elicits edema (wheal) and erythema (flare). Hereditary angioedema and related syndromes are mediated by the overproduction of bradykinin and are not responsive to antihistamines.

DIAGNOSIS

Diagnosis is based on complete history and physical examination, which should elicit identifiable triggers.

Clinical Presentation

- Patients with an acute urticaria episode present with history of pruritic, raised, erythematous lesions. Individual lesions resolve over a period of 1-24 hours.
- Angioedema usually presents with painful swelling without pruritus. The swelling can take up to 72 hours to resolve.

History

- A detailed history should elicit identifiable triggers and rule out any systemic causes. This also includes determining whether an individual lesion lasts >24 hours, in which case the diagnosis of urticarial vasculitis must be investigated by a skin biopsy.
- Any changes in environmental exposures, foods, medications, personal care products, etc., should be

determined.

- It is important to differentiate from anaphylaxis, which affects organs other than the skin, as this will be treated differently (see Anaphylaxis section).

Physical Examination

- Complete examination of the affected and nonaffected skin.
- Urticaria appears as erythematous, raised lesions that blanch with pressure.
- Angioedema appears as swelling; can often involve the face, tongue, extremities, or genitalia; and may be asymmetric.

Differential Diagnosis

- IgE-mediated allergic reaction to drugs, foods, insects, inhalant, or contact allergen.
- Non-IgE-mediated drug and food reactions (i.e., medications including NSAIDs, vancomycin, radioactive iodine, opiates, muscle relaxants, foods including tomatoes and strawberries).
- Physical urticaria.
- Mast cell release syndromes (i.e., systemic mastocytosis, cutaneous mastocytosis including urticaria pigmentosa).
- Cutaneous small-vessel vasculitis (i.e., urticarial vasculitis, systemic lupus erythematosus).
- Toxic drug eruptions.
- EM.
- Allergic contact dermatitis (i.e., poison ivy, poison oak).
- **Angioedema without urticaria** should lead to consideration of specific entities.
    - Use of ACE-inhibitors or **angiotensin II receptor blockers** (ARBs) can be associated with angioedema at any point in the course of therapy.
    - **Hereditary angioedema (HAE), or C1 INH deficiency,** is inherited in an autosomal dominant pattern; 25% of cases arise from de novo mutations.
    - **Acquired C1 INH deficiency** presents similarly to HAE but is typically associated with an underlying lymphoproliferative disorder or connective tissue disease.

Diagnostic Testing

Epicutaneous skin testing and patch testing are only indicated when symptoms are associated with specific triggers.

Laboratories

- Routine laboratory testing in the absence of a clinical history is rarely helpful in determining an etiology in chronic urticaria.
- One can consider the following limited routine laboratory testing to evaluate for systemic disease that can lead to chronic urticaria: CBC with differential, ESR, thyroid-stimulating hormone, renal and liver profiles.
- Autologous serum skin testing, assays for basophil histamine release, and autoantibodies to IgE and the high-affinity IgE receptor are available, but the utility of these tests has not been established.
- All patients with **angioedema without urticaria should be screened with a C4 level, which is reduced during and between attacks of HAE.** If the C4 level is reduced, a quantitative and functional C1 INH assay should be performed. Measuring C1 INH levels alone is not sufficient because 15% of

patients have normal levels of a dysfunctional C1 INH protein; therefore, it is important to also obtain the functional assay.

- Acquired C1 INH deficiency patients have reduced C1q, C1 INH, and C4 levels. Other patients with the acquired form have an autoantibody to C1 INH with low C4 and C1 INH levels but a normal C1 level.

Diagnostic Procedures

- A skin biopsy should be performed if individual lesions persist for >24 hours to rule out urticarial vasculitis.
  - Biopsy of acute urticarial lesions reveals dilation of small venules and capillaries located in the superficial dermis with widening of the dermal papillae, flattening of the rete pegs, and swelling of collagen fibers.
  - Chronic urticaria is characterized by a dense, nonnecrotizing, perivascular infiltrate consisting of T lymphocytes, mast cells, eosinophils, basophils, and neutrophils.
- Angioedema shows similar pathologic alterations in the deep, rather than superficial, dermis, and subcutaneous tissue.

TREATMENT

- The ideal treatment of acute urticaria with or without angioedema is identification and avoidance of specific causes. **All potential causes should be eliminated.** Most cases resolve within 1 week. In some instances, it is possible to reintroduce an agent cautiously if it is believed not to be the etiologic agent. This trial should be done in the presence of a physician with epinephrine readily available.
- Careful consideration should be given to the **elimination or substitution of each prescription or over-the-counter medication** or supplement. If a patient reacts to one medication in a class, the reaction likely will be triggered by all medications in that class. Exacerbating agents (e.g., NSAIDs, opiates, vancomycin, and alcohol) should be avoided because they may induce nonspecific mast cell degranulation and exacerbate urticaria caused by other agents.
- In patients presenting with hereditary and acquired angioedema, a prompt assessment of airway is critical, especially in those presenting with a laryngeal attack.

Medications

If acute urticaria is associated with additional systemic symptoms such as hypotension, laryngeal edema, or bronchospasm, treatment with epinephrine (0.3-0.5 mL of a 1:1000 solution IM) should be administered immediately. See Anaphylaxis section for additional information.

First Line

- **Acute urticaria and/or angioedema**
  - **Second-generation antihistamines** such as cetirizine, fexofenadine, or loratadine should be administered to patients until the hives have cleared. Higher than conventional, US Food and Drug Administration-approved doses may provide more efficacy. A first-generation antihistamine such as hydroxyzine may be added as an evening dose if needed to obtain control in refractory cases. H_2 antihistamines, such as ranitidine, may also be added to the above treatment.

- **Oral corticosteroids** should be reserved for patients with moderate to severe symptoms. Corticosteroids will not have an immediate effect but may prevent relapse.
- If a patient presents with systemic symptoms, self-administered epinephrine should be prescribed for use in the case of anaphylaxis.

- **Chronic urticaria**
  - A stepwise approach has been suggested for the treatment of chronic urticaria (*J Allergy Clin Immunol 2014;133(5):1270*).
  - Step 1: Monotherapy with a second-generation H1 antihistamine.

  - Step 2: One or more of the following:
    - Dose advancement of the second-generation H1 antihistamine, up to four times the conventional dose
    - Addition of another second-generation H1 antihistamine
    - Addition of H_2 antihistamine
    - Addition of leukotriene receptor antagonist
    - Addition of first-generation H1 antihistamine to be taken at bedtime
  - Step 3: Dose advancement of a potent antihistamine (i.e., doxepin, hydroxyzine) as tolerated. This is limited by sedation; use with caution in the elderly.
  - Step 4: Add an alternative agent.
    - Omalizumab: Proven safe and effective in several randomized clinical trials in patients with chronic urticaria not responsive to standard dose of H1 antihistamines
    - Cyclosporine
    - Other anti-inflammatory agents, immunosuppressants, or biologics
  - **Optimal duration of therapy has not been established; tapering medications after 3-6 months of symptom control has been suggested.**

- **Hereditary and acquired angioedema (disorder of C1 inhibitor)**

  Laryngeal attacks or severe abdominal attacks: C1 inhibitor concentrate, icatibant, and ecallantide are first-line agents. If none of the first-line agents are available, fresh frozen plasma can be used. Also pursue symptomatic therapy and rehydration.

REFERRAL

All patients with chronic urticaria or a history of anaphylaxis should be referred to an allergy specialist for evaluation to identify potential allergic and autoimmune triggers.

Immunodeficiency

GENERAL PRINCIPLES

Definition

- Primary immunodeficiencies (PIDs) are disorders of the immune system that result in an increased susceptibility to infection.

- Secondary immunodeficiencies are also disorders of increased susceptibility to infection but are attributable to an external source.

Classification

PIDs can be organized by the defective immune components with considerable heterogeneity in each disorder.

- **Predominantly antibody deficiencies:** The defect is primarily in the ability to make antibodies.
  - Common variable immune deficiency (CVID)
  - X-linked (Bruton) agammaglobulinemia
  - IgG subclass deficiency
  - Specific antibody deficiency
  - Selective IgA deficiency
- **Combined immunodeficiencies and syndromes:** The defect results in deficiencies in both cellular and humoral immune responses.
  - Severe combined immunodeficiencies (SCIDs)
  - DiGeorge syndrome
  - Hyper-IgE (Job) syndrome

  - **Defects of innate immunity:** Defects in germline-encoded receptors and downstream signaling pathways
  - Deficiency of Toll-like receptor (TLR) signaling
  - Mendelian susceptibility to mycobacterial diseases (MSMD)
  - Natural killer (NK) cell deficiency
  - Phagocytic cell deficiencies Chronic granulomatous disease (CGD)
- **Complement deficiencies.**
- **Diseases of immune dysregulation:** Autoimmunity and lymphoproliferation are characteristic manifestations in these disorders.

Epidemiology

- Secondary immunodeficiency syndromes, particularly HIV/AIDS, are the most common immunodeficiency disorders.
- The estimated prevalence of PIDs is approximately 1 in 1200 live births.
- Most PIDs presenting in adulthood are humoral immune defects.

Etiology

- Predominantly antibody immune deficiencies are thought to be caused by defects in B-cell maturation. Combined immunodeficiencies are caused by defective T-cell-mediated immunity and associated antibody deficiency.
- A variety of genetic mutations have been associated with specific PID syndromes.

- Secondary immunodeficiencies can be caused by medications (chemotherapy, immunomodulatory agents, corticosteroids), infectious agents (e.g., HIV), malignancy, antibody loss (e.g., nephrotic syndrome, protein losing enteropathy, or consumption during a severe underlying infection), autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis), malnutrition (vitamin D), and other underlying diseases (e.g., diabetes mellitus, cirrhosis, uremia).

DIAGNOSIS

Clinical Presentation

- The hallmark of PID is recurrent infections. Clinical suspicion should be increased by recurrent sinopulmonary infection, deep-seated infections, opportunistic infections, or disseminated infections in an otherwise healthy patient.
- Specific PIDs are often associated with particular types of pathogens (e.g., catalasepositive infections in CGD or MSMD).
- Recurrent urinary tract infections are only rarely associated with PID.
- Patients with PIDs may also present with autoimmunity, immune dysregulation, allergic diseases, and malignancies.
- **Selective IgA deficiency** is the most common immune deficiency, with a prevalence of 1 in 300-500 people.
  - Most patients are asymptomatic. Some may present with recurrent sinus and pulmonary infections. Therapy is directed at early treatment with antibiotics because IgA replacement is not available.
  - Associated autoimmune diseases are observed in 20-30% of cases. Absolute IgA-deficient patients (i.e., <7 mg/dL) are at risk for developing a severe transfusion reaction to blood products including IV immunoglobulin (IVIG), because of the presence in some individuals of IgE anti-IgA antibodies; therefore, these patients should be transfused with washed red blood cells or receive blood products only from IgA-deficient donors.

- **CVID** is the most common symptomatic PID, occurring with a frequency of 1/10,000. It includes a heterogeneous group of disorders in which most patients present in the second to fourth decade of life with recurrent sinus and pulmonary infections and are discovered to have low and dysfunctional IgG, IgA, and/or IgM antibodies with poor response to immunizations.
  - B-cell numbers are often normal, but there is decreased ability to produce immunoglobulin due to the lack of isotype-switched memory B cells. Some patients may also exhibit T-cell dysfunction.
  - CVID is largely idiopathic, although there are molecular defects in the B-cell signaling and development pathways (e.g., TACI, ICOS, BAFF-R, and CD19) with some forms of the disorder.
  - Patients with CVID are particularly susceptible to infection with encapsulated organisms. Patients may have associated gastrointestinal disease or autoimmune abnormalities (most commonly autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, pernicious anemia, and rheumatoid arthritis).
  - There is an increased incidence of malignancy, especially lymphoid and gastrointestinal malignancy.
  - Therapy consists of IVIG or subcutaneous immunoglobulin (SCIG) replacement therapy as well as prompt treatment of infections with antibiotics.
- **Specific antibody deficiency** is defined as poor or absent antibody responses to polysaccharide antigens (i.e., 23-valent pneumococcus vaccine) in the setting of normal levels of immunoglobulins and IgG subclasses.

- B-cell numbers and response to protein antigens (i.e., tetanus toxoid and diphtheria toxoid) are usually normal.
- Patients have increased susceptibility to sinopulmonary infections. Allergic diseases are also common.
- Therapeutic approaches include adequate antibiotic treatment for infections, pneumococcal conjugate vaccine, and sometimes immunoglobulin replacement.

- **X-linked (Bruton) agammaglobulinemia** clinically manifests very similarly to severe CVID and is typically diagnosed in childhood but can present in adulthood.
  - Patients usually have low levels of all immunoglobulin types and very low levels of B cells.
  - Specific genetic defect is in Bruton tyrosine kinase, which is involved in B-cell maturation.
- **Subclass deficiency.** Deficiencies of each of the IgG subclasses (IgG1, IgG2, IgG3, and IgG4) have been described.
  - These patients present with similar complaints as the CVID patients.
  - Total IgG levels may be normal. A strong association with IgA deficiency exists. There is disagreement as to whether this is a separate entity from CVID. In most cases, there is no need to evaluate IgG subclass levels.
  - Isolated subclass deficiency without recurrent infections is of unknown clinical significance.
- **Hyper-IgE syndrome (Job syndrome)** is characterized by recurrent pyogenic infections of the skin and lower respiratory tract. This syndrome can result in severe abscess and empyema formation. Some forms of the disease are associated with autosomal dominant mutation of *STAT3*.
  - The most common organism involved is *Staphylococcus aureus*, but other bacteria and fungi have been reported.
  - Patients present with recurrent infections and have associated pruritic dermatitis, coarse (lion-like) facies, growth retardation, scoliosis, retention of primary teeth, and hyperkeratotic nails.
  - Laboratory data reveal the presence of normal levels of IgG, IgA, and IgM but markedly elevated levels of IgE. A marked increase in tissue and blood eosinophils may also be observed.

- **Complement deficiencies** are a broad category of PID characterized by recurrent infections to a range of pathogens.
  - Recurrent disseminated neisserial infections are associated with a deficiency in the terminal complement system (C5-C9).
  - Systemic lupus-like disorders and recurrent infection with encapsulated organisms have been associated with deficiencies in other components of complement.
  - CH50 and AH50 are useful to screen for deficiencies of the classical pathway and alternative pathway, respectively.
- **CGD** is characterized by defective killing of intracellular pathogens by neutrophils.
  - Patients usually present with frequent infection, often with abscesses, from *S. aureus* and other catalase-positive organisms. *Aspergillus* is a particularly troublesome pathogen for patients with CGD.
  - Diagnosis is made by demonstration of defective respiratory burst with flow cytometry assay using dihydrorhodamine.
- **MSMD** is caused by defects in Th1 immunity and is associated with mutations in genes involved in interferon-γ and IL-12 signaling. Characteristic infections include mycobacterial infections (including

typical and atypical *Mycobacterium*) and *Salmonella* infections.

Diagnostic Testing

- Frequent sinopulmonary infections, recurrent and invasive infections requiring IV antimicrobial agents, infections with unusual pathogens, and family history of PID are warning signs for PIDs.
- Initial evaluation should focus on identifying possible secondary causes of recurrent infection such as allergy, medications, and anatomic abnormalities. Workup begins with a CBC with differential, HIV test, quantitative immunoglobulin levels, and complement levels. Often the evaluation will need to include enumeration of lymphocytes by flow cytometry if B-, T-, or NK-cell defects are suspected. Other specialized tests including genetic testing may be needed to make a definitive diagnosis.
- If clinical suspicion is high for an underlying antibody-predominant PID, B-cell function can be assessed by measuring immunoglobulin response to vaccinations. Preimmunization and postimmunization titers for both a protein antigen (i.e., tetanus) and a polysaccharide antigen (i.e., Pneumovax, the unconjugated 23-valent vaccine) are measured because proteins and polysaccharide antigens are handled differently by the immune system.
- Titers of specific antibodies are measured before and at 4-8 weeks after immunization.

TREATMENT

- Killed or subcomponent vaccines are safe for most patients with PID, although some patients may not produce full response. Live attenuated vaccines may be contraindicated in some individuals with PID and their families.
- Prophylactic antibiotics may be considered in some PID syndromes to prevent infections.
- IgA deficiency: No specific treatment is available. However, these patients should be promptly treated at the first sign of infection with an antibiotic that covers *Streptococcus pneumoniae* or *Haemophilus influenzae*.
- CVID should be treated with immunoglobulin replacement in forms of IVIG or SCIG. Numerous preparations of immunoglobulin are available, all of which undergo viral inactivation steps.

  Possible side effects include myalgias, vomiting, chills, and lingering headache (due to immune complex-mediated aseptic meningitis).

REFERRAL

Patients in whom a PID is being seriously considered should undergo evaluation by an allergist/clinical immunologist with expertise in diagnosing and treating PID.

12
Fluid and Electrolyte Management

Anubha Mutneja

Steven Cheng

Judy L. Jang

FLUID MANAGEMENT AND PERTURBATIONS IN VOLUME STATUS

- **Total body water (TBW).** Water comprises approximately 60% of lean body weight in men and 50% in women. TBW is distributed in two major compartments: two-thirds is **intracellular fluid** (ICF) and one-third is **extracellular fluid** (ECF). ECF is further subdivided into intravascular and interstitial spaces in a ratio of 1:4.
  - **Example:** For a healthy 70-kg man,

    TBW = 0.6 × 70 = 42 L
    - ICF = 2/3 TBW = 0.66 × 42 = 28 L
    - ECF = 1/3 TBW = 0.33 × 42 = 14 L
    - Intravascular compartment = 0.25 × 14 = 3.5 L
    - Interstitial compartment = 0.75 × 14 = 10.5 L
  - The distribution of water between intravascular and interstitial spaces can also be affected by changes to the Starling balance of forces. Low oncotic pressure (i.e., low albumin states) and high hydrostatic pressure (i.e., Na^+-retentive states) increase the movement of fluid from vascular to interstitial compartments, which is an important step in the development of edema.
  - Because the majority of water is contained in the intracellular space, the loss of water alone (without Na^+) does not typically result in the hemodynamic changes associated with volume depletion. Instead, disturbances in TBW change serum **osmolality** and electrolyte concentrations.
  - The intact kidney adapts to changes in TBW by increasing water excretion or reabsorption. This is mediated by the **antidiuretic hormone (ADH; vasopressin)**, which permits water movement across the distal nephron. Although vasopressin release is predominately responsive to osmotic cues, volume contraction can cause a nonosmotic release of vasopressin, resulting in a reduction of renal water excretion.
- **Total body Na^+**. 85-90% of **total body Na^+** is extracellular and constitutes the predominate solute in the ECF. Changes to the body's total Na^+ content typically results from a loss or gain of this Na^+-rich fluid, leading to contraction or expansion of the ECF space. Clinically, this manifests as volume depletion (hypotension, tachycardia) and volume expansion (peripheral or pulmonary edema).
  - Na^+ *concentration* is distinct from Na^+ *content*. Na^+ concentration reflects the amount of Na^+ distributed in a fixed quantity of water. An increase in TBW can decrease the Na^+ concentration even if the body's total Na^+ content remains unchanged.
  - The intact kidney can respond to altered Na^+ content in the ECF space by increasing or decreasing Na^+ reabsorption. This response is mediated by cardiovascular, renal, hepatic, and central nervous system

sensors of the effective circulating volume.

The Euvolemic Patient

- In a euvolemic patient, the goal of fluid and electrolyte administration is to maintain homeostasis. The best way to accomplish this is to allow free access to food and oral fluids.

Patients who are unable to tolerate oral input require maintenance fluids to replace renal, gastrointestinal (GI), and insensible fluid losses.

- The decision to provide maintenance IV fluid (IVF) should be thoughtfully considered and not administered by rote. Fluid administration should be reassessed *at least* daily. Patient weight, which may indicate net fluid balance, should be monitored carefully.
- Consider the **water** and **electrolyte** needs of the patient separately when prescribing IVF therapy.
  - Minimum **water** requirements for daily fluid balance can be approximated from the sum of the required urine output, stool water loss, and insensible losses.
    - The minimum urine output necessary to excrete the daily solute load is the amount of solute consumed each day (roughly 600-800 mOsm/d in an average individual) divided by the maximum amount of solute that can be excreted per liter of urine (maximum urine concentrating capacity is 1200 mOsm/L in healthy kidneys). The result is an obligate urine output of *at least* 0.5 L/d.
    - The water lost in stools is typically 200 mL/d.
    - **Insensible water losses** from the skin and respiratory tract amount to roughly 400-500 mL/d. The volume of water produced from endogenous metabolism (<250-350 mL/d) should be considered as well. The degree of insensible loss may vary tremendously depending on respiratory rate, metabolic state, and temperature (water losses increase by 100-150 mL/d for each degree of body temperature over 37°C).
    - Fluid from drain losses must be factored in as well.
    - After adding each of these components, the minimum amount of water needed to maintain homeostasis is roughly 1400 mL/d or 60 mL/h.
  - **Electrolytes** that are usually administered during maintenance fluid therapy are Na^+ and K^+ salts. Requirements depend on minimum obligatory and ongoing losses.
    - It is customary to provide **75-175 mEq Na^+/d** as NaCl. (A typical 2-g Na^+ diet provides 86 mEq Na^+/d.)
    - Generally, **20-60 mEq K^+/d** is included if renal function is normal.
    - Carbohydrate in the form of **dextrose**, **100-150 g/d**, is given to minimize protein catabolism and prevent starvation ketoacidosis.
  - Table 12-1 provides a list of common IV solutions and their contents. By combining the necessary components, one can derive an appropriate maintenance fluid regimen tailored for each patient.
  - **Example:** A patient is admitted for a procedure and is made nothing by mouth (NPO). To maintain homeostasis, you must replace 2 L of water, 154 mEq Na^+, 40 mEq K^+, and 100 g dextrose over the next 24 hours (values are within **water** and **electrolyte** requirements described earlier).
    - 2 L of water: Dose fluid at 85 mL/h (2000 mL ÷ 24 hours)
    - 154 mEq of Na^+: Use 0.45% normal saline (NS) (77 mEq Na^+/L)

- 40 mEq of K^+: Add 20 mEq/L KCl to each liter of IVF
- 100 g dextrose: Use D5 (50 g of dextrose/L)
- Order: **D5 0.45% NaCl with 20 mEq/L KCl at 85 mL/h**

The Hypovolemic Patient

GENERAL PRINCIPLES

- Volume depletion generally results from a deficit in **total body Na^+** content. This may result from **renal** or **extrarenal losses** of Na^+ from the ECF. **Water** losses alone can also

cause volume depletion, but the quantity required to do so is large, as water is lost mainly from the ICF and not the ECF, where volume contraction can be assessed.

TABLE 12-1 Commonly Used Parenteral Solutions

IV Solution	Osmolality (mOsm/L)	[Glucose] (g/L)	[Na^+] (mEq/L)	[Cl^-] (mEq/L)	HCO_3^- Equivalents (mEq/L)
D5W	278	50	0	0	0
0.45% NaCl[a]	154	—[b]	77	77	0
0.9% NaCl[a]	308	—[b]	154	154	0
3% NaCl	1,026	—	513	513	0
Lactated Ringer's[c]	274	—[b]	130	109	28

D5W, 5% dextrose in water.

[a]NaCl 0.45% and 0.9% are half-normal and normal saline, respectively.

[b]Also available with 5% dextrose.

[c]Also contains 4 mEq/L K^+, 1.5 mEq/L Ca^{2+}, and 28 mEq/L lactate.

- **Renal losses** may be secondary to enhanced diuresis, salt-wasting nephropathies, mineralocorticoid deficiency, or resolution of obstructive renal disease.
- **Extrarenal losses** include fluid loss from the GI tract (vomiting, nasogastric suction, fistula drainage,

diarrhea), respiratory losses, skin losses (especially with burns), hemorrhage, and severe third spacing of fluid in critically ill patients.

DIAGNOSIS

Clinical Presentation

- **Symptoms** include complaints of thirst, fatigue, weakness, muscle cramps, and postural dizziness. Sometimes, syncope and coma can result with severe volume depletion.
- **Signs** of hypovolemia include low jugular venous pressure, postural hypotension, postural tachycardia, and the absence of axillary sweat. Diminished skin turgor and dry mucous membranes are poor markers of decreased interstitial fluid. Mild degrees of volume depletion are often not clinically detectable, whereas larger fluid losses can lead to mental status changes, oliguria, and hypovolemic shock.

Diagnostic Testing

Laboratory studies are often helpful but must be used in conjunction with the clinical picture.

- **Urine sodium** is a marker for Na^+ avidity in the kidney.
  - Urine Na^+ <15 mEq is consistent with volume depletion, as is a fractional excretion of sodium (FeNa) <1%. The latter can be calculated as ([Urine Na^+ × Serum Cr] ÷ [Urine Cr × Serum Na^+]) × 100.
  - Concomitant metabolic alkalosis may increase urine Na^+ excretion despite volume depletion due to obligate excretion of Na^+ to accompany the bicarbonate anion. In such cases, a urine chloride of <20 mEq is often helpful to confirm volume contraction.
- **Urine osmolality** and **serum bicarbonate** levels may also be elevated.
- **Hematocrit** and **serum albumin** may be increased from hemoconcentration.

TREATMENT

- It is often difficult to estimate the **volume deficit** present, and thus, therapy is largely empiric, requiring frequent reassessments of volume status while resuscitation is under way.
- Mild volume contraction can usually be corrected via the oral route. However, the presence of hemodynamic instability, symptomatic fluid loss, or intolerance to oral administration requires IV therapy.
- The primary therapeutic goal is to protect hemodynamic stability and replenish **intravascular volume** with fluid that will preferentially expand the ECF compartment. This can be accomplished with Na^+-based solutions, because the Na^+ will be retained in the ECF.
  - **Isotonic fluid**, such as NS (0.9% NaCl), contains a Na^+ content similar to that of plasma fluid in the ECF and thus remains entirely in the ECF space. It is the initial fluid of choice for replenishing **intravascular volume**.
    - The administration of solute-free water is largely ineffective, because the majority of water will distribute to the ICF space.
    - Half-normal saline (0.45% NS) has 77 mEq of Na^+ per liter, roughly half the Na^+ content of an equal volume in the ECF. Thus, half of this solution will stay in the ECF, and half will follow the predicted distribution of water.

- Fluids can be administered as a bolus or at a steady maintenance rate. In patients with symptomatic volume depletion, a 1- to 2-L bolus is often preferable to acutely expand the intravascular space. The bolus can be repeated if necessary, although close attention should be directed toward possible signs of volume overload. Smaller boluses should be used for patients with poor cardiac reserve or significant edema. Once the patient is stable, fluids can be administered at a maintenance rate to replace ongoing losses. In patients with hemorrhage or GI bleeding, **blood transfusion** can accomplish both volume expansion and concomitant correction of anemia.

The Hypervolemic Patient

The clinical manifestations of hypervolemia result from a surplus of **total body Na^+**. It can be caused by a primary disorder of renal Na^+ retention. Alternatively, it may be secondary to decreased **effective circulating volume**, as in heart failure, cirrhosis, or profound hypoalbuminemia.

DIAGNOSIS

Clinical Presentation

- Expansion of the **interstitial compartment** may result in peripheral edema, ascites, and pleural effusions. Expansion of the **intravascular compartment** may result in pulmonary rales, elevated jugular venous pressure, hepatojugular reflux, an S_3 gallop, and elevated blood pressures.
- Because overt signs of hypervolemia may not manifest until 3-4 L of fluid retention, a gradual rise in water weight is often the earliest indication of Na^+ retention.
- **Symptoms** may include dyspnea, abdominal distention, or swelling of extremities.

Diagnostic Testing

- Laboratory studies are generally not needed, and hypervolemia is primarily a bedside diagnosis.
- **The urine [Na^+]** may be low (<15 mEq/L) with decreased **effective circulating volume** reflecting renal sodium retention.
- A CXR may show pulmonary edema or pleural effusions, but clear lung fields do not exclude volume overload.

TREATMENT

Treatment must address not only the ECF volume excess but also the underlying pathologic process. Alleviating the Na^+ excess can be accomplished by the judicious use of diuretics and by limiting Na^+ intake.

Medications

- Diuretics enhance the renal excretion of Na^+ by blocking the various sites of Na^+ reabsorption along the nephron.
  - Thiazide diuretics block the NaCl transporters in the distal convoluted tubule. They are often used for mild states of chronic Na^+ retention. Because of their specific site of action, thiazide diuretics impair urinary dilutional capacity (the ability to excrete water) and often stimulate a responsive increase in proximal tubule reabsorption.

- Loop diuretics block the Na^+-K^+-$2Cl^-$ transporter in the thick ascending loop of Henle. They are often used in circumstances requiring a brisk and immediate diuresis, such as acute volume overload. Loop diuretics impair urinary concentration (increase renal free water excretion) and enhance the excretion of divalent cations (Ca^{2+} and Mg^{2+}).
- Potassium-sparing diuretics act by decreasing Na^+ reabsorption in the collecting duct. Although the overall diuretic effect of these agents is comparatively small, they serve as useful adjunctive agents. Furthermore, because aldosterone antagonists do not require tubular secretion, they can be particularly useful in those with decreased renal perfusion or impaired tubular function.

- Treatment of the underlying disease process is critical to prevent continued Na^+ reabsorption in the kidney. Nephrotic syndrome is discussed in Chapter 13, Renal Diseases. Treatment of heart failure is discussed in Chapter 5, Heart Failure and Cardiomyopathy, and cirrhosis is addressed in Chapter 19, Liver Diseases.

Disorders of Sodium Concentration

Hypernatremia and **hyponatremia** are primarily disorders of *water balance* or *water distribution*. The body is designed to withstand both drought and deluge with adaptations to renal water handling and the thirst mechanism. A persistent abnormality in [Na^+] thus requires both an initial challenge to water balance as well as a disturbance of the adaptive response.

Hyponatremia

Hyponatremia is defined as a plasma [Na^+] <**135 mEq/L**.

GENERAL PRINCIPLES

- To maintain a normal [Na^+], the ingestion of water must be matched with an equal volume of water excretion. Any process that limits the elimination of water or expands the volume around a fixed Na^+ content may lead to a decrease in Na^+ concentration.
- Expansion of the space surrounding the Na^+ content can occur in a variety of ways:
  - **Pseudohyponatremia** refers to a laboratory phenomenon by which a high content of plasma proteins and lipids expands the nonaqueous portion of the plasma sample, leading to an errant report of a low ECF [Na^+]. This can be averted with Na^+-sensitive electrodes, and the normal ECF [Na^+] can be confirmed with a normal serum osmolality.
  - **Hyperosmolar hyponatremia** refers to circumstances in which an osmotically active solute other than Na^+ accumulates in the ECF, drawing water into the ECF and

diluting the Na^+ content. This is most commonly caused by **hyperglycemia**, resulting in a fall in plasma [Na^+] of 1.6-2.4 mEq/L for every 100 mg/dL rise in plasma glucose (*Am J Med 1999;106:399*). Other solutes, such as glycine, mannitol, or sorbitol, can be absorbed into the ECF during bladder irrigation, leading to the transient hyponatremia seen in **post-transurethral resection of the prostate (post-TURP) syndrome**. Prompt renal excretion and metabolism of the absorbed fluid usually corrects the hyponatremia rapidly, although symptomatic hyponatremia can occasionally be seen in the setting of renal insufficiency.

- Rarely, the ECF water content rises simply because the ingested quantity of water exceeds the physiologic capacity of water excretion in the kidney. This is seen in psychogenic polydipsia, water intoxication from poorly conceived drinking games, beer potomania, and the so-called “tea and toast” diet. Underlying each of these circumstances is the fact that there is a limit to renal water clearance. Urine cannot be diluted to an osmolality less than approximately 50 mOsm/L, meaning that a small amount of solute is required in even the most dilute urine. Ingestion of a high volume of water can thus exceed the capacity for excretion, particularly in those with a solute-poor diet, because the solute load required to generate urinary water loss is quickly depleted. The excess water is retained, Na^+ concentrations falls, and hyponatremia results.

- Decreased clearance of water from the kidney can also occur through a variety of processes. As mentioned previously, renal water handling is largely controlled by ADH (or vasopressin). Nonosmotic stimulation of this hormone occurs with volume contraction. Although this seems counterintuitive from an osmotic standpoint (it further reduces renal water clearance and increases water retention), it is an “appropriate” adaptive response to the threat of volume loss, tissue hypoperfusion, and impending hemodynamic collapse. Other conditions are characterized by secretion of ADH, which is “inappropriate,” stimulated by neither osmotic nor volume-related changes.
- **“Appropriate”** ADH secretion occurs with a fall in effective circulating volume. In these conditions, thirst and water retention are stimulated, protecting volume status at the cost of the osmolar status. This category is classically subdivided based on the associated assessment of ECF status.
  - **Hypovolemic hyponatremia** may result from **any** cause of net Na^+ loss, such as in thiazide use and cerebral salt wasting.
  - **Hypervolemic hyponatremia** occurs in edematous states such as congestive heart failure (CHF), hepatic cirrhosis, and severe nephrotic syndrome. Despite the expanded interstitial space, the circulating volume is reduced. Alterations in Starling forces contribute to this apparent paradox, shifting fluid from the intravascular to interstitial space.
- **“Inappropriate”** secretion of ADH is characterized by the activation of water-conserving mechanisms despite the absence of osmotic- or volume-related stimuli. Because the renal response to volume expansion remains intact, these patients are typically **euvolemic**. However, because of the rise in TBW, serum concentrations of Na^+ are decreased.
  - The most common form of this is the **syndrome of inappropriate ADH (SIADH)**. This disorder is caused by the nonphysiologic release of vasopressin from the posterior pituitary or an ectopic source. Common causes of SIADH include neuropsychiatric disorders (e.g., meningitis, encephalitis, acute psychosis, cerebrovascular accident, head trauma), pulmonary diseases (e.g., pneumonia, tuberculosis, positive-pressure ventilation, acute respiratory failure), and malignant tumors (most commonly, small-cell lung cancer).
    - **SIADH** is diagnosed by the following:

      Hypo-osmotic hyponatremia

      Urine osmolality >100 mOsm/L

      Euvolemia

      The absence of conditions that stimulate ADH secretion, including volume contraction, nausea, adrenal dysfunction, and hypothyroidism

http://internalmedicinebook.com

- **Pharmacologic agents** may also stimulate inappropriate ADH secretion. Common culprits include antidepressants (particularly selective serotonin reuptake inhibitors [SSRIs]), narcotics, antipsychotic agents, chlorpropamide, and NSAIDs.

- **Reset osmostat** is a phenomenon in which the set point for plasma osmolality is reduced. Thus, ADH and thirst responses, although functional, maintain plasma osmolality at this new, lower level. This phenomenon occurs in almost all pregnant women (perhaps in response to changes in the hormonal milieu) and occasionally in those with a chronic decreased effective circulating volume.

DIAGNOSIS

Clinical Presentation

The clinical features of hyponatremia are related to the osmotic intracellular water shift leading to cerebral edema. Therefore, the symptoms are primarily neurologic, and their severity is dependent on both the magnitude and rapidity of decrease in plasma [Na^+]. In **acute hyponatremia** (i.e., developing in <2 days), patients may complain of nausea and malaise with [Na^+] of approximately 125 mEq/L. As the plasma [Na^+] falls further, symptoms may progress to include headache, lethargy, confusion, and obtundation. Stupor, seizures, and coma do not usually occur unless the plasma [Na^+] falls acutely below 115 mEq/L. In **chronic hyponatremia** (>3 days in duration), adaptive mechanisms designed to defend cell volume occur and tend to minimize the increase in ICF volume and its symptoms.

Diagnostic Testing

The underlying cause of hyponatremia can often be ascertained from an accurate history and physical examination, including an assessment of **ECF volume status** and the **effective circulating volume**.

Three laboratory analyses, when used with a clinical assessment of volume status, can narrow the differential diagnosis of hyponatremia: (a) the **plasma osmolality**, (b) the **urine osmolality**, and (c) the **urine [Na^+]** (Figure 12-1).

- **Plasma osmolality.** Most patients with hyponatremia have a low plasma osmolality (<275 mOsm/L). If the plasma osmolality is not low, **pseudohyponatremia** and **hyperosmolar hyponatremia** must be ruled out.
- **Urine osmolality.** The appropriate renal response to hypo-osmolality is to excrete a maximally dilute urine (urine osmolality <100 mOsm/L and specific gravity <1.003). A urine sample that is not dilute suggests impaired free water excretion due to appropriate or inappropriate secretion of the ADH.
- **Urine [Na^+]** adds laboratory corroboration to the bedside assessment of effective circulating volume and can discriminate between **extrarenal** and **renal losses** of Na^+. The appropriate response to decreased effective circulating volume is to enhance tubular Na^+ reabsorption such that urine [Na^+] is <10 mEq/L. A urine [Na^+] of >20 mEq/L suggests a normal effective circulating volume or a Na^+-wasting defect. Occasionally, the excretion of a nonreabsorbed anion obligates loss of the Na^+ cation despite volume depletion (ketonuria, bicarbonaturia).

TREATMENT

- Management requires one to determine **the rate of correction**, **the appropriate intervention**, and **the presence of other underlying disorders**.

- The **rate of correction** of hyponatremia depends on the acuity of its development and the presence of neurologic dysfunction.
- **Acute symptomatic hyponatremia.** Severe symptomatic hyponatremia, with evidence of neurologic dysfunction, should generally be treated promptly with hypertonic saline;

however, any saline solution that is **hypertonic to the urine** (if the urine osmolality is known at the start of therapy) can increase the [Na+] when oral water intake is restricted.

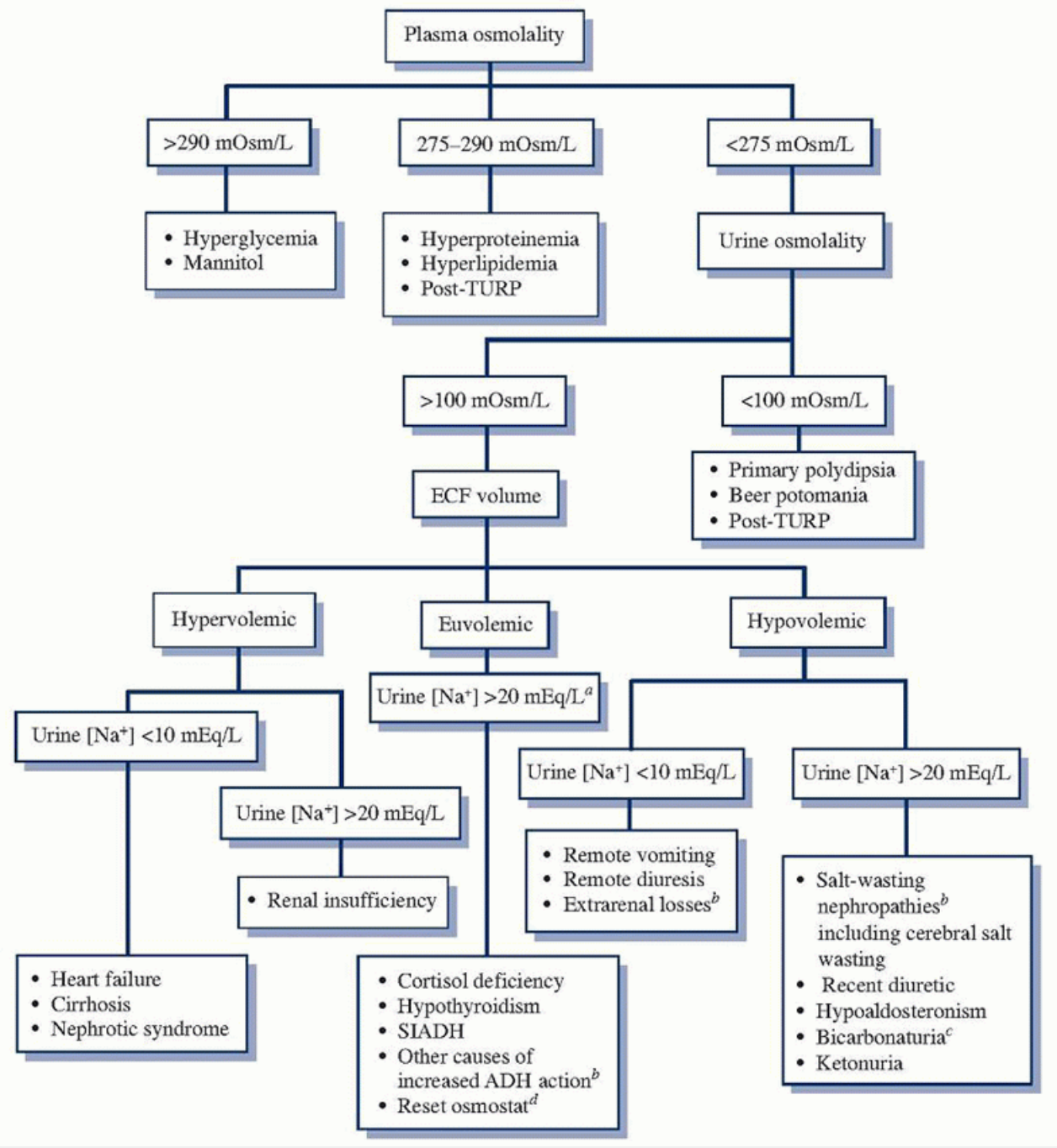


Figure 12-1. Algorithm depicting the diagnostic approach to hyponatremia. ADH, antidiuretic hormone; ECF, extracellular fluid; post-TURP, post-transurethral resection of the prostate syndrome; SIADH, syndrome of inappropriate antidiuretic hormone. [a]Urine [Na^+] may be <20 mEq/L with low Na^+ intake. [b]See text for details. [c]From vomiting-induced contraction alkalosis or proximal renal tubular acidosis. [d]Urine osmolality may be <100 mOsm/L after a water load.

- The risks of correcting hyponatremia too rapidly are volume overload and the development of **central**

pontine myelinolysis (CPM). CPM results from damage to neurons due to rapid osmotic shifts. In its most overt form, it is characterized by flaccid paralysis, dysarthria, and dysphagia, and in more subtle presentations, it can be confirmed by CT scan or MRI of the brain. The risk of precipitating CPM is increased with correction of the [Na^+] by >12 mEq/L in a 24-hour period (*J Am Soc Nephrol 1994;4:1522*). In addition to overaggressive correction, other risk factors for developing CPM include preexisting hypokalemia, malnutrition, and alcoholism.

- In patients with severe hyponatremia, in whom an immediate rise in [Na^+] is necessary, [Na^+] should be corrected 1-2 mEq/L/h for 3-4 hours. However, this initial rate of

correction should be tapered off once the patient is safe, such that the rise in [Na^+] does not exceed 10-12 mEq/L over the 24-hour period.

- **Chronic asymptomatic hyponatremia.** The risk of iatrogenic injury is actually increased in patients with chronic hyponatremia. Because cells gradually adapt to the hypo-osmolar state, an abrupt normalization presents a dramatic change from the accommodated osmotic milieu. As such, we suggest a more modest rate of correction on the order of 5-8 mEq/L over a 24-hour period.
- **Severe, symptomatic hyponatremia.** In patients with symptomatic hyponatremia, hypertonic saline provides an immediate and titratable intervention necessary to acutely raise serum Na^+ levels while avoiding the disastrous complications of overcorrection.
  - The most accurate way to correct hyponatremia entails a detailed registry matching total solute and water output with desired input. In clinical practice, this is often impractical.
  - In lieu of this, the following equation is often used to approximate the change in [Na^+] in mEq/L from the infusion of 1 L of fluid:

    $$\Delta[Na^+] = ([Na^+_i] + [K^+_i] - [Na^+_s]) \div \{TBW + 1\}$$

    $[Na^+_i]$ and $[K^+_i]$ are the sodium and potassium concentrations in the infused fluid, and $[Na^+_s]$ is the starting serum sodium (*Intensive Care Med 1997;23:309*). Recall that TBW is estimated by multiplying the lean weight (in kilograms) by 0.6 in men (and 0.5 in women). This formula does not account for ongoing electrolyte or water losses and is only a rough guide.
  - Dividing the desired rate of correction (mEq/L/h) by Δ[Na^+] (mEq/L/L of fluid) gives you the appropriate **rate of administration (liter of fluid per hour)**.
  - Because this equation does not account for ongoing losses, one **must recheck laboratory data and adjust fluid rates** to make sure the patient is improving appropriately.
  - **Example:** An 80-kg woman is seizing. Her [Na^+] is 103 mEq/L.
    - **Rate of correction:** She has symptomatic hyponatremia requiring an acute correction (1-2 mEq/L/h for the first 3-4 hours) but no more than 12 mEq/L corrected over 24 hours.
    - **Means of correction:**

      Given the acuity, the patient should be given hypertonic saline, which has 513 mEq of Na^+ per liter.

      One liter of this fluid would increase [Na^+] by 10 mEq/L.

      Δ[Na^+] = (513 − 108) ÷ (80 × 0.5 + 1) = 10 mEq/L

      Dose hypertonic saline at 200 mL/h until symptoms improve.

Rate = (2 mEq/L/h) ÷ (10 mEq/L per 1 L of saline)

- To prevent a change of >10-12 mEq/L over 24 hours, no more than 1 L of fluid should be given.

- **Asymptomatic hyponatremia**
  - **Hypovolemic hyponatremia.** In patients with asymptomatic hypovolemic hyponatremia, **isotonic** saline can be used to restore the intravascular volume. Restoration of a euvolemic state will reduce the impetus toward renal water retention, leading to normalization of [Na^+]. If the duration of hyponatremia is unknown, the process described earlier can be used to calculate the expected change from 1 L of 0.9% NS, the rate of administration, and the maximal amount that can be given to avoid overcorrection.
  - **Hypervolemic hyponatremia.** Hyponatremia in CHF and cirrhosis often reflects the severity of the underlying disease. However, the hyponatremia itself is typically asymptomatic. Although *effective* circulating volume is decreased, the administration of fluid

may worsen the volume-overloaded state. Definitive treatment requires management of the underlying condition, although restriction of water intake and increasing water diuresis may help to attenuate the degree of hyponatremia.

- Oral fluid intake should be less than daily urine output.
- Urinary excretion of water can be promoted through the use of loop diuretics, which reduce the concentration gradient necessary to reabsorb water in the distal nephron. Vasopressin antagonists may also be helpful in both euvolemic (SIADH) and hypervolemic hyponatremia (particularly CHF). When using medications to promote water loss, laboratory data and volume status must be followed extremely closely, because the effect on water and electrolyte loss cannot be accurately predicted.

- **SIADH** should first be distinguished from the previously listed conditions that stimulate vasopressin secretion. The standard first-line therapy is water restriction and correction of any contributing factors (nausea, pneumonia, drugs, etc.). If this fails or if the patient is symptomatic, the following can be attempted to promote water excretion.
  - **Water restriction.** The amount of fluid restriction necessary depends on the extent of water elimination. A useful guide to the necessary degree of fluid restriction is as follows:
    - If (Urine Na^+ + Urine K^+)/Serum Na^+ <0.5, restrict to 1 L/d.
    - If (Urine Na^+ + Urine K^+)/Serum Na^+ is 0.5-1.0, restrict to 500 mL/d.
    - If (Urine Na^+ + Urine K^+)/Serum Na^+ is >1, the patient has a negative renal free water clearance and is actively reabsorbing water. Any amount of water given may be retained, and clinicians should consider the following options to enhance free water excretion.
  - **High dietary solute load.** The volume of water excreted as urine is governed by a relatively fixed urine osmolality. Thus, increasing solute intake with a high-salt, high-protein diet or administration of oral urea (30-60 g) may increase the capacity for water excretion and improve the hyponatremia.
  - Loop diuretics impair the urinary concentrating mechanism and can enhance free water excretion.
  - Vasopressin antagonists promote a water diuresis and may be useful in the therapy of SIADH. Both IV (conivaptan) and oral (tolvaptan) preparations are approved for the treatment of euvolemic hyponatremia. However, given the risks of overcorrection, these agents should be initiated in a closely monitored inpatient setting.
  - Lithium and demeclocycline interfere with the collecting tubule's ability to respond to ADH but are rarely used because of significant side effects. They should only be considered in severe

hyponatremia that is unresponsive to more conservative measures.

Hypernatremia

GENERAL PRINCIPLES

- Hypernatremia is defined as a plasma [Na^+] **>145 mEq/L** and represents a state of **hyperosmolality** (see Disorders of Sodium Concentration section).
- Hypernatremia may be caused by a primary **Na^+ gain** or a **water deficit**, the latter being much more common. Normally, this hyperosmolar state stimulates thirst and the excretion of a maximally concentrated urine. For hypernatremia to persist, one or both of these compensatory mechanisms must be impaired.
- **Impaired thirst response** may occur in situations where access to water is limited, often due to physical restrictions (institutionalized, handicapped, postoperative, or intubated patients) or mental impairment (delirium, dementia).
- **Hypernatremia due to water loss.** The loss of water must occur in excess of electrolyte losses in order to raise [Na^+].
  - **Nonrenal water loss** may be due to evaporation from the skin and respiratory tract (insensible losses) or loss from the GI tract. Diarrhea is the most common GI cause of

    hypernatremia. Osmotic diarrhea (induced by lactulose, sorbitol, or malabsorption of carbohydrate) and viral gastroenteritis, in particular, result in disproportional water loss.
  - **Renal water loss** results from either **osmotic diuresis** or **diabetes insipidus (DI)**.
    - **Osmotic diuresis** is frequently associated with glycosuria and high osmolar feeds. In addition, increased urea generation from accelerated catabolism, high-protein feeds, and stress-dose steroids can also result in an osmotic diuresis.
    - Hypernatremia secondary to nonosmotic urinary water loss is usually caused by impaired vasopressin secretion (**central diabetes insipidus [CDI]**) or resistance to the actions of vasopressin **(nephrogenic diabetes insipidus [NDI])**. Partial defects occur more commonly than complete defects in both types.
    - The most common cause of CDI is destruction of the neurohypophysis from trauma, neurosurgery, granulomatous disease, neoplasms, vascular accidents, or infection. In many cases, CDI is idiopathic.
    - NDI may either be inherited or acquired. The latter often results from a disruption to the renal concentrating mechanism due to drugs (lithium, demeclocycline, amphotericin), electrolyte disorders (hypercalcemia, hypokalemia), medullary washout (loop diuretics), and intrinsic renal diseases.
- **Hypernatremia due to primary Na^+ gain** occurs infrequently due to the kidney's capacity to excrete the retained Na^+. However, it can rarely occur after repetitive **hypertonic saline** administration or chronic **mineralocorticoid excess**.
- **Transcellular water shift** from ECF to ICF can occur in circumstances of transient intracellular hyperosmolality, as in seizures or rhabdomyolysis.

DIAGNOSIS

Clinical Presentation

- Hypernatremia results in contraction of brain cells as water shifts to attenuate the rising ECF osmolality. Thus, the most severe symptoms of hypernatremia are neurologic, including altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, and, occasionally, coma or seizures. As with hyponatremia, the severity of the clinical manifestations is related to the *acuity* and *magnitude* of the rise in plasma [Na^+]. **Chronic hypernatremia** is generally less symptomatic as a result of adaptive mechanisms designed to defend cell volume.
- **CDI** and **NDI** generally present with complaints of polyuria and thirst. Signs of volume depletion or neurologic dysfunction are generally absent unless the patient has an associated thirst abnormality.

Diagnostic Testing

Urine osmolality and the **response to desmopressin acetate (DDAVP)** can help narrow the differential diagnosis for hypernatremia (Figure 12-2).

- The appropriate renal response to hypernatremia is a small volume of concentrated (urine osmolality >800 mOsm/L) urine. Submaximal **urine osmolality** (<800 mOsm/L) suggests a defect in renal water conservation.
  - A urine osmolality <300 mOsm/L in the setting of hypernatremia suggests complete forms of CDI and NDI.
  - Urine osmolality between 300-800 mOsm/L can occur from partial forms of DI as well as osmotic diuresis. The two can be differentiated by quantifying the daily solute excretion (estimated by the urine osmolality multiplied by urine volume in 24 hours). A daily solute excretion >900 mOsm/L defines an osmotic diuresis.
- **Response to DDAVP.** Complete forms of CDI and NDI can be distinguished by administering the vasopressin analog DDAVP (10 µg intranasally) after careful water restriction. The urine osmolality should increase by at least 50% in complete CDI and does not change in NDI. The diagnosis is sometimes difficult when partial defects are present.

http://internalmedicinebook.com

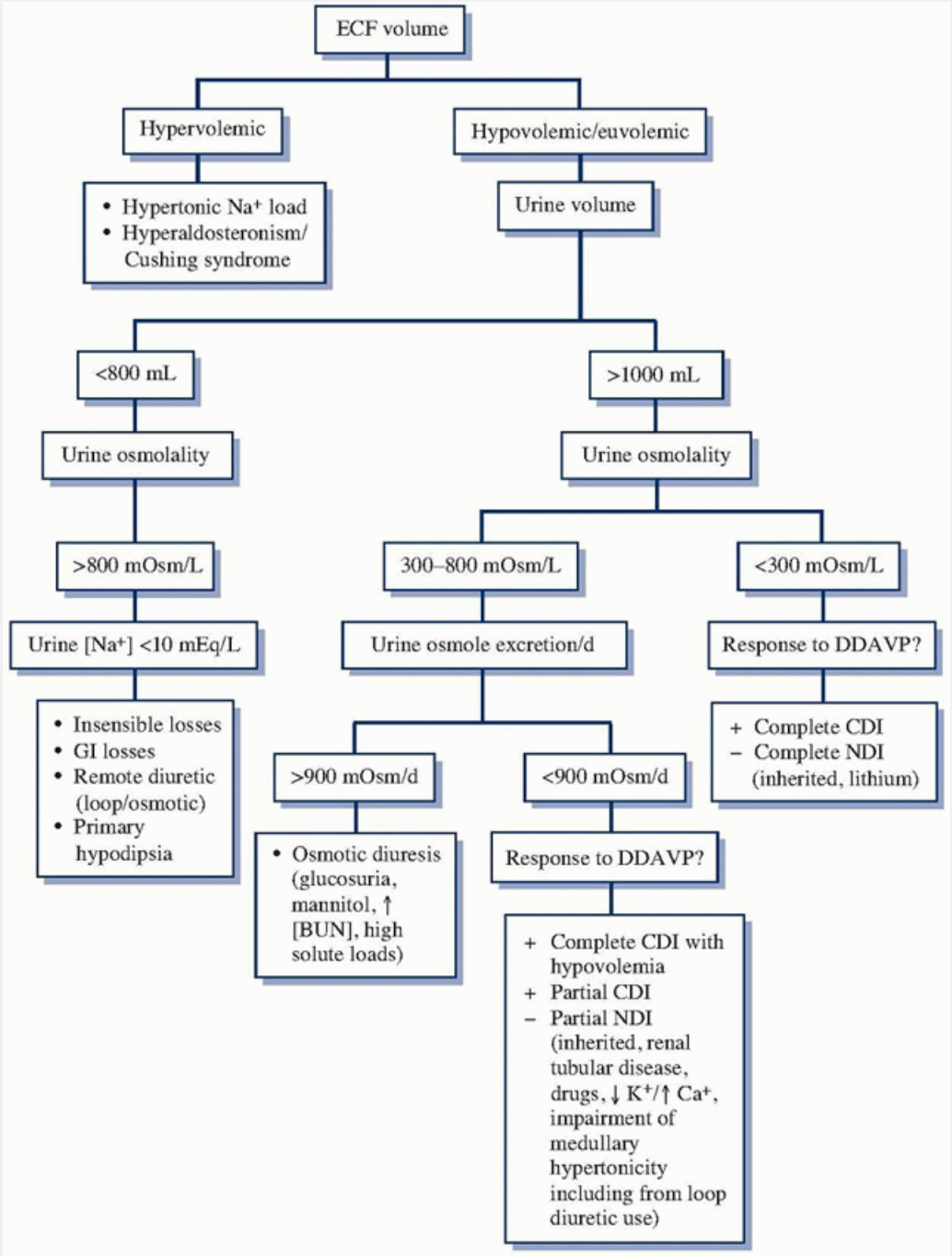


Figure 12-2. Algorithm depicting the diagnostic approach to hypernatremia. BUN, blood urea nitrogen; $\uparrow Ca^{+}$, hypercalcemia; CDI, central diabetes insipidus; DDAVP, desmopressin acetate; ECF, extracellular fluid; GI, gastrointestinal; NDI, nephrogenic diabetes insipidus; $\downarrow K^{+}$, hypokalemia; (+), conditions with increase in urine osmolality in response to desmopressin acetate; (−), conditions with little increase in urine osmolality in response to desmopressin acetate.

TREATMENT

- Management requires one to determine **the rate of correction**, **the appropriate intervention**, and **the presence of other underlying disorders**.
- The rate of correction of hypernatremia depends on the acuity of its development and the presence of neurologic dysfunction.

- **Symptomatic hypernatremia.** As in hyponatremia, aggressive correction of hypernatremia is potentially

http://internalmedicinebook.com

dangerous. The rapid shift of water into brain cells increases the risk of seizures or permanent neurologic damage. Therefore, the water deficit should be reduced gradually by roughly **10-12 mEq/L/d**.

- In **chronic asymptomatic hypernatremia**, the risk of treatment-related complications is increased due to the cerebral adaptation to the chronic hyperosmolar state. The plasma [Na^+] should be lowered at a more moderate rate (between 5-8 mEq/L/d).
- **Intervention**
  - The mainstay of management is the administration of water, preferably by mouth or nasogastric tube. Alternatively, 5% dextrose in water (D5W) or quarter NS can be given via IV.
  - Traditionally, correction of hypernatremia has been accomplished by calculating **free water deficit** by the equation:

    Free water deficit = {([Na^+] − 140)/140} × (TBW)

    While this is helpful in approximating the total water deficit, it does not provide sufficient guidance regarding the rate and content of infusate. Alternatively, we suggest approaching treatment in a manner similar to that used in the treatment of hyponatremia. The change in [Na^+] from the administration of fluids can be estimated as follows:

    $\Delta[Na^+] = ([Na^+_i] + [K^+_i] - [Na^+_s]) \div (TBW + 1)$

    $[Na^+_i]$ and $[K^+_i]$ are the sodium and potassium concentrations in the infused fluid and $[Na^+_s]$ is the starting serum sodium (*Intensive Care Med 1997;23:309*). Because hypernatremia suggests a contraction in water content, TBW is estimated by multiplying lean weight (in kilograms) by 0.5 in men (rather than 0.6) and 0.4 in women.

    An example: A 70-kg man with diarrhea (2 L/d) from laxative abuse presents with obtundation and [Na^+] = 164 mEq/L, [K^+] = 3.0. A replacement fluid of D5W with 20 mEq KCl/L is chosen.

    - The $\Delta[Na^+]$ with 1 L of this fluid would be −4 mEq/L

      (0 + 20 − 164) ÷ ([70 × 0.5] + 1)

      3 L are necessary for a $\Delta[Na^+]$ of −12 mEq/L/24 hours

      (−12 mEq/L/d) ÷ (−4 mEq/L/L of solution)
    - The hourly rate of infusion is 125 mL/h (3 L/d ÷ 24 hours/day = 0.125 L/h). However, this should be followed closely because it does not account for ongoing GI or insensible losses, which may account for another 1.4 L/d of water required to keep [Na^+] stable.
- **Specific therapies for the underlying cause**
  - **Hypovolemic hypernatremia.** In patients with mild volume depletion, Na^+-containing solutions, such as 0.45% NS, can be used to replenish the ECF as well as the water deficit. If patients have severe or symptomatic volume depletion, correction of volume status with **isotonic fluid** should take precedence over correction of the hyperosmolar state. Once the patient is hemodynamically stable, administration of hypotonic fluid can be given to replace the free water deficit.
  - **Hypernatremia from primary Na^+ gain** is unusual. Cessation of iatrogenic Na^+ is typically sufficient.

  - **DI without hypernatremia.** DI is best treated by removing the underlying cause. Despite the renal water loss, DI should not result in hypernatremia if the thirst mechanism remains intact. Therefore, therapy, if required at all, is directed toward symptomatic polyuria.

- **CDI.** Because the polyuria is the result of impaired secretion of vasopressin, treatment is best accomplished with the administration of DDAVP, a vasopressin analog.
- **NDI.** A low-Na^+ diet combined with **thiazide** diuretics will decrease polyuria through inducing mild volume depletion. This enhances proximal reabsorption of salt and water, thus decreasing urinary free water loss. Decreasing protein intake will further decrease urine output by minimizing the solute load that must be excreted.

POTASSIUM

- Potassium is the major **intracellular** cation. Of the 3000-4000 mEq of K^+ found in the average human, 98% is sequestered within cells. Thus, although ECF [K^+] is normally 3.5-5.0 mEq/L, the intracellular concentration is roughly 150 mEq/L. This difference in ICF and ECF K^+ content is maintained by the **Na^+/K^+-adenosine triphosphatase pump**.
- The K^+ intake of individuals on an average Western diet is approximately 1 mEq/kg/d, 90% of which is absorbed by the GI tract. Maintenance of the steady state necessitates matching K^+ excretion with ingestion.
- The elimination of potassium occurs predominately through **renal excretion** at the distal nephron. K^+ secretion is enhanced by distal Na^+ reabsorption, which generates a **lumen-negative gradient** and **distal urine flow rate**.
- Renal potassium handling is responsive to **aldosterone**, which stimulates the expression of distal luminal Na^+ channels, and the **serum potassium concentration**. Aldosterone secretion is, in turn, responsive to angiotensin II and hyperkalemia.

Hypokalemia

GENERAL PRINCIPLES

- Hypokalemia is defined as a plasma [K^+] <3.5 mEq/L.
- **Spurious hypokalemia** may be seen in situations in which high numbers of metabolically active cells present in the blood sample absorb the ECF potassium.
- True hypokalemia may result from one or more of the following: (a) **decreased net intake**, (b) **shift into cells**, or (c) **increased net loss**.
  - **Diminished intake** is seldom the sole cause of K^+ depletion because urinary excretion can be effectively decreased to <15 mEq/d. However, dietary K^+ restriction may exacerbate the hypokalemia from GI or renal loss.
  - **Transcellular shift.** Movement of K^+ into cells may transiently decrease the plasma [K^+] without altering total body K^+ content. These shifts can result from alkalemia, insulin, and catecholamine release. **Periodic paralysis** is a rare disorder that predisposes patients to transcellular K^+ shifts that result in episodic muscle weakness. Both hyperkalemic and hypokalemic forms have been described and can be triggered after strenuous exercise. Unlike the hyperkalemic form, the hypokalemic form can be triggered after a carbohydrate-rich meal. In the hyperkalemic form, the potassium levels are usually mildly elevated during an attack. In both forms, a later onset proximal myopathy develops, most commonly affecting the pelvic girdle

and the lower extremities.

- **Nonrenal K^+ loss.** Hypokalemia may result from the loss of potassium-rich fluids from the lower GI tract. Hypokalemia from the loss of upper GI contents is typically more attributable to renal K^+ secretion from secondary hyperaldosteronism. Rarely, in excessive sweating, loss of K^+ through the integument can provoke hypokalemia.

- **Renal K^+ loss** accounts for most cases of *chronic* hypokalemia. This may be caused by factors that increase the lumen-negative gradient, thus enhancing K^+ secretion, or that augment distal urine flow rate.
  - **Augmented distal urine flow** occurs commonly with diuretic use and osmotic diuresis (e.g., glycosuria). Bartter and Gitelman syndromes mimic diuretic use and promote renal K^+ loss by the same mechanism.
  - A variety of disorders promote K^+ loss by increasing the **lumen-negative gradient**, which drives K^+ secretion. This can be achieved with the reabsorption of a cation (Na^+) or presence of a nonreabsorbed anion.

    Distal Na^+ reabsorption is largely influenced by mineralocorticoid activity.

    Primary mineralocorticoid excess can be seen in primary hyperaldosteronism due to an adrenal adenoma or adrenocortical hyperplasia.

    Cortisol also has an affinity for mineralocorticoid receptors but is typically converted quickly to cortisone, which has markedly less mineralocorticoid activity. Still, if cortisol is present in abundance (Cushing syndrome) or fails to be converted to cortisone (syndrome of mineralocorticoid excess), it may mimic hyperaldosteronism.

    Secondary hyperaldosteronism can be seen in any situation with a decreased effective circulating volume.

    Constitutive activation of the distal renal epithelial Na^+ channel, independent of aldosterone, occurs in **Liddle syndrome**.
  - Increased distal delivery of a nonreabsorbable anion can also potentiate the lumennegative gradient that drives K^+ secretion. Examples include bicarbonate (metabolic alkalosis or type 2 renal tubular acidosis [RTA]), ketones, and hippurate (from toluene intoxication or glue sniffing).

DIAGNOSIS

Clinical Presentation

- The clinical features of K^+ depletion vary greatly, and their severity depends in part on the degree of hypokalemia. Symptoms seldom occur unless the plasma [K^+] is <3.0 mEq/L.
- Fatigue, myalgias, and muscular weakness or cramps of the lower extremities are common. Smooth muscle function may also be affected and may manifest with complaints of constipation or frank paralytic ileus. Severe hypokalemia may lead to complete paralysis, hypoventilation, or rhabdomyolysis.

Diagnostic Testing

When the etiology is not immediately apparent, **renal K^+ excretion** and the **acid-base status** can help identify the cause.

- **Urine K^+**. The appropriate response to hypokalemia is to excrete <25 mEq/d of K^+ in the urine. Urinary K^+ excretion can be measured with a 24-hour urine collection or estimated by multiplying the spot urine [K^+] by the total daily urine output. A spot urine [K^+] may be helpful (urine [K^+] <15 mEq/L suggests appropriate K^+ conservation), but the results can be confounded by a variety of factors. Alternatively, the transtubular potassium gradient (TTKG), which estimates the potassium gradient between the urine and blood in the distal nephron, can be calculated as follows:

  TTKG = (Urine K^+/Serum K^+) ÷ (Urine Osmolality/Serum Osmolality)

  A TTKG <2 suggests a nonrenal source, whereas a TTKG >4 suggests inappropriate renal K^+ secretion.
- **Acid-base status.** Intracellular shifting and renal excretion of K^+ are often closely linked with the acid-base status. Hypokalemia is generally associated with metabolic alkalosis

  and can play a critical role in the maintenance of metabolic alkalosis. The finding of metabolic acidosis in a patient with hypokalemia thus narrows the differential significantly, implying lower GI loss, distal RTA, or the excretion of a nonreabsorbable anion from an organic acid (diabetic ketoacidosis [DKA], hippurate from toluene intoxication).
- **ECG** changes associated with hypokalemia include flattening or inversion of the T wave, a prominent U wave, ST-segment depression, and a prolonged QU interval. Severe K^+ depletion may result in a prolonged PR interval, decreased voltage, and widening of the QRS complex.

TREATMENT

The **therapeutic goals** are to safely correct the K^+ deficit and to minimize ongoing losses through treatment of the underlying cause. Hypomagnesemia should also be sought in all hypokalemic patients and corrected to allow effective K^+ repletion.

- Correction of the K^+ deficit can be accomplished with either oral or IV therapy.
- **Oral therapy.** It is generally safer to correct the K^+ deficit via the oral route when hypokalemia is mild and the patient can tolerate oral administration. Oral doses of 40 mEq are generally well tolerated and can be given as often as every 4 hours. Traditionally, 10 mEq of potassium salts are given for each 0.10 mEq/L decrement in serum [K^+]. However, with increasing severity of hypokalemia, this grossly underestimates the K^+ necessary to normalize *total* K^+ content. Furthermore, as the K^+ shifts back to the intracellular space, it may appear as though K^+ supplementation is doing very little to correct ECF [K^+]. In such cases, potassium supplementation should be increased and continued until serum levels rise.
- **IV therapy.** Patients with imminently life-threatening hypokalemia and those who are unable to take anything by mouth require IV replacement therapy with KCl. The maximum concentration of administered K^+ should be no more than 40 mEq/L via a peripheral vein or 100 mEq/L via a central vein. The rate of infusion should not exceed 20 mEq/h unless paralysis or malignant ventricular arrhythmias are present. Ideally, KCl should be mixed in NS because dextrose solutions may initially exacerbate hypokalemia (as a result of insulin-mediated movement of K^+). Rapid IV administration of K^+ should be used judiciously and requires close observation.

Hyperkalemia

GENERAL PRINCIPLES

- Hyperkalemia is defined as a plasma [K^+] >**5.0 mEq/L**.
- **Pseudohyperkalemia** represents an artificially elevated plasma [K^+] due to K^+ movement out of cells immediately before or following venipuncture. Contributing factors include repeated fist clenching, hemolysis, and marked leukocytosis or thrombocytosis.
- True hyperkalemia occurs as a result of (a) **transcellular shift**, (b) **increased exposure to K^+**, and most commonly, (c) **decreased renal K^+ excretion**. Combinations of these mechanisms often underlie cases of hyperkalemia in clinical practice, and decreased renal excretion is nearly always some component of the pathophysiology.
  - **Transcellular shift.** Insulin deficiency, hyperosmolality, nonselective β-blockers, digitalis, metabolic acidosis (excluding those from organic acids), and depolarizing muscle relaxants, such as succinylcholine, release K^+ from predominate ICF stores into the ECF compartment. Exercise-induced hyperkalemia results from release of K^+ from muscles. Familial periodic paralysis, mentioned previously, is a rare cause of hyperkalemia. Massive cellular destruction, as seen in tumor lysis syndrome, also liberates cellular K^+ stores and releases them into the ECF.
  - **Increased exposure to K^+** is rarely the sole cause of hyperkalemia unless there is an impairment in renal excretion. Foods with a high content of K^+ include salt substitutes,

dried fruits, nuts, tomatoes, potatoes, spinach, bananas, and oranges. Juices derived from these foods may be especially rich sources.

  - **Decreased renal K^+ excretion.** In the setting of hyperkalemia, the kidney is capable of generating a significant urinary excretion of K^+. This process can be impaired by a number of processes, including intrinsic renal disease, decreased delivery of filtrate to the distal nephron, adrenal insufficiency, and hyporeninemic hypoaldosteronism (type 4 RTA).
- **Drugs** may also be implicated in the genesis of hyperkalemia through a variety of mechanisms. Common culprits include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics, NSAIDs, and cyclosporine. Heparin and ketoconazole can also contribute to hyperkalemia through the decreased production of aldosterone, although these agents alone are typically insufficient to sustain a clinically significant hyperkalemia.

DIAGNOSIS

Clinical Presentation

- The most serious effect of hyperkalemia is cardiac arrhythmogenesis secondary to potassium's pivotal role in membrane potentials. Patients may present with palpitations, syncope, or even sudden cardiac death.
- Severe hyperkalemia causes partial depolarization of the skeletal muscle cell membrane and may manifest as weakness, potentially progressing to flaccid paralysis and hypoventilation if the respiratory muscles are involved.

Diagnostic Testing

- If the etiology is not readily apparent and the patient is asymptomatic, **pseudohyperkalemia** should be excluded by rechecking laboratory data.
- An assessment of **renal [K^+] excretion** and the **renin-angiotensin-aldosterone axis** can help narrow the differential diagnosis when the etiology is not immediately apparent.
  - Low aldosterone levels suggest either adrenal disease (renin levels elevated) or hyporeninemic hypoaldosteronism (renin levels low; occurs with type 4 RTA as well as chloride shunting or Gordon syndrome).
  - High aldosterone levels, typically accompanied by high renin levels, suggest aldosterone resistance (pseudohypoaldosteronism) but can also be seen in K^+-sparing diuretics.
- **ECG** changes include increased T-wave amplitude or peaked T waves. More severe degrees of hyperkalemia result in a prolonged PR interval and QRS duration, atrioventricular conduction delay, and loss of P waves. Progressive widening of the QRS complex and its merging with the T wave produce a sine wave pattern. The terminal event is usually ventricular fibrillation or asystole.

TREATMENT

Severe hyperkalemia with ECG changes is a medical emergency and requires immediate treatment directed at minimizing membrane depolarization and acutely reducing the ECF [K^+]. **Acute therapy** may consist of some or all of the following (the hypokalemic effect is additive).

- **Calcium gluconate** decreases membrane excitability but does not lower [K^+]. The usual dose is 10 mL of a 10% solution infused over 2-3 minutes. The effect begins within minutes but is short lived (30-60 minutes), and the dose can be repeated if no improvement in the ECG is seen after 5-10 minutes.
- **Insulin** causes K^+ to shift into cells and temporarily lowers the plasma [K^+]. A commonly used combination is 10-20 units of regular insulin and 25-50 g of glucose administered IV. Hyperglycemic patients should be given the insulin alone.

- **$NaHCO_3$** is effective for severe hyperkalemia associated with metabolic acidosis. In the acute setting, it can be given as an IV isotonic solution (three ampules of $NaHCO_3$ in 1 L of 5% dextrose).
- **β_2-Adrenergic agonists** promote cellular uptake of K^+. The onset of action is 30 minutes, lowering the plasma [K^+] by 0.5-1.5 mEq/L, and the effect lasts for 2-4 hours. Albuterol can be administered in a dose of 10-20 mg as a continuous nebulized treatment over 30-60 minutes.
- **Longer term** means for [K^+] removal.
  - Increasing distal Na^+ delivery in the kidney enhances renal K^+ clearance. This can be achieved with the administration of saline in patients who appear volume depleted. Otherwise, diuretics can be used if renal function is adequate.
  - **Cation exchange resins**, such as sodium polystyrene sulfonate (Kayexalate), promote the exchange of Na^+ for K^+ in the GI tract. When given by mouth, the usual dose is 25-50 g mixed with 100 mL 20% sorbitol to prevent constipation. This generally lowers the plasma [K^+] by 0.5-1.0 mEq/L within 1-2 hours and lasts for 4-6 hours. Sodium polystyrene sulfonate can also be administered as a retention

enema consisting of 50 g resin in 150 mL tap water. Enemas should be avoided in postoperative patients because of the increased incidence of colonic necrosis, especially following renal transplantation. Newer agents such as sodium zirconium cyclosilicate are being studied and have shown improved safety profiles in preliminary studies.

- **Dialysis** should be reserved for patients with renal failure and those with severe lifethreatening hyperkalemia who are unresponsive to more conservative measures.
- **Chronic therapy** may involve dietary modifications to avoid high K^+ foods (see Potassium, Hyperkalemia, Etiology section), correction of metabolic acidosis with oral alkali, the promotion of kaliuresis with diuretics, and/or administration of exogenous mineralocorticoid in states of hypoaldosteronism.

CALCIUM

- Calcium is essential for bone formation and neuromuscular function.
- Approximately 99% of body calcium is in bone; most of the remaining 1% is in the ECF. Nearly 50% of serum calcium is ionized (free), whereas the remainder is complexed to albumin (40%) and anions such as phosphate (10%).
- **Calcium balance** is regulated by **parathyroid hormone** (PTH) and **calcitriol**.
  - **PTH** increases serum calcium by stimulating bone resorption, increasing calcium reclamation in the kidney, and promoting renal conversion of vitamin D to calcitriol. Serum calcium regulates PTH secretion by a negative feedback mechanism: Hypocalcemia stimulates and hypercalcemia suppresses PTH release.
  - **Calcitriol** [1,25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D_3, or $1,25(OH)_2D_3$] is the active form of vitamin D. It stimulates intestinal absorption of calcium and is one of many factors that provide feedback to the parathyroid gland.

Hypercalcemia

GENERAL PRINCIPLES

- A serum calcium **>10.3 mg/dL** with a normal serum albumin or an ionized calcium **>5.2 mg/dL** defines hypercalcemia.
- Clinically significant hypercalcemia typically requires both an increase in ECF calcium and a decrease in renal calcium clearance. Underlying disturbances to calcium metabolism are thus often masked by compensatory mechanisms until the patient develops a

concomitant disorder, such as decreased renal clearance from volume depletion. More than 90% of cases are due to **primary hyperparathyroidism** or **malignancy**.
- **Primary hyperparathyroidism** causes most cases of hypercalcemia in *ambulatory* patients. It is a common disorder, especially in elderly women, in whom the annual incidence is approximately 2 in 1000. Nearly 85% of cases are due to an **adenoma** of a single gland, 15% to **hyperplasia** of all four glands, and 1% to **parathyroid carcinoma**.
- **Malignancy** is responsible for most cases of hypercalcemia among *hospitalized* patients. Patients usually have advanced, clinically obvious disease. In these patients, hypercalcemia may develop from stimulation of osteoclast bone resorption from tumor cell products, tumor derived **PTH-related peptides** (PTHrPs), and

tumor calcitriol production.

- Less common causes account for about 10% of cases of hypercalcemia:
  - **Increased vitamin D activity** occurs with exogenous exposure to vitamin D or increased generation of calcitriol in chronic granulomatous diseases (e.g., sarcoidosis, tuberculosis).
  - The **milk-alkali syndrome** describes the acute or chronic development of hypercalcemia, alkalosis, and renal failure that may result from the ingestion of large quantities of calcium-containing antacids.
  - **Other.** Hyperthyroidism, adrenal insufficiency, prolonged immobilization, Paget disease, and acromegaly may be associated with hypercalcemia. **Familial hypocalciuric hypercalcemia** is a rare, autosomal dominant disorder of the calcium-sensing receptor, which is characterized by asymptomatic hypercalcemia from childhood and a family history of hypercalcemia.

DIAGNOSIS

Clinical Presentation

Clinical manifestations generally are present only if serum calcium exceeds 12 mg/dL and tend to be more severe if hypercalcemia develops rapidly. Most patients with **primary hyperparathyroidism** have asymptomatic hypercalcemia that is found incidentally.

- Renal manifestations include polyuria and nephrolithiasis. If serum calcium rises above 13 mg/dL, renal failure with nephrocalcinosis and ectopic soft tissue calcifications are possible.
- GI symptoms include anorexia, vomiting, constipation, and rarely, signs of pancreatitis.
- Neurologic findings include weakness, fatigue, confusion, stupor, and coma.
- Osteopenia and frequent fractures may occur from the disproportional resorption of bone in hyperparathyroidism. Rarely, **osteitis fibrosa cystica** can develop when hyperparathyroidism is profound and prolonged, resulting in “brown tumors” and marrow replacement.

Diagnostic Testing

- The history and physical examination should focus on (a) the duration of symptoms of hypercalcemia, (b) clinical evidence of any of the unusual causes of hypercalcemia, and (c) symptoms and signs of malignancy (which almost always precede **malignant hypercalcemia**). If hypercalcemia has been present for more than 6 months without an obvious etiology, primary hyperparathyroidism is almost certainly the cause.
- **Serum calcium** should be interpreted with knowledge of the serum albumin, or an ionized calcium should be measured. **Corrected $[Ca^{2+}]$** = $[Ca^{2+}]$ + {0.8 × (4.0 − [albumin])}. Many patients with primary hyperparathyroidism will have a calcium level that is chronically within the high-normal range.
- Intact **serum PTH** should be measured, because these assays are independent of renal function.
  - Elevations in ECF calcium typically result in suppression of PTH. Thus, the finding of a normal or elevated intact PTH in the setting of hypercalcemia is suggestive of primary hyperparathyroidism.

  - When the intact PTH is appropriately suppressed, **PTHrP** can be measured to investigate possible humoral hypercalcemia of malignancy.
- **$1,25(OH)_2D_3$** levels are elevated in granulomatous disorders, primary hyperparathyroidism, calcitriol overdose, and acromegaly. **$25(OH)D_3$** levels are elevated with noncalcitriol vitamin D intoxication.
- **Serum phosphorus** is often decreased in hyperparathyroidism due to stimulation of phosphaturia,

whereas Paget disease and vitamin D intoxication both tend to have increased phosphorus levels.

- **Urine calcium** may be elevated in primary hyperparathyroidism due to a filtered load of calcium that exceeds the capacity for renal reabsorption. If the family history and clinical picture are suggestive, patients with **familial hypocalciuric hypercalcemia** can be distinguished from patients with primary hyperparathyroidism by documenting a low calcium clearance by 24-hour urine collection (<200 mg calcium per day) or fractional excretion of calcium (<1%).
- **ECG** may reveal a shortened QT interval and, with very severe hypercalcemia, variable degrees of atrioventricular block.

TREATMENT

- **Acute management** of hypercalcemia is warranted if severe symptoms are present or with serum calcium >12 mg/dL. The following regimen is presented in the order that therapy should be given.
  - **Correction of hypovolemia** with 0.9% saline fluid is mandatory in patients who demonstrate volume depletion, because hypovolemia prevents effective calciuresis. Maintenance fluids can be continued after achieving euvolemia to sustain a urine output of 100-150 mL/h. The patient should be monitored closely for signs of volume overload.
  - **Loop diuretics** can be used if signs of volume overload limit further saline administration while hypercalcemia persists. These agents reduce paracellular reabsorption of calcium in the loop of Henle and thus may slightly enhance calcium excretion. They should not be used in euvolemic or hypovolemic patients because they may further contract the ECF volume and prevent adequate restoration of the volume status.
  - **IV bisphosphonates** can be used to decrease the liberation of calcium from bone in persistent hypercalcemia. Pamidronate 60 mg is infused over 2-4 hours; for severe hypercalcemia (>13.5 mg/dL), 90 mg can be given over the same duration. A hypocalcemic response is typically seen within 2 days and may persist for 2 weeks or longer. Treatment can be repeated after 7 days if hypercalcemia recurs. Zoledronate is a more potent bisphosphonate that is given as a 4-mg dose infused over at least 15 minutes. Hydration should precede bisphosphonate use. Renal insufficiency is a relative contraindication.
- Other options
  - **Calcitonin** inhibits bone resorption and increases renal calcium excretion. Salmon calcitonin, 4-8 IU/kg IM or SC q6-12h, lowers serum calcium 1-2 mg/dL within several hours in 60-70% of patients. Although it is less potent than other inhibitors of bone resorption, it has no serious toxicity, is safe in renal failure, and may have an analgesic effect in patients with skeletal metastases.
  - **Glucocorticoids** are effective in hypercalcemia due to hematologic malignancies and granulomatous production of calcitriol. The initial dose is 20-60 mg/d of prednisone or its equivalent. After serum calcium stabilizes, the dose should be gradually reduced to the minimum needed to control symptoms of hypercalcemia. Toxicity (see Chapter 25, Arthritis and Rheumatologic Diseases) limits the usefulness of glucocorticoids for long-term therapy.
  - **Gallium nitrate** inhibits bone resorption as effectively as the IV bisphosphonates and has a similar delayed onset of 2 days. It is given as a 100- to 200-mg/m^2/d continuous infusion for up to 5 days, unless normocalcemia is achieved sooner. There is, however,

a significant risk of nephrotoxicity, and it is contraindicated if the serum creatinine is >2.5 mg/dL.

http://internalmedicinebook.com

- **Dialysis.** Hemodialysis and peritoneal dialysis using low calcium dialysate are effective for patients with very severe hypercalcemia (>16 mg/dL) and CHF or renal insufficiency.

- **Chronic management** of hypercalcemia
  - **Primary hyperparathyroidism.** In many patients, this disorder has a benign course, with minimal fluctuation in serum calcium concentration and no obvious clinical sequelae. Parathyroidectomy is indicated in patients with (a) corrected serum calcium >1.0 mg/dL above the upper limit of normal, (b) creatinine clearance <60 mL/min, (c) age <50 years, and (d) bone density at hip, lumbar spine, or distal radius >2.5 standard deviations below peak bone mass (T score <−2.5) and/or previous fragility fracture (*J Clin Endocrinol Metab 2009;94:335*). Surgical intervention typically has a high success rate (95%) with low morbidity and mortality.
  - **Medical therapy** may be a reasonable option in asymptomatic patients who are not surgical candidates. Management consists of liberal oral hydration with a high-salt diet, daily physical activity to lessen bone resorption, and avoidance of thiazide diuretics. Oral bisphosphonates and estrogen replacement therapy or raloxifene in postmenopausal women can be considered in the appropriate clinical context. Cinacalcet, an activator of the calciumsensing receptor, has also been shown to reduce PTH secretion and serum calcium levels.
  - **Malignant hypercalcemia.** Bisphosphonate and glucocorticoid therapy with a calciumrestricted diet (<400 mg/d) can be tried, although these maneuvers rarely yield longterm success unless the malignancy responds to treatment. **Denosumab** may be used in patients with persistent hypercalcemia of malignancy in whom bisphosphonates may be contraindicated due to renal failure. It is given at a dose of 120 mg SC weekly for 4 weeks and then monthly.

Hypocalcemia

GENERAL PRINCIPLES

- A serum calcium **<8.4 mg/dL** with a normal serum albumin or an ionized calcium **<4.2 mg/dL** defines hypocalcemia.
- **Pseudohypocalcemia** describes the situation in which the total calcium is reduced due to hypoalbuminemia, but the **corrected [Ca^{2+}]** (see Calcium, Hypercalcemia, Diagnostic Testing section) and ionized calcium remain within the normal ranges.
- **Effective hypoparathyroidism.** Reduced PTH activity can result from decreased PTH release from autoimmune, infiltrative, or iatrogenic (e.g., postthyroidectomy) destruction of parathyroid tissue. In rare patients, hypoparathyroidism is congenital, as in DiGeorge syndrome or **familial hypocalcemia**. Release of PTH is also impaired with both hypomagnesemia (<1 mg/dL) and severe hypermagnesemia (>6 mg/dL).
- **Vitamin D deficiency** lowers total body calcium but does not usually affect serum calcium levels unless the deficiency is severe, because the resultant secondary hyperparathyroidism often corrects serum calcium levels. Significant vitamin D deficiency can occur in the elderly or those with limited sun exposure, in advanced liver disease (due to decreased synthesis of precursors), and in nephrotic syndrome. Reduced activity in vitamin D activation via 1-α-hydroxylase activity can be seen with vitamin D-dependent rickets and chronic renal insufficiency.
- Serum calcium levels may also be reduced by profound elevations in serum phosphorus, which binds with the calcium and deposits in a variety of tissues. Calcium can also be bound by citrate (during transfusion of citrate-containing blood products or with continual renal replacement using citrate anticoagulation) as well as

and fluoroquinolones. Increased binding to albumin can also be seen in the context of alkalemia, which increases the exposure of negatively charged binding sites on albumin.

- **Other.** A low serum free calcium level is common in critically ill patients perhaps due to a cytokine-mediated decrease in PTH and calcitriol release with target organ resistance to their effects.

DIAGNOSIS

Clinical Presentation

- Clinical manifestations vary with the degree of hypocalcemia and rate of onset.
- Acute, severe hypocalcemia may cause laryngospasm, confusion, seizures, or vascular collapse with bradycardia and decompensated heart failure.
- Acute, moderate hypocalcemia may cause increased excitability of nerves and muscles, leading to circumoral or distal paresthesias and tetany.
- **Trousseau sign** is the development of carpal spasm when a blood pressure cuff is inflated above systolic pressure for 3 minutes. **Chvostek sign** refers to twitching of the facial muscles when the facial nerve is tapped anterior to the ear. The presence of these signs is known as **latent tetany**.
- Clues to the diagnosis may be provided by a bedside evaluation for (a) previous neck surgery (postoperative hypoparathyroidism), (b) systemic diseases (autoimmune, infiltrative disorders), (c) family history of hypocalcemia, (d) drug-induced hypocalcemia, and (e) conditions associated with vitamin D deficiency (e.g., uremia).

Diagnostic Testing

- Laboratory data should be used to evaluate the calcium-PTH axis as well as concurrent mineral abnormalities.
- **Albumin** should be measured any time there is an abnormality in serum calcium levels to rule out pseudohypocalcemia. As mentioned previously, calcium can be corrected by adding {0.8 × (4 − [albumin])} to the total serum calcium level.
- **Serum PTH** that is low or inappropriately normal in the setting of hypocalcemia is indicative of hypoparathyroidism. A high PTH is often found with vitamin D deficiency, PTH resistance, and hyperphosphatemia.
- **Serum phosphorus** is often helpful in identifying vitamin D deficiency (low calcium, low phosphorus) or intravascular chelation of calcium (low calcium, high phosphorus).
- **Vitamin D** stores are usually assessed by measuring only $25(OH)D_3$ because calcitriol [$1,25(OH)_2D_3$] levels can be normalized through the compensatory increase of 1-α-hydroxylase activity.
- **Magnesium** deficiency should always be ruled out during management of hypocalcemia.
- **ECG** may show a prolonged QT interval and bradycardia.

TREATMENT

Acute management of symptomatic hypocalcemia requires prompt and aggressive therapy.

- **Phosphorus** must first be checked. In severe hyperphosphatemia (>6.5 mg/dL), administration of calcium will increase the calcium-phosphorus product and may exacerbate the formation of ectopic

calcifications. In acute, symptomatic hypocalcemia with severe hyperphosphatemia, dialysis may be needed to acutely manage the mineral abnormalities. If the hypocalcemia is asymptomatic, a reduction of phosphorus should precede aggressive calcium supplementation.

- **Hypomagnesemia**, if present, must be treated first in order to effectively correct the hypocalcemia. Two grams of magnesium sulfate can be given IV over 15 minutes followed by an infusion (see Magnesium, Hypomagnesemia, Treatment section) and may even be given empirically if renal failure is not present.

- **Calcium supplementation.** IV calcium should be reserved for severe or symptomatic hypocalcemia and can be administered as calcium chloride or calcium gluconate. Calcium gluconate is typically favored due to reduced risk of tissue toxicity with extravasation. Calcium gluconate is often prepared as a 10% solution (100 mg of calcium gluconate per mL). One ampule (10 mL) of calcium gluconate thus contains 1000 mg of calcium gluconate and approximately 90 mg of elemental calcium.
  - When necessary to treat severe or symptomatic hypocalcemia, an initial dose of 90-180 mg of elemental calcium can be achieved with 1-2 g of **calcium gluconate** (equal to 10-20 mL or one to two ampules of 10% calcium gluconate) mixed in 50-100 mL of D5W administered over 10-20 minutes.
  - The effect of initial treatment is only *transient*, and maintenance of calcium levels typically requires a continuous infusion of 0.5-1.5 mg/kg/h of elemental calcium. A solution comprised of 1 L D5W with 100 mL of 10% calcium gluconate contains approximately 900 mg of elemental calcium per liter, approximating 1 mg of elemental calcium per milliliter of fluid. Infusion is typically begun at a rate of 50 mL/h (approximately 50 mg of elemental calcium per hour) and titrated up as needed.
- **Chronic management.** Treatment requires calcium supplements and vitamin D or its active metabolite to increase intestinal calcium absorption.
  - **Oral calcium supplements.** Calcium carbonate (40% elemental calcium) or calcium acetate (25% elemental calcium) can be given with the goal administration of 1-2 g of *elemental* calcium PO tid. Calcium supplementation should be given apart from meals to minimize binding with phosphorus and maximize enteric absorption. Serum levels should be checked once to twice per week to guide ongoing therapy.
  - **Vitamin D.** Simple dietary deficiency can be corrected by the use of ergocalciferol 400-1000 IU/d. However, in conjunction with other hypocalcemic disorders, larger doses may be required. A 6- to 8-week regimen of 50,000 IU should be dosed weekly in those with underlying impairments in vitamin D metabolism (i.e., renal insufficiency) and daily in patients with severe malnutrition or malabsorption.
  - In comparison, **calcitriol** has a much more rapid onset of action. The initial dosage is 0.25 µg daily, and most patients are maintained on 0.5-2.0 µg daily. The dose can be increased at 2- to 4-week intervals. Because calcitriol increases enteric absorption of phosphorus as well as calcium, phosphorus levels should be monitored and oral phosphate binders initiated if phosphorus exceeds the normal range.

COMPLICATIONS

Development of hypercalcemia. In the event that hypercalcemia develops, vitamin D and calcium supplements should be stopped. Once serum calcium falls to normal, both forms of supplementation should be restarted at lower doses. Hypercalcemia due to calcitriol usually resolves within 1 week.

PHOSPHORUS

- Phosphorus is critical for bone formation and cellular energy metabolism.
- Approximately 85% of **total body phosphorus** is in bone, and most of the remainder is within cells. Thus, serum phosphorus levels may not reflect total body phosphorus stores.
- **Phosphorus balance** is determined primarily by four factors:
  - **PTH** regulates the incorporation and release of minerals from bone stores and decreases proximal tubular reabsorption of phosphate, causing urinary wasting.
  - The **phosphate concentration** itself regulates renal proximal reabsorption.

  - **Insulin** lowers serum levels by shifting phosphate into cells.
  - **Calcitriol** [1,25(OH)2D3] increases serum phosphate by enhancing intestinal phosphorus absorption.

Hyperphosphatemia

GENERAL PRINCIPLES

- A serum phosphate **>4.5 mg/dL** defines hyperphosphatemia.
- **Hyperphosphatemia** is caused by (a) **transcellular shift**, (b) **increased intake**, and most commonly, (c) **decreased renal excretion**. In clinical practice, renal insufficiency is usually present and serves as the major predisposing factor toward the development of hyperphosphatemia.
- **Transcellular shift** occurs in rhabdomyolysis, tumor lysis syndrome, and massive hemolysis as phosphorus is released from cells into the ECF. Metabolic acidosis and hypoinsulinemia reduce phosphorus flux into cells and contribute to the hyperphosphatemia sometimes seen in DKA.
- **Increased intake** leading to hyperphosphatemia usually occurs in the setting of renal insufficiency, either with dietary indiscretion in chronic kidney disease or as an iatrogenic complication. The latter can be seen when Phospho-Soda enemas (e.g., Fleet) or active vitamin D analogs are given to patients with renal insufficiency.
- **Decreased renal excretion** occurs most commonly in the setting of renal failure. Occasionally, hypoparathyroidism and pseudohypoparathyroidism reduce renal phosphorus clearance as well.

DIAGNOSIS

Clinical Presentation

- Signs and symptoms are typically attributable to hypocalcemia and the metastatic calcification of soft tissues. Occasionally, skin deposition can result in severe pruritus. **Calciphylaxis** describes the tissue ischemia that may result from the calcification of smaller blood vessels and their subsequent thrombosis.
- Chronic hyperphosphatemia contributes to the development of renal osteodystrophy (see Chapter 13, Renal Diseases).

Diagnostic Testing

The elevated serum phosphorus can be accompanied by hypocalcemia as a result of **intravascular chelation** of calcium by phosphorus.

TREATMENT

- **Acute hyperphosphatemia** is treated by increasing renal excretion of phosphorus, and as such, treatment is limited when renal insufficiency is present.
  - **Recovery of renal function** will often correct the hyperphosphatemia in the patient within 12 hours. Saline and/or acetazolamide (15 mg/kg q4h) can be given to further encourage phosphaturia, if needed.
  - **Hemodialysis** may be required, especially if irreversible renal insufficiency or symptomatic hypocalcemia is present.
- **Chronic hyperphosphatemia** is almost always associated with chronic kidney disease. Its management consists of reducing phosphorus intake through dietary modification and the use of phosphate binders. This is discussed more fully in Chapter 13, Renal Diseases.

Hypophosphatemia

GENERAL PRINCIPLES

- A serum phosphate **<2.8 mg/dL** defines hypophosphatemia.
- Hypophosphatemia may be caused by (a) **impaired intestinal absorption**, (b) **increased renal excretion**, or (c) **transcellular shift** into cells. Often, there are several mechanisms that work in concert to lower serum phosphate.
  - **Impaired intestinal absorption** occurs with the malabsorption syndromes, the use of oral phosphate binders, or vitamin D deficiency from any cause (see Calcium, Hypocalcemia, Etiology section). Chronic alcoholism is often associated with poor intake of both phosphate and vitamin D, resulting in total body phosphorus depletion.
  - **Increased renal excretion** occurs with high levels of PTH, as seen in hyperparathyroidism. This can be particularly pronounced in patients with secondary or tertiary hyperparathyroidism who undergo renal transplantation, because the high PTH causes a profound phosphaturic effect on the functional allograft. Hypophosphatemia may also occur from osmotic diuresis and disorders of proximal tubular transport such as familial X-linked hypophosphatemic rickets and Fanconi syndrome.
  - **Transcellular shift** is stimulated by respiratory alkalosis as well as insulin. The latter is responsible for the paradoxical reduction in phosphorus during treatment of malnutrition with hyperalimentation (the refeeding syndrome). The endogenous increase in insulin during treatment shifts phosphorus intracellularly, further reducing serum phosphorus in the malnourished individual. Phosphorus can also be rapidly absorbed into bone following parathyroidectomy for severe hyperparathyroidism (hungry bone syndrome).

DIAGNOSIS

Clinical Presentation

Signs and symptoms typically occur only if total body phosphate depletion is present and the serum phosphorus level is <1 mg/dL. These end-organ effects are due to the inability to form adenosine triphosphate and the impaired tissue oxygen delivery that occurs with a decrease in red blood cell 2,3-diphosphoglycerate. These include muscle injury (rhabdomyolysis, impaired diaphragmatic function, and heart failure), neurologic abnormalities (paresthesias, dysarthria, confusion, stupor, seizures, and coma), and rarely, hemolysis and platelet dysfunction.

Diagnostic Testing

- The cause is usually apparent from the clinical situation in which the hypophosphatemia occurs. If not, measurement of **urine phosphorus excretion** helps define the mechanism. Renal excretion of >100 mg by 24-hour urine collection or a fractional excretion of phosphate >5% during hypophosphatemia indicates excessive renal loss.
- Low serum **25(OH)D_3** suggests dietary vitamin D deficiency or malabsorption. An elevated **intact PTH** may occur in primary or secondary hyperparathyroidism.

TREATMENT

- **Acute moderate hypophosphatemia** (1.0-2.5 mg/dL) is common in the hospitalized patient and is often due simply to **transcellular shifts**, requiring no treatment if asymptomatic, except correction of the underlying cause.
- **Acute severe hypophosphatemia** (<1.0 mg/dL) may require IV phosphate therapy when associated with serious clinical manifestations. IV preparations include potassium

phosphate (1.5 mEq potassium/mmol phosphate) and sodium phosphate (1.3 mEq sodium/mmol phosphate).
  - An infusion of phosphate, 0.08-0.16 mmol/kg in 500 mL 0.45% saline, is given via IV over 6 hours (1 mmol phosphate = 31 mg phosphorus). IV repletion should be stopped when the serum phosphorus level is >1.5 mg/dL and when the patient can tolerate oral therapy. Because of the need to replenish intracellular stores, 24-36 hours of phosphate administration may be required.
  - Extreme care must be used to avoid hyperphosphatemia, which may lead to hypocalcemia. If hypotension occurs, acute hypocalcemia should be suspected, and the infusion should be stopped or slowed. Further doses should be based on symptoms and on the serum calcium and phosphorus levels, which should be measured every 8 hours.
- **Chronic hypophosphatemia.** Vitamin D deficiency, if present, should be treated first (see Calcium, Hypocalcemia, Treatment section) followed by oral supplementation of 0.5-1.0 g elemental phosphorus PO bid to tid. Preparations include Neutra-Phos (250 mg elemental phosphorus and 7 mEq of Na^+ and K^+ per capsule) and Neutra-Phos K^+ (250 mg elemental phosphorus and 14 mEq K^+ per capsule). Contents of the capsules should be dissolved in water. Fleet Phospho-Soda (815 mg phosphorus and 33 mEq sodium per 5 mL) is an alternative oral agent. Limiting side effects include nausea and diarrhea.

MAGNESIUM

- **Magnesium** plays an important role in neuromuscular function.
- Approximately 60% of body magnesium is stored in bone, and most of the remainder is found in cells. Only 1% is in the ECF. As a result, the serum magnesium is a poor predictor of intracellular and total body stores and may grossly underestimate total magnesium deficits.
- The main determinant of magnesium balance is the **magnesium concentration** itself, which directly influences renal excretion. Hypomagnesemia stimulates tubular reabsorption of magnesium, whereas hypermagnesemia inhibits it.

Hypermagnesemia

GENERAL PRINCIPLES

- A serum magnesium **>2.2 mEq/L** defines hypermagnesemia.
- Most cases of clinically significant hypermagnesemia are **iatrogenic**, occurring with large doses of magnesium-containing antacids or laxatives and during treatment of preeclampsia with IV magnesium. Because renal excretion is the only means of lowering serum magnesium levels, the presence of significant renal insufficiency can lead to magnesium toxicity even with therapeutic doses of these antacids and laxatives.
- Mild, insignificant elevations in magnesium can occur in end-stage renal disease patients, theophylline intoxication, DKA, and tumor lysis syndrome.

DIAGNOSIS

Clinical Presentation

- Signs and symptoms are usually seen when the serum magnesium level is >4 mEq/L.
- Neuromuscular abnormalities usually include hyporeflexia (usually the first sign of magnesium toxicity), lethargy, and weakness that can progress to paralysis and diaphragmatic involvement, leading to respiratory failure.
- Cardiac findings include hypotension, bradycardia, and cardiac arrest.

Diagnostic Testing

The **ECG** may reveal bradycardia and prolonged PR, QRS, and QT intervals with magnesium levels of 5-10 mEq/L. Complete heart block or asystole may eventually ensue with levels >15 mEq/L.

TREATMENT

- **Prevention.** In the setting of significant renal insufficiency, the inadvertent administration of magnesium-containing medications (e.g., Maalox, magnesium citrate) should be avoided.
- **Asymptomatic hypermagnesemia.** In the setting of normal renal function, normal magnesium levels will quickly be attained with removal of the magnesium load.
- **Symptomatic hypermagnesemia**
  - Prompt supportive therapy is critical, including mechanical ventilation for respiratory failure and a temporary pacemaker for significant bradyarrhythmias.
  - The effects of hypermagnesemia can be antagonized quickly by the administration of 10% calcium gluconate 10-20 mL IV (1-2 g) over 10 minutes.
  - Renal excretion can be encouraged with saline administration.
  - With significant renal insufficiency, hemodialysis is required for definitive therapy.

Hypomagnesemia

GENERAL PRINCIPLES

- A serum magnesium **<1.3 mEq/L** defines hypomagnesemia.

- Hypomagnesemia is most commonly caused by impaired intestinal absorption and increased renal excretion.
  - **Decreased intestinal absorption** occurs in malnutrition, as is common in chronic alcoholics or any malabsorption syndrome. Magnesium can also be lost through prolonged diarrhea and nasogastric aspiration. Hypomagnesemia has been described with chronic use of proton pump inhibitors (PPIs), presumably due to impaired intestinal absorption.
  - **Increased renal excretion** of magnesium can occur from increased renal tubular flow (as occurs with osmotic diuresis) as well as impaired tubular function (as seen with resolving acute tubular necrosis [ATN], loop diuretics, and Bartter and Gitelman syndromes).
- **Drugs.** Several medications similarly induce defects in tubular magnesium transport including aminoglycosides, amphotericin B, cisplatin, pentamidine, and cyclosporine.

DIAGNOSIS

Clinical Presentation

- Neurologic manifestations include lethargy, confusion, tremor, fasciculations, ataxia, nystagmus, tetany, and seizures.
- Atrial and ventricular arrhythmias may occur, especially in patients treated with digoxin.

Diagnostic Testing

- Low serum [Mg^{2+}] in conjunction with an appropriate clinical scenario is sufficient to establish the diagnosis of **magnesium deficiency**. However, due to the slow exchange of magnesium between the bone and intracellular pools (see Magnesium section), a normal serum level does not exclude total body **magnesium deficiency**.
- The etiology of hypomagnesemia usually is evident from the clinical context, but if there is uncertainty, measurement of **urine magnesium excretion** is helpful. A 24-hour urine magnesium of >2 mEq (or >24 mg) or a fractional excretion of magnesium of

>2% during hypomagnesemia suggests **increased renal excretion**. The fractional excretion of magnesium is calculated by

(Urine Mg^{2+}/Urine Cr) ÷ [(Serum Mg^{2+} × 0.7)/Serum Cr] × 100

- Hypocalcemia (see Calcium, Hypocalcemia, Etiology section) and/or hypokalemia (see Potassium, Hypokalemia, Etiology section) can often be found as a result of hypomagnesemia-induced derangements in mineral homeostasis.
- **ECG** abnormalities may include a prolonged PR and QT interval with a widened QRS. **Torsades de pointes** is the classically associated arrhythmia.

TREATMENT

- In patients with normal renal function, excess magnesium is readily excreted, and there is little risk of causing hypermagnesemia with recommended doses. However, *magnesium must be given with extreme care in the presence of renal insufficiency*.
- The route of magnesium administration depends on whether clinical manifestations from magnesium deficiency are present.

- **Asymptomatic hypomagnesemia** can be treated orally. Numerous preparations exist, including Mag-Ox 400 (240 mg elemental magnesium per 400-mg tablet), UroMag (84 mg per 140-mg tablet), and sustained-release Slow-Mag (64 mg per tablet). Typically, approximately 240 mg of elemental magnesium is administered daily for mild deficiency, whereas more severe hypomagnesemia may require up to 720 mg/d of elemental magnesium. The major side effect is diarrhea. Normalization of serum magnesium levels can be deceiving, because the administered magnesium slowly shifts to replete intracellular and bone stores. Furthermore, abrupt increases in serum levels stimulate renal excretion. Thus, serum levels should be followed closely, and replacement should be maintained until patients demonstrate stable normalization of serum magnesium concentrations.
- **Severe symptomatic hypomagnesemia** should be treated with 1-2 g magnesium sulfate (1 g magnesium sulfate = 96 mg elemental magnesium) IV over 15 minutes. To account for gradual redistribution to severely depleted intracellular stores, replacement therapy may need to be maintained, often for 3-7 days. Serum magnesium should be measured daily and the infusion rate adjusted to maintain a serum magnesium level of <2.5 mEq/L. Tendon reflexes should be tested frequently, because hyporeflexia suggests hypermagnesemia. Reduced doses and more frequent monitoring must be used even in mild renal insufficiency.

ACID-BASE DISTURBANCES

GENERAL PRINCIPLES

- The normal ECF **pH is 7.40 ± 0.03**. Perturbations in pH can occur with changes in the ratio of $[HCO_3^-]$ to partial pressure of carbon dioxide (pCO_2) as described by the **Henderson-Hasselbalch equation**:

  $pH = 6.1 + \log([HCO_3^-] \div [pCO_2 \times 0.3])$

- Maintenance of pH is essential for normal cellular function. Three general mechanisms exist to keep it within a narrow window:
  - **Chemical buffering** is mediated by HCO_3^- in the ECF and by protein and phosphate buffers in the ICF. The normal $[HCO_3^-]$ is 24 ± 2 mEq/L.
  - **Alveolar ventilation** minimizes variations in the pH by altering the pCO_2. The normal pCO_2 is 40 ± 5 mm Hg.

  - **Renal H^+ handling** allows the kidney to adapt to changes in acid-base status via HCO_3^- reabsorption and excretion of titratable acid (e.g., $H_2PO_4^-$) and NH_4^+.
- **Acidemia** and **alkalemia** refer to processes that lower and raise pH regardless of mechanism. They can be caused by metabolic or respiratory disturbances:
  - **Metabolic acidosis** is characterized by a decrease in the plasma $[HCO_3^-]$ due to either HCO_3^- loss or the accumulation of acid.
  - **Metabolic alkalosis** is characterized by an elevation in the plasma $[HCO_3^-]$ due to either H^+ loss or HCO_3^- gain.

- **Respiratory acidosis** is characterized by an elevation in pCO_2 resulting from alveolar hypoventilation.
- **Respiratory alkalosis** is characterized by a decrease in pCO_2 resulting from hyperventilation.

DIAGNOSIS

Analysis should be systematic so that accurate conclusions are drawn and appropriate therapy initiated. Once the acid-base process is correctly identified, further diagnostic studies may be undertaken to determine the precise etiologies at play.

- **Step 1.** Check arterial blood gas. Acidemia is present when pH is <7.37 and alkalemia when pH >7.43.
- **Step 2.** Establish the primary disturbance by determining whether the change in $[HCO_3^-]$ or pCO_2 can account for the observed deflection in pH.
  - In acidemia, a decreased $[HCO_3^-]$ suggests metabolic acidosis, and an elevated pCO_2 suggests respiratory acidosis. In alkalemia, an elevated $[HCO_3^-]$ suggests metabolic alkalosis, whereas a decreased pCO_2 suggests respiratory alkalosis.
  - A **combined disorder** is present when pH is normal but the pCO_2 and $[HCO_3^-]$ are both abnormal. Changes in both pCO_2 and $[HCO_3^-]$ can cause the change in pH.
- **Step 3.** Determine whether compensation is appropriate.
  - The **compensatory mechanism** is an adaptation to the primary acid-base disturbance intended to stabilize the changing pH. A respiratory process that shifts the pH in one direction will be compensated by a metabolic process that shifts the pH in the other and vice versa.
  - The effect of compensation is to attenuate, *but not completely correct*, the primary change in pH.
  - The expected compensations for the various primary acid-base derangements are given in Table 12-2.
  - An inappropriate compensatory response suggests the presence of a combined disorder.
  - Example: In a patient with metabolic acidosis, respiratory compensation attenuates the metabolic disturbance to pH by lowering pCO_2. However, if the pCO_2 is higher than expected, respiratory compensation is insufficient, revealing a respiratory acidosis with the primary metabolic acidosis. If pCO_2 is lower than expected, compensation is excessive, revealing a concomitant respiratory alkalosis.
- **Step 4.** Determine the **anion gap**.
  - In normal individuals, the total serum cations are balanced with the total serum anions. Total cations are comprised of measured cations (MCs) and unmeasured cations (UCs), whereas total anions are comprised of measured anions (MAs) and unmeasured anions (UAs). Certain forms of acidosis are characterized by an increase in the pool of UAs. The **anion gap (AG)** is merely a way of demonstrating the accumulation of this UA.
  - $AG = [Na^+] - ([Cl^-] + [HCO_3^-])$. The normal AG is 10 ± 2 mEq/L.

    AG = the excess of unmeasured anions (vs. unmeasured cations) = UA − UC

TABLE 12-2 Expected Compensatory Responses to Primary Acid-Base Disorders

Disorder	Primary Change	Compensatory Response
Metabolic acidosis	↓ [$HCO_3$2]	↓ pCO_2 1.2 mm Hg for every 1 mEq/L ↓ [$HCO_3$2] OR pCO_2 = last two digits of pH
Metabolic alkalosis	↑ [$HCO_3$2]	↑ pCO_2 0.7 mm Hg for every 1 mEq/L ↑ [$HCO_3$2]
Respiratory acidosis	↑ pCO_2	
Acute		↑ [$HCO_3$2] 1.0 mEq/L for every 10 mm Hg ↑ pCO_2
Chronic		↑ [$HCO_3$2] 3.5 mEq/L for every 10 mm Hg ↑ pCO_2
Respiratory alkalosis	↓ pCO_2	
Acute		↓ [$HCO_3$2] 2.0 mEq/L for every 10 mm Hg ↓ pCO_2
Chronic		↓ [$HCO_3$2] 5.0 mEq/L for every 10 mm Hg ↓ pCO_2

Since total cations = total anions:

MC + UC = MA + UA

Rearranging the equation:

UA − UC = MC − MA

MCs are Na^+; MAs are Cl^- and HCO_3^-.

- Because albumin is the principal UA, the AG should be corrected if there are gross changes in serum albumin levels.

  $AG_{correct}$ = AG + {(4 − [albumin]) × 2.5}

- An elevated AG suggests the presence of metabolic acidosis with a circulating anion (Table 12-3).

- **Step 5.** Assess the delta gap.
  - To maintain a stable total anion content, every increase in an UA should be met with a decrease in [HCO_3^-]. Comparing the change in the AG (ΔAG) with the change in the [HCO_3^-] (Δ[HCO_3^-]) is a simple way of making sure that each change in the AG is accounted for.
  - If the ΔAG = Δ[HCO_3^-], this is a simple AG metabolic acidosis.
  - If the ΔAG > Δ[HCO_3^-], the [HCO_3^-] did not decrease as much as expected. This is a metabolic alkalosis **and** AG metabolic acidosis.

    Example: A patient with DKA has been vomiting prior to admission. He has an AG of 20 and an

$[HCO_3^-]$ of 20. His ΔAG = 10 and $\Delta[HCO_3^-]$ = 4, revealing an AG metabolic acidosis (DKA) with a metabolic alkalosis (vomiting).

- If the ΔAG < $\Delta[HCO_3^-]$, the $[HCO_3^-]$ decreased more than expected. This is a nongap metabolic acidosis **and** AG metabolic acidosis.
  Example: A patient is admitted with fevers and hypotension after a prolonged course of diarrhea. She has an AG of 15 and an $[HCO_3^-]$ of 12. Her ΔAG is 5 and her $\Delta[HCO_3^-]$ is 12, revealing a nongap metabolic acidosis (diarrhea) and an AG metabolic acidosis (lactic acidosis).

TABLE 12-3 The Four Primary Acid-Base Disorders and Their Common Etiologies

	Acidosis	Alkalosis
Metabolic	Gap • Ketoacids (starvation, alcoholic, diabetic) • Exposures (methanol, ethylene glycol, salicylates) • Lactic acid (shock, drug related) • Profound uremia	Generation • Loss of H^+-rich fluids (GI loss) • Contraction alkalosis • Alkali administration
	Nongap • Nonrenal HCO_3^- loss (diarrhea) • Renal $HCO_3$2 loss (type 2 RTA) • ↓ H secretion (type 1 RTA) • Hypoaldosteronism (type 4 RTA)	Maintenance • Volume contraction • Chloride depletion • Hypokalemia
Respiratory	Depression of respiratory center Neuromuscular failure Lung disease	CNS stimulation Hypoxemia Anxiety

	Type 1 RTA	Type 2 RTA	Type 4 RTA
Serum [K]	↓ or nl	↓ or nl	↑
Serum $[HCO_3]$	<10	15-20	>15
Urine pH	>5.3	Varies	<5.3

CNS, central nervous system; GI, gastrointestinal; nl, normal; RTA, renal tubular acidosis.

Metabolic Acidosis

GENERAL PRINCIPLES

- The causes of a metabolic acidosis can be divided into those that cause an **elevated anion gap** and those with a **normal anion gap**. Many of the causes seen in clinical practice can be found in Table 12-3.
- AG acidosis results from exposure to acids, which contribute an unmeasured anion to the ECF. Common causes are DKA, lactic acidosis, and toxic alcohol ingestions.
- Non-anion gap acidosis can result from the loss of [HCO_3^-] from the GI tract. Renal causes due to renal excretion of [HCO_3^-] or disorders of renal acid handling are referred to collectively as **renal tubular acidoses (RTAs)**.
- Enteric [HCO_3^-] loss occurs most commonly in the setting of severe diarrhea.
- The three forms of RTA correlate with the three mechanisms that facilitate renal acid handling: proximal bicarbonate reabsorption, distal H^+ secretion, and generation of NH_3, the principle urinary buffer. Urinary buffers reduce the concentration of free H^+ in the filtrate, thus attenuating the back leak of H^+, which occurs at low urinary pH.
    - **Proximal (type 2) RTA** is caused by impaired proximal tubular HCO_3^- reabsorption. Causes include inherited mutations (cystinosis), heavy metals, drugs (tenofovir, ifosfamide, carbonic anhydrase inhibitors), and multiple myeloma and other monoclonal gammopathies.
    - **Distal (type 1) RTA** results from impaired distal H^+ secretion. This may occur due to impairment in H^+ secretion, as seen with a variety of autoimmune (Sjögren syndrome,

lupus, rheumatoid arthritis) or renal disorders. Hypercalciuria is another main cause of distal RTA in adults. It can also be caused by a back leak of H^+ due to increased membrane permeability, as seen with amphotericin B.
    - **Distal hyperkalemic (type 4) RTA** may result from either low aldosterone levels or from aldosterone resistance. The resulting hyperkalemia reduces the availability of NH3 to buffer urinary H^+. Hyporeninemic hypoaldosteronism is seen with some frequency in patients with diabetes. Certain drugs, including NSAIDs, β-blockers, and cyclosporine, have also been implicated.
    - Occasionally, the kidney is unable to secrete sufficient H^+ due to an impaired luminal gradient. In these situations, poor filtrate delivery or impaired Na^+ reabsorption in the distal nephron is responsible for decreasing the voltage gradient, which augments H^+ secretion. This can be seen with marked volume depletion, urinary tract obstruction, sickle cell nephropathy, and amiloride or triamterene use.

DIAGNOSIS

The first step in narrowing the differential diagnosis for a metabolic acidosis is to calculate the **anion gap**.

- The specific cause of an **elevated anion gap** can usually be determined by clinical history. However, specific laboratory studies are available to identify certain anions such as lactate, acetoacetate, acetone, and β-hydroxybutyrate. (It should be noted that the use of nitroprusside to detect ketones may fail to identify ketoacidosis due to β-hydroxybutyrate.) The presence of an alcohol (methanol, ethanol, ethylene

glycol) can also be determined with laboratory assays. Clinical suspicion for toxic alcohol ingestion is corroborated by an increased **osmolal gap**. This gap is the difference between measured and calculated serum osmolality:

$[Osm]_{meas} - \{([Na^+] \times 2) + ([glucose] \div 18) + ([BUN] \div 2.8)\}$

- If a **normal anion gap** is present, the GI HCO_3^- losses can be differentiated from RTAs via the **urine anion gap** (UAG). The **UAG** is the difference between the major measured anions and cations in urine: $[Na^+]_u + [K^+]_u - [Cl^-]_u$. Because NH_4^+ is the major unmeasured urinary cation, a negative UAG reflects high NH_4^+ excretion, an appropriate response to a metabolic acidosis. Conversely, a positive UAG signifies low NH_4^+ excretion, which in the face of a metabolic acidosis suggests a renal tubular defect.
- Serum $[K^+]$ and urine pH can be helpful in distinguishing between the RTAs.
  - Types 1 and 2 are typically associated with hypokalemia, whereas type 4 is characterized by hyperkalemia.
  - Urine pH is low (usually <5.3) in type 4 RTA because the defect is in the generation of the NH3 buffer, and the mechanism for H^+ secretion is intact. In contrast, urine pH is inappropriately high in type 1 RTA (urine pH >5.3). In type 2 RTA, the urine pH is variable. It is elevated during the initial bicarbonaturia, when filtered bicarbonate exceeds the threshold for reabsorption, and low when the filtered load is below this threshold.

TREATMENT

- **Ketoacidosis** attributable to ethanol abuse and starvation can be corrected with the resumption of caloric intake through oral intake or dextrose-containing fluids and by correction of any volume depletion that may be present. The treatment of DKA is described in Chapter 23, Diabetes Mellitus and Related Disorders.
- **Lactic acidosis** will resolve once the underlying cause is treated and tissue perfusion is restored. Often, this involves aggressive therapeutic maneuvers for the treatment of shock as described in Chapter 8, Critical Care. The administration of alkali does not appear to have clear benefit

in lactic acidosis, and it may lead to a rebound metabolic alkalosis once the underlying cause is managed. Its use in dire circumstances or severe acidosis remains controversial.
- Management of toxic ingestions is described in Chapter 28, Toxicology.
- **Normal AG metabolic acidosis.** Treatment with $NaHCO_3$ is appropriate for patients with a normal AG metabolic acidosis. The HCO_3^- deficit can be calculated in mEq:

  HCO_3^- deficit = $\{0.5 \times$ lean weight $\times [24^- (HCO3^-)]\}$

  However, this assumes a volume of distribution equal to 50% of total body weight. In reality, the distribution of HCO_3^- increases with the severity of the acidosis and may exceed 100% of total body weight in very severe acidosis. It should be noted that the standard 650-mg tablet of oral $NaHCO_3$ provides only 7 mEq of HCO_3^-, whereas one ampule of IV $NaHCO_3$ contains 50 mEq. Still, parenteral $NaHCO_3$ should always be prescribed with caution because of the potential adverse effects, including

pulmonary edema, hypokalemia, and hypocalcemia.

- **Treatment of the RTAs.** Correction of the chronic acidemia with alkali administration is warranted in order to prevent its catabolic effect on bone and muscle.
  - In *distal (type 1) RTA*, correction of the metabolic acidosis requires oral HCO_3^- replacement on the order of 1-2 mEq/kg/d with $NaHCO_3$ or sodium citrate. Potassium citrate replacement may be necessary for patients with hypokalemia, nephrolithiasis, or nephrocalcinosis. Underlying conditions should be sought and treated.
  - In *proximal (type 2) RTA*, much larger amounts of alkali (10-15 mEq/kg/d) are required to reverse the acidosis. Administration of potassium salts minimizes the degree of hypokalemia associated with alkali therapy.
  - Management of *type 4 RTA* requires correction of the underlying hyperkalemia. This consists of dietary K^+ restriction (40-60 mEq/d) and possibly a loop diuretic with or without oral $NaHCO_3$ (0.5-1 mEq/kg/d). Mineralocorticoid administration (fludrocortisone, 50-200 µg PO daily) should be used in patients with primary adrenal insufficiency and may be considered in other causes of hypoaldosteronism.

Metabolic Alkalosis

GENERAL PRINCIPLES

- Development of a persistent metabolic alkalosis requires both generation (an inciting cause) and maintenance (a persistent impairment of the corrective renal response).
- Generation often occurs with a primary increase in the plasma [HCO_3^-] and may be due to either **HCO_3^- gain** from alkali administration or, more commonly, **excessive H^+ loss**. The latter may result from the loss of H^+-rich fluids, including upper GI secretions. **Contraction alkalosis** refers to the contraction of volume around a fixed content of bicarbonate.
- Maintenance requires a concomitant impairment in renal HCO_3^- excretion, because the kidney normally has a large capacity to excrete HCO_3^-. This occurs as a result of a **decreased glomerular filtration rate (GFR)** or enhanced tubular HCO_3^- reabsorption from **chloride depletion**, **volume contraction**, and **hypokalemia**. A decrease in filtered chloride is sensed by the macula densa and, as a result of tubuloglomerular feedback, reduces filtered HCO_3^- and stimulates aldosterone release. It also limits adaptive distal HCO_3^- secretion. Metabolic alkalosis is often described as being **chloride responsive** or **chloride unresponsive**.

DIAGNOSIS

Clinical Presentation

Because key causes of metabolic alkalosis are related to volume contraction, patients may present with signs of volume depletion. Occasionally, patients demonstrate hypertension or mild ECF expansion as a result of mineralocorticoid excess.

Diagnostic Testing

- The etiology of metabolic alkalosis is often obvious from the history. Common causes include loss of

http://internalmedicinebook.com

upper GI secretions through vomiting or excessive urinary H^+ loss from diuretics.

- Urine electrolytes are generally useful in identifying the etiology of a metabolic alkalosis when the history and physical are unrevealing.
  - A **urine [Cl^-]** <20 mEq/L is consistent with **chloride-responsive** metabolic alkalosis and usually indicates volume depletion. A urine [Cl^-] >20 mEq/L indicates a chloride-unresponsive cause (see Table 12-3).
  - Urine [Na^+] is not reliable in predicting the effective circulating volume in these conditions, because *bicarbonaturia obligates renal Na^+ loss* even in volume depletion.
- **Serum potassium** levels are often low in metabolic alkalosis due to transcellular shifts. Furthermore, hypokalemia contributes to alkalosis by increasing tubular H^+ secretion and Cl^- wasting.

TREATMENT

- **Chloride-responsive** metabolic alkaloses are most effectively treated with saline resuscitation until euvolemia is achieved. The increase in filtered chloride leads to improved renal handling of the bicarbonate load.
- **Chloride-unresponsive** metabolic alkaloses do not respond to saline administration and are often associated with a normal or expanded ECF volume.
  - Mineralocorticoid excess can be managed with a K^+-sparing diuretic (amiloride or spironolactone) and repletion of the K^+ deficit.
  - The alkalosis from excessive alkali administration will quickly resolve once the HCO_3^- load is withdrawn, assuming normal renal function.
  - Given that the presence of hypokalemia will continue to perpetuate some degree of alkalosis regardless of other interventions, potassium must be repleted in all cases of metabolic alkalosis.
  - Acetazolamide can be used if the alkalosis persists despite the above interventions or if saline administration is limited by a patient's volume overload. This therapy promotes bicarbonaturia, although renal K^+ loss is enhanced as well. Acetazolamide can be dosed at 250 mg q6h × 4 or as a single dose of 500 mg.
  - Severe alkalemia (pH >7.70) with ECF volume excess and/or renal failure can be treated with isotonic (150 mEq/L) HCl administered via a central vein. The amount of HCl required can be calculated as follows: (0.5 × lean weight in kg) × ([HCO_3^-] − 24). Correction should occur over 8-24 hours.

Respiratory Acidosis

GENERAL PRINCIPLES

The causes of respiratory acidosis can be divided into hypoventilation from (a) **respiratory center depression**, (b) **neuromuscular failure**, (c) **decreased respiratory system compliance**, (d) **increased airway resistance**, and (e) **increased dead space** (see Table 12-3).

DIAGNOSIS

- Symptoms of respiratory acidosis result from changes in the cerebrospinal fluid (CSF) pH. A very severe hypercapnia may be well tolerated if it is accompanied by renal compensation and a relatively normal pH. Conversely, a modest rise in pCO_2 can be very symptomatic if acute.
- Initial symptoms and signs may include headache and restlessness, which may progress to generalized hyperreflexia/asterixis and coma.

TREATMENT

- Treatment is directed at correcting the underlying disorder and improving ventilation (see Chapter 10, Pulmonary Diseases).
- Administration of $NaHCO_3$ to improve the acidemia may *paradoxically worsen the pH* in situations of limited ventilation. The administered HCO_3^- will combine with H^+ in the tissues and form pCO_2 and water. If ventilation is fixed, this extra CO_2 generated cannot be blown off and worsening hypercapnia will result. Therefore, HCO_3^- should, in general, be avoided in *pure* respiratory acidoses.

Respiratory Alkalosis

GENERAL PRINCIPLES

The common causes of hyperventilation resulting in respiratory alkalosis are given in Table 12-3.

DIAGNOSIS

Clinical Presentation

- The rise in CSF pH that occurs with **acute respiratory alkalosis** is associated with a significant reduction in cerebral blood flow that may lead to light-headedness and impaired consciousness. Generalized membrane excitability can result in seizures and arrhythmias. Symptoms and signs of acute hypocalcemia (see Calcium, Hypocalcemia, Clinical Presentation section) may be evident from the abrupt fall in ionized calcium that can occur.
- **Chronic respiratory alkalosis** is usually asymptomatic because a normal pH is well defended by compensation.

Diagnostic Testing

The rise in pH from **acute respiratory alkalosis** can cause a reduced ionized calcium, a profound hypophosphatemia, and hypokalemia.

TREATMENT

- Treatment of respiratory alkalosis should focus on identifying and treating the underlying disease.
- In intensive care unit patients, this may involve changing the ventilator settings to decrease ventilation (see Chapter 8, Critical Care).

13
Renal Diseases

Rajesh Rajan
Seth Goldberg
Daniel W. Coyne

Evaluation of the Patient with Renal Disease

DIAGNOSIS

Clinical Presentation

- Renal disease often is asymptomatic or presents with nonspecific complaints. Its presence is frequently first noted on abnormal routine laboratory data, generally as an elevated serum creatinine (Cr) level. An abnormal urinalysis or sediment, with proteinuria, hematuria, or pyuria, may also indicate renal disease.
- When the decline in renal function is acute or advanced, a variety of nonspecific symptoms may be present. Generalized malaise, worsening hypertension, dependent or generalized edema, or decreasing urine output may accompany more severe renal insufficiency.

Diagnostic Testing

The focus of the initial evaluation of the patient with renal disease is to determine the need for emergent dialysis. Then, investigations to identify the etiology are undertaken, while differentiating components of acute and chronic disease.

- **Basic diagnostic testing**
  - A basic evaluation includes electrolytes (with calcium and phosphorus), Cr, blood urea nitrogen (BUN), and albumin. When Cr is stable over days to weeks, it can be used to estimate glomerular filtration rate (GFR), which can be calculated by the Cockcroft-Gault formula for Cr clearance:

    [(140 - age) (ideal body weight in kg) (0.85 for women)] / (72 × Cr in mg/dL)
  - However, as Cr is secreted by the tubules, particularly as renal function worsens, this formula has the tendency to overestimate the GFR.
  - The Modification of Diet in Renal Disease (MDRD) formulas can calculate the GFR and take into account BUN, albumin, and race in addition to age and gender (*http://mdrd.com*). When the MDRD GFR is >60 mL/min/1.73 m^2, chronic kidney disease (CKD) should not be diagnosed unless other evidence of renal damage (e.g., proteinuria) is present.
  - The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation is based on the same variables as the MDRD equation but performs better and with less bias than the MDRD equation, especially in patients with higher GFR.
- **Urine studies**

  Routine urine studies include a urine dipstick (for protein, blood, glucose, leukocyte esterase, nitrites, pH, and specific gravity) as well as a freshly voided specimen for microscopic examination (looking for cells, casts, and crystals). The urine sample is centrifuged at 2100 rpm for 5 minutes, and then most of the supernatant is poured off. The pellet is resuspended by gently tapping the side of the tube.
  - **Proteinuria** can be estimated from a spot urine protein-to-creatinine ratio, where the serum Cr must be stable to ensure a steady state in the urine. A normal ratio is <250 mg of protein per gram of Cr. A 24-

hour urine collection for protein can be obtained when the serum Cr is not at a stable baseline.

- **Hematuria** (more than three red blood cells [RBCs] per high-power field) can represent an infectious, inflammatory, or malignant process anywhere along the urinary tract. Dysmorphic RBCs (with rounded protuberances) suggest a glomerular source of bleeding and can be accompanied by RBC casts formed within the tubules. The absence of RBCs in a patient with a positive dipstick for blood suggests hemolysis or rhabdomyolysis (forms of pigment nephropathy).
- **White blood cells** (WBCs) in the urine represent an infectious or inflammatory process. This may be seen with a urinary tract infection (UTI), parenchymal infections such as pyelonephritis or abscess, or acute interstitial nephritis (AIN). Urine eosinophils can be identified with the Giemsa stain when evaluating for AIN, atheroembolic disease, or prostatitis, although the sensitivity of this test is low. WBC casts are consistent with AIN and pyelonephritis but can also be seen as part of an active sediment in inflammatory glomerular diseases.
- **Additional biochemistry tests can be ordered to evaluate for specific etiologies and will be discussed in the individual sections below.**

- **Imaging**
  - **Renal ultrasonography** can document the presence of two kidneys, assess size, and identify hydronephrosis or renal cysts. Small kidneys (<9 cm) generally reflect chronic disease, although kidneys may be large (generally >13 cm) in diabetes, HIV, deposition disorders, and polycystic kidney disease. A discrepancy in kidney size of >2 cm suggests unilateral renal artery stenosis with atrophy of the affected kidney. The presence of hydronephrosis suggests obstructive nephropathy. Retroperitoneal fibrosis can encase the ureters and prevent dilation despite the presence of an obstruction.
  - **CT** has less utility in the evaluation of kidney disease because the iodinated contrast dye can be nephrotoxic and may cause worsening renal function. However, noncontrast helical CT scanning has become the test of choice in evaluating nephrolithiasis.
  - **MRI** and magnetic resonance angiography (MRA) can be helpful in evaluating renal masses, detecting renal artery stenosis, and diagnosing renal vein thrombosis. Unlike standard arteriography, MRA does not require the administration of nephrotoxic contrast agents but does employ gadolinium-based contrast agents, which are associated with the development of nephrogenic systemic fibrosis (NSF) in patients with advanced renal failure or dialysis dependence (*Clin Radiol 2014;69:661*). Guidelines that limit the use of gadolinium in at-risk patients have decreased the incidence of NSF. The available contrast agents should be used with caution when necessary.
  - **Radionuclide scanning** uses technetium isotopes to assess the contribution of each kidney to the overall renal function, providing important information if unilateral nephrectomy is being considered for malignancy or for living donation. Renal scanning is also useful in transplantation, where renal perfusion and excretion of the tracer can be followed.
- **Diagnostic procedures**
  - **Kidney biopsy** can determine diagnosis, classify disease, guide therapy, and provide prognostic information in many settings, particularly in the evaluation of glomerular or deposition diseases. Biopsy of a native kidney may be indicated in adults with unexplained proteinuria, hematuria, or renal dysfunction. Biopsy of a renal transplant allograft may be necessary to distinguish acute rejection from medication toxicity and other causes of renal dysfunction. Shrunken fibrotic kidneys are unlikely to yield useful diagnostic information; they also have an increased risk of postprocedural bleeding, and

biopsy should generally be avoided in these cases.

- Preparative measures for native kidney biopsy include avoiding aspirin and antiplatelet agents for 5-7 days and reversing anticoagulation before procedure,

ultrasonography (to document the presence of two kidneys and assess size and location), urinalysis or urine culture to exclude infection, blood pressure control, and correction of coagulation parameters. If uremic platelet dysfunction is suspected by an elevated bleeding time (>10 minutes) or abnormal platelet function assays, IV desmopressin acetate (DDAVP at 0.3 μg/kg) can be infused 30 minutes prior to biopsy. Patients on dialysis should not receive heparin immediately after the biopsy. If body habitus precludes a percutaneous approach, a transjugular renal biopsy can be performed.

- Serial blood counts should be obtained at 6-hour intervals overnight. A hemoglobin drop of approximately 10% is common after the procedure. Difficulty voiding after the procedure may represent urethral clot obstructing the flow of urine.

Acute Kidney Injury

GENERAL PRINCIPLES

Definition

There is no precise definition for acute kidney injury (AKI). It may be characterized by an abrupt increase in serum Cr ≥0.3 mg/dL within 48 hours or a similar increase over a few weeks or months.

Classification

Renal failure can be classified as oliguric or nonoliguric based on the amount of urine output. Cutoffs of approximately 500 mL/d or 25 mL/h for 4 hours are frequently used in clinical practice.

Etiology

Etiologies of AKI are classically divided according to the anatomic location of the physiologic defect. **Prerenal** disease involves a disturbance of renal perfusion, whereas **postrenal** disease involves obstruction of the urinary collecting system. **Intrinsic** renal disease involves the glomeruli, microvasculature, tubules, or interstitium of the kidneys. Table 13-1 lists some of the common causes of AKI.

TABLE 13-1 Causes of Acute Renal Failure

Prerenal	Intrinsic	Postrenal
Hypovolemia Hypotension (including sepsis) Loss of autoregulation (NSAIDs, RAAS blockers) Abdominal	Tubular: Ischemic ATN, toxic ATN (contrast, pigment, uric acid) Vascular: Glomerulonephritis, dysproteinemia, thrombotic microangiopathy (HUS, TTP), atheroembolic disease Interstitial: Acute interstitial nephritis, pyelonephritis	Urethral obstruction Ureteral obstruction (bilateral, or unilateral if solitary kidney)

compartment syndrome
Renal artery stenosis
Heart failure
Hepatic cirrhosis

ATN, acute tubular necrosis; HUS, hemolytic-uremic syndrome; RAAS, renin-angiotensin-aldosterone system; TTP, thrombotic thrombocytopenic purpura.

Prerenal

- The term **prerenal azotemia** implies preserved intrinsic renal function in the setting of renal hypoperfusion and reduced GFR. The effective circulating volume is decreased, resulting from intravascular volume depletion, low cardiac output, or disordered vasodilation (hepatic cirrhosis).
- When the cause is true volume depletion, presentation involves a history of excessive fluid loss, reduced intake, or orthostatic symptoms. The physical exam may reveal dry mucous membranes, poor skin turgor, and orthostatic vital signs (drop in blood pressure by at least 20/10 mm Hg or an increase in heart rate by 10 bpm after standing from a seated or lying position). The central venous pressure is typically <8 cm H2O.
- Low cardiac output causes prerenal azotemia via a drop in the effective circulating volume, despite total body volume overload. In addition, sympathetic and neurohormonal systems are activated, leading to the stimulation of the renin-angiotensin-aldosterone system as well as antidiuretic hormone (ADH), promoting further salt and water retention. This can lead to increased reabsorption of urea nitrogen in relation to creatinine, and patients present with a prerenal pattern on laboratory investigations. In heart failure, diuresis may paradoxically improve the prerenal azotemia by unloading the ventricles and improving cardiac function (see Chapter 5, Heart Failure and Cardiomyopathy). The use of ultrafiltration was evaluated and found to be inferior to pharmacologic therapies; it resulted in more adverse events in the treatment of acute decompensated heart failure (*N Engl J Med 2012;367:2296-304*).
- Hepatic failure leads to splanchnic vasodilation and venous pooling, which diminishes the effective circulating volume and activates the renin-angiotensin-aldosterone system along with ADH secretion, despite total body volume overload. This can progress to the **hepatorenal syndrome** (HRS), which is characterized by a rise in serum creatinine of >1.5 mg/dL that is not reduced with administration of albumin (1 g/kg of body weight) and after a minimum of 2 days off diuretics. The diagnosis of HRS should be in the absence of shock, nephrotoxic agents, or findings of renal parenchymal disease (*N Engl J Med 2009;361:1279*). Spontaneous bacterial peritonitis, overdiuresis, gastrointestinal bleeding, or large-volume paracentesis can precipitate HRS in a cirrhotic patient. Management of the renal disease is supportive, and if definitive treatment of the liver disorder (either through recovery or via transplantation) can occur, renal recovery is common. Temporizing measures include treatment of the underlying precipitating factor (e.g., peritonitis, gastrointestinal bleeding) and withholding diuretics. Dialytic support can be used as a bridge to transplantation in appropriate candidates. Additional treatment options are discussed further in Chapter 19, Liver Diseases.
- In the volume-depleted patient, certain medications can block the ability of the kidney to autoregulate blood flow and GFR. NSAIDs inhibit the counterbalancing vasodilatory effects of prostaglandins and can induce AKI in volume-depleted patients. Angiotensinconverting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can cause efferent arteriolar vasodilation and a drop in the GFR.

- Abdominal compartment syndrome, from intestinal ischemia, obstruction, or massive ascites, can compromise flow through the renal vasculature via increased intra-abdominal pressure (IAP). An IAP >20 mm Hg, measured via a pressure transducer attached to the bladder catheter, suggests the diagnosis.

Postrenal

- Postrenal failure occurs when the flow of urine is obstructed anywhere within the urinary collecting system. Common causes include **prostatic enlargement, bilateral kidney stones, or malignancy**. The increased intratubular hydrostatic pressure leads to the diminished GFR. Bilateral involvement (or unilateral obstruction to a solitary kidney) is required to produce a significant change in the Cr level. When the diagnosis is suspected,

  a renal ultrasound should be performed early to evaluate for hydronephrosis. However, hydronephrosis may be less pronounced when there is concomitant volume depletion or if retroperitoneal fibrosis has encased the ureters, preventing their expansion.
- Treatment depends on the level of obstruction. When urethral flow is impeded (usually by prostatic enlargement in men), placement of a bladder catheter can be both diagnostic and therapeutic; **a postvoid residual urine volume >300 mL** strongly suggests the diagnosis. When the upper urinary tract is involved, urologic or radiologic decompression is necessary, with stenting or placement of percutaneous nephrostomy tubes.
- Relief of bilateral obstruction is frequently followed by a **postobstructive diuresis**. Serum electrolytes need to be closely monitored if polyuria ensues, and replacement of approximately half of the urinary volume with 0.45% saline is recommended.
- Crystals may cause micro-obstructive uropathy within the tubules. IV acyclovir and the protease inhibitor indinavir can induce AKI by this mechanism. The urine may show evidence of crystals, although sometimes not until urine flow is reestablished. Treatment is typically supportive after the offending agent is discontinued. As with relief of other forms of obstructive uropathy, a polyuric phase may occur.

Intrinsic Renal

Causes of intrinsic renal failure can be divided anatomically into tubular, glomerular/vascular, and interstitial categories. Disease can be primarily renal in nature or part of a systemic process.

- **Tubular**
  - **Ischemic acute tubular necrosis (ATN)** is the most common cause of renal failure in the intensive care setting and is the end result of any process that leads to significant hypoperfusion of the kidneys, including sepsis, hemorrhage, or any prolonged prerenal insult.
    - The injury results in the sloughing of renal tubular cells, which can congeal with cellular debris in a matrix of Tamm-Horsfall protein to form granular casts. These have a “muddy brown” appearance and are strongly suggestive of ATN in the proper context. The fractional excretion of sodium (FE_{Na}) (>1%) and fractional excretion of urea (FE_{Urea}) (>35%) are typically elevated as the tubules lose their ability to concentrate the urine.
    - Management of ATN is supportive, with avoidance of further nephrotoxic insults. Fluid management is aimed at maintaining euvolemia. Volume deficits, if present, should be corrected. If volume overload and oliguria become evident, a diuretic challenge is reasonable, typically with IV furosemide (40-120 mg boluses or a continuous drip at 10-20 mg/h). This has not been shown to hasten recovery but can

simplify overall management.

- Recovery from ATN may take days to weeks to occur but can be expected in >85% of patients with a previously normal Cr. Dialysis may be necessary to bridge the time to recovery.

- Toxic ATN can result from endogenous chemicals (e.g., hemoglobin, myoglobin) or exogenous medications (e.g., iodinated contrast, aminoglycosides). These forms share many of the diagnostic features of ischemic ATN.

  - **Iodinated contrast** is a potent renal vasoconstrictor and is toxic to renal tubules. When renal injury occurs, the Cr typically rises 24 hours after exposure and peaks in 3-5 days. Risk factors for contrast nephropathy include CKD, diabetes, volume depletion, heart failure, higher contrast volumes, and use of hyperosmolar contrast. Preventative measures include periprocedure hydration and discontinuation of diuretics. Isotonic saline at 1-2 mL/kg/h started 3-12 hours before the procedure along with a goal of postprocedural diuresis of 150 mL/h has been found to be beneficial in reducing contrast-induced injury in high-risk populations. Alternatively, sodium bicarbonate at 150 mEq/L (three ampules in 5% dextrose in water [D5W]) can be given at 3 mL/kg/h for 1 hour prior to exposure, then at 1 mL/kg/h for 6 hours

    after the procedure (*Cardiology 2014;128:62*). Acetylcysteine has not been shown to reduce the incidence of contrast nephropathy.

  - **Aminoglycoside nephrotoxicity** is typically nonoliguric, occurs from direct toxicity to the proximal tubules, and results in the renal wasting of potassium and magnesium. Replacement of these electrolytes may become necessary. A similar pattern of potassium and magnesium loss is seen in cisplatin toxicity. A prolonged exposure to the aminoglycoside of at least 5 days is required. Peak and trough levels correlate poorly with the risk of developing renal injury. Risk may be minimized by avoiding volume depletion and by using the extended-interval dosing method (see Chapter 15, Antimicrobials).

  - **Pigment nephropathy** results from direct tubular toxicity by hemoglobin and myoglobin. Vasoconstriction may also play a role. The diagnosis may be suspected by a positive urine dipstick test for blood but an absence of RBCs on microscopic examination. In **rhabdomyolysis**, the creatine kinase (CK) level is elevated to at least 10 times the upper limit of normal with a disproportionate rise in Cr, potassium, and phosphorus. Aggressive IV fluid administration should be initiated immediately, and large volumes are required to replace the fluid lost into necrotic muscle tissue. If urine flow is established, alkalinization with sodium bicarbonate (150 mEq/L, three ampules) can increase the solubility of these pigments, although this maneuver may worsen the hypocalcemia.

  - In **tumor lysis syndrome**, acute uric acid nephropathy can result. In addition to the elevated Cr, there is typically hyperuricemia, hyperphosphatemia, and hypocalcemia. A ratio of urine uric acid to urine Cr that is >1 is consistent with this diagnosis, as is the finding of uric acid crystals in the urine sediment. Prophylaxis with allopurinol 600 mg can decrease uric acid production. Rasburicase (15 mg/kg IV) is highly effective at depleting uric acid levels and can be given as prophylaxis or as treatment. Alkalinization of the urine should be avoided if hyperphosphatemia is present because this could increase the risk of calcium phosphate precipitation in the urine.

- **Glomerular/vascular**

  - The finding of **dysmorphic urinary RBCs, RBC casts, or proteinuria in the nephrotic range (>3.5 g/d)** strongly suggests the presence of a glomerular disease. Glomerular diseases are described individually in further detail later in this chapter.

  - A small subgroup of glomerular diseases can present with rapidly deteriorating renal function, termed

rapidly progressive glomerulonephritis (RPGN). A nephritic picture is common, with RBC casts, edema, and hypertension. A renal biopsy may reveal the specific underlying disease, but crescent formation in >50% of glomeruli is usually present. For those deemed to have salvageable renal function, management is with highdose pulse glucocorticoid therapy (IV methylprednisolone 7-15 mg/kg/d for 3 days) followed by a course of oral prednisone (1 mg/kg/d for 1 month, then tapered over the next 6-12 months).

Cyclophosphamide is typically added to this regimen, with monthly IV doses (1 g/m^2) having less cumulative toxicity than the daily oral dosing strategy (2 mg/kg/d).

- Thrombotic microangiopathy (TMA) includes both **hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP)**. Causes include diarrheal bacterial toxins and medications (mitomycin C, clopidogrel, cyclosporine, tacrolimus), and it may be associated with pregnancy or malignancies of the gastrointestinal tract. Atypical HUS has been described in patients with mutations in the genes coding for proteins that regulate the complement cascade, such as factor H and factor I. These patients have normal *ADAMTS13* activity and do not have Shiga toxin-associated diarrhea. Eculizumab has been found to be a safe and effective way of treating atypical HUS (*Pediatr Nephrol 2014;29:841*). Diagnosis and therapy are discussed in Chapter 20, Disorders of Hemostasis and Thrombosis.

- **Atheroembolic disease** can be seen in patients with diffuse atherosclerosis after undergoing an invasive aortic or other large artery manipulation, including cardiac catheterization, coronary bypass surgery, aortic aneurysm repair, and placement of an intra-aortic balloon pump. Physical findings may include retinal arteriolar plaques, lower extremity livedo reticularis, and areas of digital necrosis. Eosinophilia, eosinophiluria, and hypocomplementemia may be present, and WBC casts may be found in the urine sediment. However, in many cases, the only laboratory abnormality is a rising Cr that follows a stepwise progression. Renal biopsy shows cholesterol clefts in the small arteries. Anticoagulation may worsen embolic disease and should be avoided if possible. No specific treatment is available. Many patients progress to CKD and even to endstage renal disease (ESRD).

- **Interstitial**
  - **AIN** involves inflammation of the renal parenchyma, typically caused by medications or infections. The classic triad of **fever, rash, and eosinophilia** is seen in less than one-third of patients, and its absence does not exclude the diagnosis. Pyuria, WBC casts, and eosinophiluria are also suggestive of AIN. β-Lactam antibiotics are the most frequently cited causative agents, but nearly all antibiotics can be implicated. The time course typically requires exposure for at least 5-10 days before renal impairment occurs. Other medications, such as proton pump inhibitors and allopurinol, have been associated with AIN. NSAIDs can produce AIN with nephrotic range proteinuria. Streptococcal infections, leptospirosis, and sarcoidosis have all been implicated in AIN.
  - Treatment is principally the withdrawal of the offending agent. Renal recovery typically ensues, although the time course is variable, and temporary dialytic support may be necessary in severe cases. A short course of prednisone at 1 mg/kg/d may hasten recovery.
  - Parenchymal infections with **pyelonephritis or renal abscesses** are uncommon causes of AKI. Bilateral involvement is usually necessary to induce a rise in Cr. Urine findings include pyuria and WBC casts, and antibiotic therapy is guided by culture results.

DIAGNOSIS

- Uncovering the cause of AKI requires careful attention to the events preceding the rise in Cr. In the

hospitalized patient, blood pressure patterns, hydration status, medications, and iodinated contrast use must be investigated. Antibiotic dose and duration as well as PRN medications should not be overlooked.

- Evidence of ongoing hypovolemia or hypoperfusion is suggestive of prerenal disease. Most causes of postrenal disease are identified on ultrasound by dilation of the collecting system or by massive urine output on placement of a bladder catheter. When promptly corrected, prerenal and postrenal disorders can show a rapid decrease in the serum Cr, and failure of this to occur can suggest an alternative diagnosis.
- **Urinary casts** point toward an intrinsic cause of AKI. Granular casts ("muddy brown") suggest ATN, WBC casts suggest an inflammatory or infectious interstitial process, and RBC casts strongly suggest glomerular disease. Identification of crystals in the urine sediment may be supportive of kidney disease related to intoxication of ethylene glycol, uric acid excretion, tumor lysis syndrome, or medications such as acyclovir and indinavir. This underscores the importance of examining fresh urinary sediment in the evaluation of AKI.

Various laboratory parameters can be used to differentiate prerenal states from ATN in oliguric patients and are summarized in Table 13-2. The basis for these tests is to evaluate tubular integrity, which is preserved in prerenal disease and lost in ATN. In states of hypoperfusion, the kidneys should avidly reabsorb sodium, resulting in a low FE_{Na}: $FE_{Na} = [(U_{Na} \times P_{Cr})/(P_{Na} \times U_{Cr})] \times 100$, where U is urine and P is plasma.

TABLE 13-2 Laboratory Findings in Oliguric Acute Kidney Injury

Diagnosis	BUN:Cr	FE_{Na} (%)	Urine Osmolality (mOsm/kg)	Urine Na	Urine SG	Sediment
Prerenal azotemia	>20:1	<1%	>500	<20	>1.020	Bland
Oliguric ATN	<20:1	>1%	<350	>40	Variable	Granular casts

ATN, acute tubular necrosis; BUN, blood urea nitrogen; Cr, creatinine; FE_{Na}, fractional excretion of sodium; SG, specific gravity.

- **A value <1% suggests renal hypoperfusion with intact tubular function.** Loop diuretics and metabolic alkalosis can induce natriuresis, increase the FE_{Na}, and mask the presence of renal hypoperfusion. The FE_{Urea} can instead be calculated in these settings, where a value of <35% suggests a prerenal process.
- Contrast and pigment nephropathy can result in a low FE_{Na} due to early vasoconstriction ("prerenal" drop in glomerular perfusion), as can glomerular diseases due to intact tubular function. The FE_{Na} also has limited utility when AKI is superimposed on CKD because the underlying tubular dysfunction makes the test difficult to interpret.
- With hypoperfusion, the urine is typically concentrated, containing an osmolality >500 mOsm/kg and a high specific gravity (>1.020). In ATN, concentrating ability is lost and the urine is usually isosmolar to the

serum (isosthenuria). In the blood, the ratio of BUN to Cr is normally <20:1, and an elevation is consistent with hypovolemia.

TREATMENT

- Disease-specific therapies were covered earlier. In general, treatment of AKI is primarily supportive in nature. Volume status must be evaluated to correct for hypovolemia or hypervolemia. Volume deficits, if present, should be corrected, after which the goal of fluid management should be to keep input equal to output. In the oliguric volume-overloaded setting, a trial of diuretics (usually high-dose loop diuretics in a bolus or as a continuous drip) may simplify management, although it has not been shown to hasten recovery.
- Electrolyte imbalances should be corrected in the setting of AKI. Hyperkalemia, when mild (<6 mEq/L), may be treated with dietary potassium restriction and potassium-binding resins (e.g., sodium polystyrene sulfonate). When further elevated or accompanied by ECG abnormalities, immediate medical therapy is indicated, with calcium gluconate, insulin and glucose, inhaled β-agonists, and possibly bicarbonate (see Chapter 12, Fluid and Electrolyte Management). Severe hyperkalemia that is refractory to medical management is an indication for urgent dialysis.
- Mild **metabolic acidosis** can be treated with oral sodium bicarbonate, 650-1300 mg thrice daily. Severe acidosis (pH <7.2) can be temporized with IV sodium bicarbonate but requires monitoring for volume overload, rebound alkalosis, and hypocalcemia. Acidosis that is refractory to medical management is an indication for urgent dialysis.

SPECIAL CONSIDERATIONS

All patients with AKI require daily assessment to determine the need for renal replacement therapy. Severe acidosis, hyperkalemia, or volume overload refractory to medical

management mandates the initiation of dialysis. Certain drug and alcohol intoxications (methanol, ethylene glycol, or salicylates) should be treated with hemodialysis. Uremic pericarditis (with a friction rub) or encephalopathy should also be treated promptly with renal replacement therapy. Patients suffering from acute oliguric renal failure who are not expected to recover promptly likely benefit from earlier initiation of dialysis.

Glomerulopathies

GENERAL PRINCIPLES

- The presentation of glomerular diseases can be thought of as existing on a continuum. On one end is the nephrotic syndrome, characterized by proteinuria >3.5 g/d and accompanied by hypoalbuminemia, hyperlipidemia, and edema, and on the other end of the spectrum is the nephritic syndrome, characterized by hematuria, hypertension, edema, and renal insufficiency. Most specific disease entities present somewhere in between and have overlapping features but with a tendency to produce one syndrome over the other.
- When a glomerular process is suspected, it may be useful to check antinuclear antibodies (ANA), complement levels (C3, C4), cryoglobulins, and viral (HIV, hepatitis B and C) serologies. A serum protein electrophoresis (SPEP) and urine immunofixation can be performed in proteinuric patients to evaluate for a monoclonal

gammopathy and may be suspected by a large protein-albumin gap.

- When a nephritic process is suspected by the clinical presentation, testing for antiglomerular basement membrane (anti-GBM) antibodies, antineutrophil cytoplasmic antibodies (ANCA), and anti-streptolysin-O (ASO) titers may be helpful in narrowing the differential diagnosis.
- Biopsy findings also correlate with these syndromes. Nephrotic diseases typically show injury along the filtration barrier, with thickening of the GBM or fusion of the podocyte foot processes. By comparison, nephritic diseases generally show varying degrees of mesangial cell proliferation and mesangial deposition and, with more aggressive disease, may reveal crescent formation.
- Nephrotic diseases are more likely to be minimal change disease, membranous nephropathy, focal segmental glomerulosclerosis, diabetic nephropathy, and deposition dysproteinemias.
- Nephritic syndromes are more likely to be membranoproliferative glomerulonephropathy, IgA nephropathy/Henoch-Schönlein purpura, postinfectious glomerulonephritis, lupus nephritis, anti-GBM disease, and granulomatosis with polyangiitis.

TREATMENT

- Many disorders share the same features, and general therapeutic maneuvers can be addressed as a group. Specific therapies for individual glomerular diseases are discussed in the following text.
- Glomerular disease presenting with proteinuria should rely on treatment with **ACE inhibitors or ARBs** to reduce the intraglomerular pressure. Efficacy can be monitored by serial urine protein-to-Cr ratios. Electrolytes and Cr should be checked within 1-2 weeks of initiation of therapy or an increase in dose to document stability of renal function and potassium. Modest dietary protein restriction to 0.8 g/kg/d may slow progression, but this remains controversial.
- Edema and volume overload can usually be effectively managed with **diuretics** combined with **sodium restriction**. Aggressive treatment of hypertension can also slow progression of renal disease.

- The hyperlipidemia associated with the nephrotic syndrome responds to dietary modification and **statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors)**.
- The nephrotic syndrome produces a hypercoagulable state and can predispose to thromboembolic complications. Deep venous thrombi and renal vein thrombosis may occur and should be treated with heparin anticoagulation followed by long-term warfarin therapy. Prophylactic anticoagulation is controversial and may be beneficial in severely nephrotic patients, particularly with membranous nephropathy (MN). Exact mechanisms of thrombosis remain controversial but likely include urinary loss of anticlotting proteins, increased synthesis of clotting factors, or local activation of the glomerular hemostasis system.
- When **immunosuppression** is considered, the risk of therapy should always be weighed against the potential benefit. Renal salvageability should be addressed, and patients with advanced disease on presentation who are unlikely to benefit from such treatment may be better served by avoiding the risks of high-dose immunosuppression. Cytotoxic agents (e.g., cyclophosphamide, chlorambucil) require close monitoring of WBC counts, checked at least weekly at the initiation of therapy. Dose adjustments may be needed to maintain the WBC count >3500 cells/μL. Rituximab, a monoclonal antibody directed against CD20, has shown promise in a variety of immune-mediated disorders, including severe lupus nephritis (LN), MN, and ANCA-positive vasculitis, where it has been given IV as four weekly doses of 375 mg/m^2 (*N Engl J Med 2010;363:221*).

Minimal Change Disease

GENERAL PRINCIPLES

Epidemiology

Minimal change disease (MCD) is the most common cause of the nephrotic syndrome in children but has a second peak in adults aged 50-60 years. Typically, there is sudden onset of proteinuria with hypertension and edema as well as the full nephrotic syndrome, although renal insufficiency is unusual.

Associated Conditions

Secondary forms of MCD may accompany certain malignancies (Hodgkin disease and solid tumors being the most common). A form of interstitial nephritis associated with NSAID use may also be associated with MCD.

DIAGNOSIS

The kidney biopsy reveals normal glomeruli on light microscopy and negative immunofluorescence. Electron microscopy shows effacement of the foot processes as the only histologic abnormality.

TREATMENT

- In adults, treatment with oral prednisone at 1 mg/kg/d may induce remission (decrease in proteinuria) in 8-16 weeks. Once in remission, the steroids can be tapered over 3 months and then discontinued. The urine protein excretion should be followed during this taper.
- Relapse may occur in up to 75% of adults. Reinstitution of prednisone is often effective. If the patient is steroid dependent or steroid resistant, cytotoxic agents may be needed, with cyclophosphamide 2 mg/kg/d or chlorambucil 0.2 mg/kg/d. Cyclosporine 5 mg/kg/d is an alternative therapy. Rituximab may be beneficial in frequently relapsing or glucocorticoid-dependent MCD (*Kidney Int 2013;83:511*).

Membranous Nephropathy

GENERAL PRINCIPLES

- MN usually presents with the nephrotic syndrome or heavy proteinuria, whereas renal function is often normal or near normal. Disease progression is variable, with one-third remitting spontaneously, one-third progressing to ESRD, and one-third with an intermediate course.
- Secondary forms of MN are associated with systemic lupus erythematosus (SLE; class V), viral hepatitis, syphilis, or solid organ malignancies. Medications such as gold and penicillamine can also induce this process.

DIAGNOSIS

Kidney biopsy shows thickening of the GBM on light microscopy, with “spikes” on silver stain, representing areas of normal basement membrane interposed between subepithelial deposits. These deposits correlate with IgG and C3 on immunofluorescence and are also seen on electron microscopy. Antibodies to the podocyte antigen phospholipase A_2 receptor have been implicated in 70% of adult idiopathic MN, although serologic testing is currently only used in the research setting.

http://internalmedicinebook.com

TREATMENT

Because of the generally good prognosis, specific therapy should be reserved for patients at higher risk for progression (reduced GFR, male gender, age >50 years, hypertension) or heavy proteinuria. Treatment options include regimens with prednisone 0.5 mg/kg/d and cytotoxic agents (chlorambucil 0.2 mg/kg/d or cyclophosphamide 2.5 mg/kg/d) on alternating months for 6-12 months.

Focal Segmental Glomerulosclerosis

GENERAL PRINCIPLES

- Focal segmental glomerulosclerosis (FSGS) is not a single disease but rather a descriptive classification for diseases with shared histopathology. Presentation is with the nephrotic syndrome, hypertension, and renal insufficiency.
- Secondary forms of FSGS are associated with obesity, vesicoureteral reflux, and HIV infection (FSGS of the collapsing variant). HIV can also induce secondary forms of other glomerular diseases such as MN and membranoproliferative glomerulonephropathy.

DIAGNOSIS

The kidney biopsy reveals focal and segmental sclerosis of glomeruli under light microscopy. The degree of interstitial fibrosis and tubular atrophy (rather than glomerular scarring) correlates with prognosis. Immunofluorescence shows staining for C3 and IgM in areas of sclerosis, representing areas of trapped immune deposits. Electron microscopy shows effacement of the podocyte foot processes.

TREATMENT

For patients with nephrotic range proteinuria, a trial of prednisone 1 mg/kg/d can be attempted for 16 weeks. Patients who relapse after a period of apparent responsiveness may benefit from a repeat course of steroids. Nonresponders and relapsers may respond to

treatment with cyclosporine 5 mg/kg/d. Cyclophosphamide and mycophenolate mofetil can also be used. Induction of a complete remission (<0.3 g/d of proteinuria) or a partial remission (50% reduction in proteinuria and <3.5 g/d) is associated with significantly slower loss of renal function.

Diabetic Nephropathy

GENERAL PRINCIPLES

Diabetic nephropathy (DN) is the most common cause of ESRD in the United States. Albuminuria correlates with the risk of progression and is classified as absent (<30 mg/g Cr), formerly microalbuminuria (30-300 mg/g Cr), or formerly macroalbuminuria (>300 mg/g Cr). Early disease has glomerular hyperfiltration with an elevated GFR, followed by a linear decline that may progress to ESRD.

DIAGNOSIS

Diagnostic Testing

Kidney biopsy is not usually performed, unless the rate of renal decline is more rapid than would be anticipated or other diagnoses are suspected. Histology for DN shows glomerular sclerosis with nodular mesangial expansion (Kimmelstiel-Wilson nodules) on light microscopy. Immunofluorescence does not reveal immune deposition. Electron microscopy may show GBM thickening.

TREATMENT

Treatment is centered on aggressive control of glucose and blood pressure. Specific hyperglycemic therapy is discussed further in Chapter 23, Diabetes Mellitus and Related Disorders. An ACE inhibitor or ARB is considered the first-line agent in the treatment of hypertension in diabetic patients and can offer better control of proteinuria. Studies combining ACE inhibitors with an ARB or the direct renin inhibitor aliskiren have shown worse renal and cardiovascular outcomes (*N Engl J Med 2008;358:1547*).

Deposition Disorders/Dysproteinemias

GENERAL PRINCIPLES

Dysproteinemias include **amyloidosis, light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), fibrillary glomerulopathy, and immunotactoid glomerulopathy**. Multiple myeloma may be associated with amyloidosis or LCDD. These disorders can affect the kidney in a variety of ways, including glomerular or tubular deposition, formation of insoluble protein casts in the tubules (micro-obstructive cast nephropathy), or through hypercalcemia and volume depletion. Glomerular deposition is typically associated with heavy proteinuria due to overflow as well as disruption of filtration barrier integrity.

DIAGNOSIS

Diagnostic Testing

Diagnosis is suggested by an abnormal monoclonal protein found in the SPEP, urine protein electrophoresis, or serum free light chains. Immunoglobulin (Ig) chains are not

detected by routine urine dipstick and may be missed unless glomerular involvement has led to general protein leakage. Rarely, these tests are negative, and only tissue biopsy can make the diagnosis.

Diagnostic Procedures

- Biopsy of the kidney can show characteristic deposits. For amyloidosis, this appears as Congo Red-positive β-pleated fibrils of 10 nm in diameter under electron microscopy. Immunofluorescence can identify the specific Ig chains for LCDD (more likely to occur with kappa light chains) and HCDD. Fibrillary and immunotactoid deposits are Congo Red negative. The fibrils of fibrillary glomerulopathy (12-20 nm) are typically thicker than those for amyloid, whereas the microtubules of immunotactoid glomerulopathy are even wider (20-60 nm) with a visible lumen in cross-section. Immunotactoid glomerulonephropathy has a strong association with myelodysplastic disorders.
- When cast nephropathy is implicated in a dysproteinemic disorder, the biopsy shows enlarged tubules filled with proteinaceous material. Immunofluorescence can identify the specific components of these casts.

TREATMENT

Melphalan and prednisone are beneficial in the treatment of amyloidosis and LCDD. Chemotherapy aimed at the underlying disease can be effective in reversing renal disease. When cast nephropathy is present on biopsy, a course of plasmapheresis in conjunction with treatment of the myeloma may stabilize renal function. There is no specific treatment for fibrillary or immunotactoid glomerulopathy, although addressing an underlying malignancy, if present, may slow progression in the latter.

Membranoproliferative Glomerulonephropathy

GENERAL PRINCIPLES

Primary idiopathic membranoproliferative glomerulonephropathy (MPGN) is uncommon. Hepatitis C accounts for most cases of secondary MPGN, frequently in association with cryoglobulinemia. Other secondary causes include HIV, SLE, chronic infections, and various malignancies.

DIAGNOSIS

Clinical Presentation

MPGN can present with the nephrotic syndrome, nephritic syndrome, or a combination of both. Classically, there are three defined subtypes of MPGN (I, II, and III). However, as the molecular basis for disease is elucidated, an alternate classification has been proposed (*N Engl J Med 2012;366:1119*).

- Types I and III are mediated through immune complex formation.
- Type II MPGN (also called dense-deposit disease) and the related disorder C3 glomerulonephritis (C3GN) depend on activation of the alternative complement pathway. Both C3 and C4 are usually low in the immune complex-mediated forms of MPGN, whereas only C3 is low in type II MPGN. The antibody C3 nephritic factor may be present in type II MPGN, stabilizing the C3-convertase and promoting complement consumption. Deficiencies of or antibodies against the complement regulators (factors H and I) may also activate the complement cascade.

Diagnostic Testing

Kidney biopsy shows mesangial proliferation and hypercellularity on light microscopy, with “lobulization” of the glomerular tuft. Accumulation of debris along the filtration barrier may lead to a damage-repair cycle that results in duplication of the GBM, giving a double-contour or “tram track” appearance on silver stain. Immunofluorescence can show granular mesangial and capillary wall deposits of Ig in the immune complex-mediated forms, whereas only the C3 staining is positive in type II MPGN or C3GN. Electron microscopy can show subendothelial (type I) or intramembranous (type II) deposits. Type III disease has subendothelial and subepithelial deposits.

TREATMENT

- In adult idiopathic MPGN, treatment with immunosuppression has not shown a consistent benefit, although this may have been a result of the lumping together of pathophysiologically dissimilar diseases under the older classification scheme.
- Treatment of the secondary forms is targeted at the underlying disease. If renal function is rapidly

deteriorating in the presence of cryoglobulins, plasmapheresis may help stabilize disease. Case reports have demonstrated possible efficacy of eculizumab, an anti-C5 monoclonal antibody, in the treatment of type II MPGN (*N Engl J Med 2012;366:1161*).

IgA Nephropathy/Henoch-Schönlein Purpura

GENERAL PRINCIPLES

- IgA nephropathy is typically idiopathic, characterized by a nephritic picture with microscopic (and less commonly macroscopic) hematuria and mild nonnephrotic range proteinuria.
- Presentation is most commonly in the second or third decade of life, generally following a slowly progressive course. Some patients may exhibit a crescentic form with a rapid decline in renal function resulting in ESRD.
- Henoch-Schönlein purpura is a related disorder that may represent a systemic form of the same disease, with vasculitic involvement of the skin (palpable purpura of the lower trunk and extremities), gastrointestinal tract, and joints.

DIAGNOSIS

Diagnostic Testing

Kidney biopsy shows increased mesangial cellularity on light microscopy, with IgA and C3 deposition on immunofluorescence. Abnormally glycosylated IgA is thought to be responsible for immune complex formation and mesangial deposition. Although serum IgA levels do not correlate with disease activity, events that potentially lead to overproduction (concurrent upper respiratory infection) or decreased clearance (hepatic cirrhosis) may predispose to disease.

TREATMENT

Aggressiveness of therapy depends on severity of disease. For patients with a benign course, conservative management with ACE inhibitors, ARBs, or fish oil (omega-3 fatty acids) may prevent deterioration of renal function, although the benefit of fish oil remains controversial. Progressive disease may benefit from a course of prednisone 1 mg/kg/d with or without cytotoxic agents.

Postinfectious Glomerulonephropathy

GENERAL PRINCIPLES

- Postinfectious glomerulonephropathy classically presents with the nephritic syndrome, hematuria, hypertension, edema, and renal insufficiency. Proteinuria may be present and is usually in the subnephrotic range.
- It is classically associated with streptococcal infection, which typically affects children under the age of 10 years, after a latent period of 2-4 weeks from onset of pharyngitis or skin infection. However, bacterial endocarditis, visceral abscesses, and ventriculoperitoneal shunt infections can also lead to this immune complex-mediated disease.
- Low complement levels are usually seen. ASO titers may be elevated serially, as may anti-DNaseB antibodies in streptococcal-associated disease.

http://internalmedicinebook.com

DIAGNOSIS

Kidney biopsy reveals subepithelial humps on light and electron microscopy corresponding to the deposits on immunofluorescence (IgG, C3). There is widespread mesangial proliferation as well as an infiltration of polymorphonuclear cells.

TREATMENT

Treatment is primarily supportive. Resolution of the underlying infection typically leads to renal recovery in 2-4 weeks, even in cases where dialytic support was needed. A brisk diuresis should be anticipated in the recovery period.

Lupus Nephritis

GENERAL PRINCIPLES

LN can manifest as proteinuria of varying degrees with dysmorphic RBCs and RBC casts and renal insufficiency. Positive lupus serology (e.g., ANA, anti-double-stranded DNA antibodies) and hypocomplementemia are often present during acute flares.

DIAGNOSIS

Renal biopsy can provides diagnostic and prognostic information. The World Health Organization classification has five major categories based on histologic appearance. Class I has normal glomeruli, classes II to IV have increasing degrees of mesangial proliferation, and class V has an appearance similar to MN. Immunofluorescence is usually positive for IgG, IgA, IgM, C1q, C3, and C4, for the “full-house” fluorescence pattern.

TREATMENT

Aggressiveness of therapy considers the renal and extrarenal manifestations of the disease.

- Classes I and II LN rarely require specific treatment, and therapy is directed at the extrarenal manifestations.
- Class III LN, when mild or moderate, can generally be treated with a short course of high-dose steroids (prednisone 1 mg/kg/d).

- Patients with severe class III LN, class IV and V LN, or severe nephritic syndrome should undergo pulse IV methylprednisolone (7-15 mg/kg/d for 3 days) followed by oral prednisone at 0.5-1.0 mg/kg/d. A second agent such as monthly IV cyclophosphamide 0.5-1.0 g/m^2 or oral mycophenolate mofetil 1000 mg thrice daily for a course of 6 months should be used. Remission can be maintained for several years with mycophenolate mofetil 1000 mg twice daily, which was shown to be superior to azathioprine 2 mg/kg/d in preventing relapse (*N Engl J Med 2011;365:1886*).

Pulmonary-Renal Syndromes

GENERAL PRINCIPLES

Several distinct clinical entities make up the pulmonary-renal syndromes where there is vasculitic involvement of the alveolar and glomerular capillaries. Typically, this results in rapidly progressive renal failure often with concurrent pulmonary involvement in the form of alveolar hemorrhage. A nephritic picture predominates, with dysmorphic RBCs and RBC casts in the urine. Arthralgias and fever may represent other systemic manifestations.

DIAGNOSIS

- In **anti-GBM antibody disease**, circulating antibody to the α-3 chain of type IV collagen is deposited in the basement membrane of alveoli and glomeruli, resulting in linear staining on immunofluorescence. **Goodpasture syndrome** includes pulmonary involvement and can present with life-threatening alveolar hemorrhage. The presence of anti-GBM antibody in the serum supports the diagnosis, and 10-30% of patients will have a positive ANCA serology as well.
- In **granulomatosis with polyangiitis** (GPA; formerly known as Wegener granulomatosis), vasculitic lesions involve the small vessels of the kidneys and may also involve the lungs, skin, and gastrointestinal tract. As in anti-GBM antibody disease, pulmonary hemorrhage may be life threatening. Biopsy findings include a small-vessel vasculitis with noncaseating granuloma formation in the kidneys, lungs, or sinuses.
  - GPA is part of a group of diseases known as *pauci-immune glomerulonephritis* (referring to the absence of immunostaining deposits), which includes Churg-Strauss syndrome (asthma and eosinophilia) and microscopic polyangiitis.
  - In GPA, there is a positive cytoplasmic ANCA directed against serine proteinase-3, whereas in microscopic polyangiitis and Churg-Strauss syndrome, there is a positive perinuclear ANCA directed against myeloperoxidase.

TREATMENT

- In **anti-GBM antibody disease**, the goal of therapy is to *clear the pathogenic antibody* while suppressing new production. Treatment is with daily total volume plasmapheresis for approximately 14 days in conjunction with cyclophosphamide 2 mg/kg/d and glucocorticoids (IV methylprednisolone 7-15 mg/kg/d for 3 days, followed by oral prednisone 1 mg/kg/d). Immunosuppression is tapered over 8 weeks. Serial measurement of the anti-GBM antibody level is useful to monitor therapy, with plasmapheresis and immunosuppression continuing until it is undetectable.

  Poor response to therapy is predicted by the presence of oliguria, Cr >5.7 mg/dL, or dialysis dependence on presentation. Even if the likelihood of renal recovery is low, evidence of pulmonary involvement warrants aggressive therapy.

- Treatment of **GPA** is with combined prednisone 1 mg/kg/d (with taper) and cyclophosphamide (IV at 1 g/m^2 monthly or orally at 2 mg/kg/d) for at least 3 months to induce remission. Therapy should then continue with oral steroids for 1 year to prevent relapse. More aggressive management with plasmapheresis and pulse IV steroids may be beneficial for patients presenting with pulmonary hemorrhage or dialysis dependence. Rituximab given IV as four weekly doses of 375 mg/m^2, in combination with steroids, has also been approved for treatment of GPA (*N Engl J Med 2010;363:221*).

  Double-strength sulfamethoxazole-trimethoprim given twice daily has been shown to reduce extrarenal

relapses and to prevent *Pneumocystis (carinii) jirovecii* infection in patients on high-dose immunosuppression.

Polycystic Kidney Disease

GENERAL PRINCIPLES

- Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder resulting in cystic enlargement of the kidney and occurs in approximately 1 in 1000 persons. Approximately 20% of patients with ADPKD do not have a positive family history.
- There are two well-described mutations in the polycystin genes, *PKD1* and *PKD2*. *PKD1* is the most common and present in approximately 85% of ADPKD. *PKD2* is associated with a later onset of disease.
- The mechanism by which cysts form is unclear. The polycystin gene products primarily localize to the cilia of the tubular apical membrane. Disordered regulation of cell division may lead to overgrowth of the tubular segment, eventually pinching off from the rest of the collecting system. Cyst formation affects only a relatively small percentage of tubules, suggesting a “two-hit” hypothesis where a sporadic mutation of the wild-type allele results in local cystogenesis

DIAGNOSIS

Clinical Presentation

- Hypertension is an early feature of ADPKD. As the affected tubules enlarge, they impinge upon the blood flow to neighboring glomeruli, rendering them ischemic. This is turn activates the renin-angiotensin-aldosterone system, leading to systemic hypertension. Onset of kidney failure is highly variable, with half of patients reaching ESRD by the age of 60.
- Cerebral aneurysms, hepatic cysts, mitral valve prolapse, and colonic diverticula are found in association with ADPKD. As cysts enlarge, they may result in a palpable flank mass. Gross hematuria and pain may indicate cyst hemorrhage into the collecting system. Flank pain may also be caused by cyst infection or stretching of the renal capsule.

Diagnostic Testing

- Differentiation from other cystic diseases (acquired cystic disease, medullary sponge kidney, medullary cystic kidney disease) can be made by the presence of enlarged cystic kidneys rather than shrunken or normal-sized cystic kidneys. Acquired cystic disease is often seen in patients with CKD as well as patients on dialysis. The cysts are typically bilateral in atrophic kidneys.
- Ultrasonography reveals multiple cysts. In the setting of a positive family history, a diagnosis of ADPKD can be made from ultrasound findings, with criteria differing according to age. At least three cysts are required in patients under the age of 40 years. In patients aged 40-59 years, at least two cysts in each kidney are needed. For patients age 60 years and older, the diagnosis requires at least four cysts in each kidney.

- Patients with a family history of cerebral aneurysms or with symptoms attributable to a cerebral aneurysm should undergo evaluation with brain MRI/MRA.
- Genetic testing may be considered if patients have equivocal imaging results or if a definitive diagnosis is required.

TREATMENT

- There is currently no specific treatment to prevent cyst formation or slow cyst growth. Aggressive control of hypertension should be practiced, and blockade of the renin-angiotensin-aldosterone system with an ACE inhibitor or ARB is recommended as firstline therapy.
- Gross hematuria from cyst hemorrhage can usually be managed with bed rest, hydration, and analgesia. Resolution may take 5-7 days.
- Cyst infections are generally treated with antibiotics that achieve good penetration into the cysts. Sulfamethoxazole-trimethoprim and ciprofloxacin are the antibiotics of choice. The absence of bacterial growth in the urine does not rule out infection because the cystic fluid does not necessarily communicate with the rest of the collecting system.
- Pain that persists without an obvious hemorrhagic or infectious cause may respond to cyst reduction surgery, particularly if there is a culprit cyst that can be identified and targeted.
- As the underlying mechanism for cyst growth is clarified, newer treatment options are emerging. Past trials investigating the antimetabolites sirolimus and everolimus have been disappointing. A large study of tolvaptan in ADPKD showed a significant reduction in the cyst growth rate but with an uncertain benefit in long-term renal function coupled with signals of potential hepatotoxicity; formal approval awaits the results of further investigation (*N Engl J Med 2012;367:2407*).

Nephrolithiasis

GENERAL PRINCIPLES

- **Calcium-based stones** are the most common and appear predominantly as calcium oxalate or calcium phosphate salts. These stones are radiopaque. Calcium phosphate stones can appear as elongated, blunt crystals and form in alkaline urine. Calcium oxalate stones can be found in acidic or alkaline urine and can be dumbbell shaped or appear as paired pyramids (giving them an envelope appearance when viewed on end).
- **Uric acid stones** can be idiopathic or develop as part of hyperuricosuric states such as gout and myeloproliferative disorders. These stones are radiolucent and are found in acidic urine. Uric acid crystals exhibit a variety of shapes, with needles and rhomboid forms being the most common.
- **Struvite stones** contain magnesium, ammonium, and phosphate, and develop in alkaline urine associated with urea-splitting organisms (e.g., *Proteus*, *Klebsiella*). They are radiopaque and can extend to fill the renal pelvis, taking on a staghorn configuration. On microscopy, struvite crystals have a characteristic coffin-lid shape.
- **Cystine stones** are uncommon and can form as the result of an autosomal recessive disorder. These stones have an intermediate radiolucency and appear as hexagonal crystals in the urine.

DIAGNOSIS

Clinical Presentation

Patients often present with costovertebral angle or flank pain, which can radiate to the scrotum or labia. Hematuria with nondysmorphic RBCs may be noted. Oliguria and AKI

are uncommon but can result if there is bilateral obstruction or if a solitary functioning kidney is affected.

Diagnostic Testing

http://internalmedicinebook.com

- Basic laboratory investigation should include urine culture, pH, microscopy, and serum calcium, phosphate, parathyroid hormone, and uric acid levels. Urine should be strained and passed stones analyzed for composition.
- A plain abdominal film may reveal the radiopaque stones composed of calcium salts, struvite, or cystine; however, noncontrast CT scanning has replaced other imaging modalities as the study of choice for suspected nephrolithiasis.
- Recurrent stone formers should undergo a more extensive evaluation, with 24-hour urine collections for calcium, phosphate, uric acid, citrate, oxalate, and cystine. This collection should not be done during an acute episode in a hospitalized patient but rather reserved for when the patient is on his or her usual outpatient diet.

TREATMENT

- General treatment consists of **hydration** to increase urine output and analgesia. If the stone is obstructing outflow or is accompanied by infection, removal is indicated with urgent urologic or radiologic intervention.
- After passage of a stone, treatment is directed at **prevention of recurrent stone formation**. Regardless of stone type, the foundation of therapy is maintenance of high urine output (2-3 L/d) with oral hydration and a low-sodium diet (<2 g/d).
- For calcium oxalate stones, a low-calcium diet is no longer recommended given the risks of osteoporosis. Instead, patients should be on a normal-calcium diet with no added calcium supplements. Oxalate-rich foods (e.g., spinach, rhubarb) should be avoided. Thiazide diuretics may reduce calciuria, and potassium citrate may be added in patients with hypocitraturia.
- Uric acid stones can be prevented or reduced in size by allopurinol or urinary alkalinization with citrate, bicarbonate, or acetazolamide. A low-protein diet may also prevent these stones.
- Struvite calculi frequently require surgical intervention for their removal. Extracorporeal shock wave lithotripsy can be used as adjunctive therapy. Monthly urine cultures should be obtained, and if positive, aggressive antibiotic treatment is indicated.
- Cystine stones require extensive urinary alkalinization to a pH of 7.0-7.5 to induce solubility. D-penicillamine and mercaptopropionylglycine can further increase solubility through breakage and exchange of disulfide bonds. Side effects of D-penicillamine and mercaptopropionylglycine include fever, rash, arthritis, myelosuppression, hepatotoxicity, and vitamin B_6 deficiency.

Management of Chronic Kidney Disease

GENERAL PRINCIPLES

- CKD is divided into five stages based on the estimated GFR (Figure 13-1). To be classified as stage 1 or stage 2, *there must be an accompanying structural or functional defect* (e.g., proteinuria, hematuria) because the GFR is normal or near normal in these stages.
- Patients are usually asymptomatic until significant renal function is lost (late stage 4 and stage 5). However, *complications including hypertension, anemia, and mineral bone disorders* (renal osteodystrophy [ROD] and secondary hyperparathyroidism) often develop during stage 3 and thus must be investigated and addressed before patients become symptomatic.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g 3–30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	Low	Moderate	High
	G2	Mildly decreased	60–89	Low	Moderate	High
	G3a	Mildly to moderately decreased	45–59	Moderate	High	Very high
	G3b	Moderately to severely decreased	30–44	High	Very high	Very high
	G4	Severely decreased	15–29	Very high	Very high	Very high
	G5	Kidney failure	<15			

Figure 13-1. Stages of chronic kidney disease. CKD, chronic kidney disease; GFR, glomerular filtration rate. (From KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2103;3[Suppl]:5-14.)

- The decline in GFR may be followed by plotting the reciprocal of Cr versus time, revealing a linear decrement. This can be useful in end-stage planning and in predicting when renal replacement therapy will be needed. A steeper than anticipated decline in GFR suggests a superimposed renal insult.
- Initiation of dialysis based solely on a target GFR has not shown a mortality benefit (*N Engl J Med 2010;363:609*). Dialysis should be started prior to the worsening of the patient's metabolic or nutritional status.

Risk Factors

- **Decreased renal perfusion** can lead to a decline in GFR. This can occur with true volume depletion or diminished effective circulating volume (e.g., congestive heart failure, hepatic cirrhosis). **NSAIDs** can be particularly deleterious in this setting because they block the renal autoregulatory mechanisms to preserve GFR. ACE inhibitors or ARBs also produce a reversible decrement in GFR.
- **Uncontrolled hypertension** leads to hyperfiltration, which may lead to worsening proteinuria and further

damage to the glomeruli.

- **Albuminuria has also been identified as a risk factor for progression of renal disease. A prognostic scale has been developed incorporating both the GFR and degree of albuminuria to predict the likelihood to renal failure (see Figure 13-1).**
- **Nephrotoxic agents**, such as iodinated contrast agents and aminoglycosides, should be avoided when possible. Careful attention to drug dosing is mandatory, frequently

guided by the estimated GFR or CKD stage. Drug levels should be monitored where appropriate.

- Patients undergoing coronary angiography are at particular risk for worsening CKD. **Contrast nephropathy and atheroembolic disease** are potential complications, and the risks and benefits of the procedure must be weighed with the patient prior to proceeding.
- **UTI or obstruction** should be considered in all patients with an unexplained drop in renal function. Worsening renal artery stenosis may also lead to a more rapid decline in GFR as well as sudden worsening in previously controlled hypertension.
- **Renal vein thrombosis** may occur as a complication of the nephrotic syndrome and can exacerbate CKD. Hematuria and flank pain may be present.

TREATMENT

Treatment of CKD is focused on avoidance of risk factors (listed earlier), dietary modification, blood pressure control, adequate treatment of the associated conditions (listed in the following text), and ultimately, preparation for renal replacement therapy.

- **Dietary restrictions**
  - **Sodium restriction** to <3 g/d is usually adequate for most CKD patients. Restriction to <2 g/d should be used if heart failure or refractory hypertension is present. A 24-hour urine sodium level of 100 mEq roughly correlates with a 2 g/d diet.
  - Fluid restriction is generally not required in CKD patients and, if excessive, may lead to volume depletion and hypernatremia. Restriction is appropriate in patients with dilutional hyponatremia.
  - **Potassium should be restricted** to 60 mEq/d in individuals with hyperkalemia. Tomato-based products, bananas, potatoes, and citrus drinks are high in potassium and should be avoided in these patients.
  - **Dietary phosphate restriction** should be to 800-1000 mg/d. Dairy products, dark colas, and nuts should be avoided in hyperphosphatemia. Oral binders (calcium carbonate or acetate, lanthanum carbonate, sevelamer carbonate) can be used if dietary restrictions are unable to control phosphate levels.
- **Hypertension**
  - Uncontrolled hypertension accelerates the rate of decline of renal function. Blood pressure control to <140/90 mm Hg is recommended for patients with CKD (*JAMA 2014;311:507*).
  - **ACE inhibitors or ARBs** should be used preferentially in the CKD population. They lower intraglomerular pressure and possess renoprotective properties beyond the antihypertensive effect, particularly in proteinuric states. Due to their effects on intrarenal hemodynamics, a 30% rise in serum Cr should be anticipated and tolerated; a further rise should prompt a search for possible renal artery stenosis. The Cr and serum potassium should be checked approximately 1-2 weeks after a dose

adjustment. Combined therapy with ACE inhibitors and ARBs is not recommended due to an increased risk of hyperkalemia and AKI without statistical benefit in mortality or long-term renal protection (*N Engl J Med 2013;369:1892*).

- **Diuretics** are also beneficial in achieving euvolemia in hypertensive CKD patients. Thiazide diuretics become less effective as the GFR falls below 30 mL/min, whereas loop diuretics retain their efficacy, although higher doses may be required for the desired effect.

- **Anemia**
  - A normocytic anemia is common in CKD and should be searched for once the GFR falls below 60 mL/min (stage 3).
  - Alternate causes for an anemia should be entertained in the appropriate setting and iron stores assessed. If the transferrin saturation is <25% and there is no evidence of iron

overload (ferritin <1000 ng/mL), consideration should be given to iron repletion with 1 g of an IV preparation of iron dextran (1000 mg once with test dose of 25 mg), ferric gluconate (125 mg, eight doses), or iron sucrose (100 mg, 10 doses).

  - Erythropoiesis-stimulating agents (ESAs), such as epoetin and darbepoetin, can effectively reduce but do not prevent the need for RBC transfusions. ESA therapy increases the risk of stroke and thrombotic and cardiovascular events and worsens outcomes in patients with cancer. These agents should not be started in CKD unless the hemoglobin is <10 g/dL, other causes of anemia such as iron deficiency are addressed, and reduction in transfusions is a goal. The minimum dose that maintains the hemoglobin above the need for transfusion and *below 11 g/dL* should be used. Correction of iron deficiency frequently decreases the ESA dose requirement and may defer the need for ESA. Targeting the hemoglobin to higher levels has been associated with increased cardiovascular mortality, and this risk may be related to the higher doses of ESA (*N Engl J Med 2010;363:1146*).

- **Bone mineral disorders**
  - CKD bone mineral disorders increase in prevalence as the GFR declines through stage 3 and more advanced disease. They include disorders of bone turnover and secondary hyperparathyroidism.
  - **Osteitis fibrosa cystica** is commonly associated with secondary hyperparathyroidism and increased bone turnover, resulting in bone pain and fractures. Adynamic bone disease is a low-turnover state with suppressed parathyroid hormone (PTH) levels. Osteomalacia can involve deposition of aluminum into bone and is less commonly seen today with the decreased use of aluminum-based phosphate binders.
  - In CKD, starting in stage 3, vitamin D deficiency, low calcium, and elevated phosphate can all contribute to **secondary hyperparathyroidism**. The general goal of therapy is to suppress PTH toward normal while maintaining normal serum calcium and phosphate. This can be addressed in three steps: repletion of vitamin D stores (25-OH vitamin D), control of dietary phosphate with binders, and administration of active vitamin D (1,25-dihydroxyvitamin D or an analog).
  - Deficient stores (25-OH vitamin D <30 ng/mL) should be corrected with oral ergocalciferol 50,000-IU capsule weekly or every other week or cholecalciferol 2000-4000 IU daily. The duration of treatment depends on severity of the deficiency, with levels <5 ng/dL warranting at least 12 weeks of treatment. Once at goal, maintenance therapy can rely on either monthly ergocalciferol 50,000 IU or daily cholecalciferol 1000-2000 IU.
    - Phosphate control can be difficult as GFR declines, even with appropriate dietary restriction. Phosphate binders inhibit gastrointestinal absorption. Calcium-based binders are effective when

given with meals as calcium carbonate (200 mg of elemental calcium per 500-mg tablet) or calcium acetate (169 mg of elemental calcium per 667-mg tablet). In general, the total daily elemental calcium administered should be <1500 mg. Lanthanum carbonate and sevelamer carbonate are non-calcium-based alternatives.

- Active vitamin D (1,25-dihydroxyvitamin D) and its synthetic analogs are potent suppressors of PTH and can be administered if serum PTH remains elevated. Options include daily calcitriol (0.25-1 µg), paricalcitol (1-5 µg), or doxercalciferol (1-5 µg). Calcium levels need to be monitored regularly and doses adjusted to avoid hypercalcemia.
- Cinacalcet is a calcimimetic that acts on the parathyroid gland to suppress PTH release. It should be used only in dialysis patients and usually in conjunction with active vitamin D, because it may induce significant hypocalcemia and is relatively ineffective as monotherapy.

- **Metabolic acidosis.** As renal function deteriorates, the kidney is unable to appropriately excrete sufficient acid, resulting in metabolic acidosis (mixed high and normal anion gap).

To compensate, alkaline buffer is released from the skeleton but can ultimately worsen bone mineral disease.

  - Treatment with **sodium bicarbonate** 650-1300 mg thrice daily can help maintain the serum bicarbonate level at 22 mEq/L. Such therapy, however, can increase the sodium load and contribute to edema or hypertension.
  - Citrate, another alkaline source, should not be used in the CKD or ESRD population because it can dramatically enhance gastrointestinal absorption of aluminum and lead to aluminum toxicity or osteomalacia.

- **Hyperlipidemia.** Therapy with statins combined with ezetimibe has shown improved cardiovascular outcomes with fewer major atherosclerotic events in patients with moderate to severe CKD and in the dialysis population, although the benefit in patients on dialysis was less (*Lancet 2011;377:2181*). Use of lipid-lowering therapy is appropriate in patients with atherosclerotic disease at all stages of CKD.
- **Preparation for renal replacement therapy**
  - Patients should be counseled at an early stage to determine preferences for renal replacement therapies, including hemodialysis, peritoneal dialysis (PD), and eligibility for renal transplantation.
  - In stage 4 CKD, preparation for the creation of a permanent vascular access for hemodialysis should be initiated by protecting the nondominant forearm from IV catheters and blood draws. Timely referral for vein mapping and to an access surgeon can facilitate the creation and maturation of an arteriovenous (AV) access.

RENAL REPLACEMENT THERAPIES

Approach to Dialysis

TREATMENT

- **Modalities**
  - Renal replacement therapy is indicated when conservative medical management is unable to control the metabolic derangements of kidney disease. This applies to the acute and chronic settings. Common acute indications include **hyperkalemia**, **metabolic acidosis**, and **volume overload** that

are refractory to medical management. Uremic **encephalopathy** or **pericarditis**, as well as certain **intoxications** (methanol, ethylene glycol, or salicylates), can all be indications to initiate dialytic therapy acutely. In the chronic setting, renal replacement therapy is typically begun prior to the worsening of the metabolic or nutritional status of the patient.

- Dialysis works by solute diffusion and water transport across a selectively permeable membrane. In hemodialysis, blood is pumped counter-currently to a dialysis solution within an extracorporeal membrane. This can be performed intermittently (3-4 hours during the day) or in a continuous 24-hour fashion depending on hemodynamic stability or goals of therapy. PD uses the patient's peritoneal membrane as the selective filter, and dialysis fluid is instilled into the peritoneal cavity.
- Transplantation offers the best long-term survival and most completely replaces the filtrative and endocrine functions of the native kidney. However, it carries the risks that accompany long-term immunosuppression.

- **Diffusion**

  The selectively permeable membrane contains pores that allow electrolytes and other small molecules to pass by diffusion while holding back larger molecules and cellular components of the blood. Movement relies on the molecular size and the concentration gradient, where Cr, urea, potassium, and other waste products of metabolism pass into the dialysis solution while alkaline buffers (bicarbonate or lactate) enter the blood from the dialysis solution.

- **Ultrafiltration/convection**
  - Removal of water is termed ultrafiltration (UF). It can be achieved in hemodialysis via a transmembrane hydrostatic pressure that removes excess fluid from the blood compartment. In PD, water follows its osmotic gradient into the relatively hyperosmolar dialysis solution (usually with dextrose providing the osmotic driving force).
  - As water is removed from the vascular compartment, it drags along solute. This is termed convective clearance. This usually accounts for only a small fraction of the total clearance but can be significantly increased if a physiologic “replacement fluid” is infused into the patient concurrently to prevent hypovolemia. This strategy is frequently employed by continuous hemodialysis modalities (see the following text).

Hemodialysis

GENERAL PRINCIPLES

- Hemodialysis is by far the most commonly used form of renal replacement therapy in the United States. Intermittent hemodialysis (IHD) typically runs for 3-4 hours per session and is performed three times weekly. Outpatient, in-center hemodialysis for ESRD generally uses this modality, although variations are available for patients undergoing home treatments.
- Continuous renal replacement therapy (CRRT) can be used in specialized circumstances, particularly when the patient's hemodynamic status would not tolerate the rapid fluid shifts of IHD. Although less efficient (with slower blood flows) and using slower UF rates, CRRT can achieve equivalent clearances of both solute and fluid compared to IHD due to its continuous, 24-hour nature. The slower blood flows usually necessitate anticoagulation (with systemic heparin or regional citrate) to prevent the filter from clotting. Continuous modalities require specialized nursing and an intensive care setting.

- The most frequently employed form of CRRT is continuous venovenous hemodiafiltration (CVVHDF).
- In CVVHDF, blood is slowly pumped counter-currently to a dialysis solution (diffusion), and a replacement fluid (a "cleansed" physiologic solution devoid of uremic toxins) is infused into the circuit to balance most of the ultrafiltrate (convection).

- Sustained low-efficiency dialysis (SLED) is essentially a hybrid form of IHD and CRRT used in an intensive care setting. Intermediate blood flows lower the clotting risk if anticoagulation is not used, while intermediate treatment lengths (8-10 hours) still allow for adequate clearances. Patients also spend a significant portion of the day off the machine to allow for nonbedside testing, procedures, and physical therapy.
- **Prescription and adequacy**
  - IHD typically runs for 3-4 hours and can ultrafilter 3-4 L safely in hemodynamically stable patients. In the chronic setting, IHD is generally performed three times weekly, although the longer interdialytic interval on the weekend has been associated with a heightened mortality risk (*N Engl J Med 2011;365:1099*). In the acute setting, the appropriate interval is not clearly known, although a thrice-weekly schedule is likely adequate; daily assessment should be performed to reevaluate dialytic needs.
  - Adequacy is assessed by calculating the clearance of BUN, which serves as a surrogate marker of the "uremic factors." The urea reduction ratio (URR) can be calculated by the following:

    URR = [(predialysis BUN - postdialysis BUN) / (predialysis BUN)] × 100

    A reduction rate of >65% is considered adequate in the chronic setting (*N Engl J Med 2002;347:2010*). An adequacy target is less well defined for AKI.

  - Intensive daily hemodialysis was not shown to be superior to standard thrice-weekly treatments (*N Engl J Med 2008;359:7*).
  - Clearance is measured differently in CRRT where dialytic therapy is taking place around the clock, effectively serving as an extracorporeal "GFR." Drug dosing needs to be adjusted accordingly. An estimate of this clearance can be calculated by the sum of the dialysis fluid and replacement fluid, and net UF rates are expressed as the number of milliliters per minute. For most circumstances, this approximates a clearance of 20-50 mL/min.
  - With CRRT, the net UF rate can be adjusted as needed, according to the patient's hemodynamic status. One must be vigilant in checking electrolyte levels (particularly ionized calcium and phosphorus) to ensure they remain within the desired ranges. Calcium levels are especially important to follow when regional citrate anticoagulation is being used.
  - Phosphate, which is predominantly intracellular, is generally poorly removed by IHD; however, in CRRT, there is continuous efflux of this anion, and significant hypophosphatemia can occur.

COMPLICATIONS

- Nontunneled catheters are typically placed in the internal jugular or femoral vein and carry the same risks as other central venous catheters (infection, bleeding, pneumothorax). They are almost exclusively used in the inpatient setting and are generally used for 1-2 weeks. Tunneled catheters have lower rates of infection and can be used for 6 months while a more definitive access is maturing (AV fistula or graft).
  - Fevers and rigors, particularly during dialysis, should prompt a search for an infectious cause, and empiric antibiotic coverage for staphylococci and gram-negative bacteria should be administered.

- The catheter should then be replaced after a period of defervescence and sterilization of the blood (at least 48 hours). Documented bacteremia should be treated with antibiotics for at least 3 weeks.

- Thrombosis of an AV fistula or graft can frequently be recanalized by thrombolysis or thrombectomy. Stenotic regions can be evaluated by a fistulogram, and treatment may encompass angioplasty or stent deployment.
- Intradialytic hypotension is most commonly due to intravascular volume depletion from rapid UF. Antihypertensive medications may also contribute. Infectious causes should be sought in the appropriate setting. Acute treatment of the drop in blood pressure includes infusion of normal saline (as 200-mL boluses) and reduction of the UF rate.
- Dialysis disequilibrium is an uncommon syndrome that may occur in severely uremic patients undergoing their first few treatments. Rapid clearance of toxins is thought to induce cerebral edema by osmolar shifts and can present as nausea, emesis, headache, confusion, or seizures. Occurrence can be prevented or ameliorated by initiating patients on dialysis with slower blood flows and shorter treatments.

Peritoneal Dialysis

GENERAL PRINCIPLES

- Historically, PD has been used in the acute setting for hemodynamically unstable patients. However, with the development and availability of safe and effective continuous hemodialysis, use of PD in the treatment of AKI in adults has been mostly abandoned in the United States. Currently, its use is primarily in the treatment of ESRD.

- There are two modalities in use: manual exchanges and automated cycler exchanges.
  - The manual modality, also called continuous ambulatory peritoneal dialysis (CAPD), has the patient instill dialysis fluid into the peritoneum for a specified length of time, after which the dialysate is drained and replaced by another dwell.
  - The automated modality, also called continuous cycling peritoneal dialysis (CCPD), typically operates overnight where a machine runs a preprogrammed set of exchanges while the patient sleeps. A final fill usually remains in the peritoneum and is carried during the daytime for continued solute exchange.
- Both PD modalities require strict adherence to sterile technique, and careful patient selection is necessary. Generally, PD should not be used if there is a history of recent abdominal surgery or if multiple peritoneal adhesions are present.
- **Prescription and adequacy**
  - The choice between CAPD and CCPD usually depends on patient preference and on the transport characteristics of the peritoneal membrane. Manual exchanges (i.e., CAPD) can be used as a backup modality, particularly in the hospital where nurse staffing or machine availability may be limited.
  - In writing PD orders, the following variables must be specified: dwell volume, dwell time, number of exchanges, and dextrose concentration of the dialysis solution. The dwell volume is typically between 2-3 L. The dextrose concentration can be 1.50%, 2.50%, or 4.25%, providing the osmotic gradient for fluid removal. Higher dextrose concentrations allow for greater UF but also lead to more glucose absorption and worsening control of diabetes. Icodextrin is a glucose polymer preparation that can be used in longer dwell because it is minimally absorbed and thus maintains an effective osmotic gradient up to 18 hours.

Commercially available PD solutions may have colorcoded tabs, and patients may know these better than the actual concentrations (yellow for 1.50%, green for 2.50%, red for 4.25%). A sample order set for manual CAPD would be 2.5 L, four exchanges, 6 hours each, with 2.5% dextrose.

- PD is less efficient than conventional hemodialysis. However, given its continuous nature, solute clearance and UF can approximate that of other modalities. Larger volumes and more frequent exchanges can assist with solute exchange. Increasing the concentration of dextrose can promote greater UF in volume-overloaded patients.
- *Residual renal function is very important in the PD population, and avoidance of nephrotoxins should be practiced* (*J Am Soc Nephrol 2002;13:1307*).

COMPLICATIONS

- **Peritonitis** typically presents with diffuse abdominal pain and cloudy peritoneal fluid. A sample should be sent for cell count, differential, Gram stain, and culture. A WBC count of >100 cells/μL, of which at least 50% are neutrophils, supports the diagnosis.
  - Empiric therapy should cover for both gram-positive and gram-negative organisms, with a first-generation cephalosporin (cefazolin or cephalothin) and ceftazidime at 15-20 mg/kg of each in the longest dwell of the day (*Perit Dial Int 2005;25:107*). If a methicillin-resistant organism is suspected, use vancomycin (30 mg/kg every 5-7 days) for gram-positive coverage and a third-generation cephalosporin for gram-negative coverage, including *Pseudomonas*.
  - The intraperitoneal route is the preferred method of administration, unless the patient is overtly septic, in which case IV antibiotics should be used. Antibiotics can be tailored once culture results are known and should be continued for 2-3 weeks. Multiple organisms, particularly if gram negative, should prompt a search for intestinal perforation.
- Tunnel or exit site infections may present with local erythema, tenderness, or purulent drainage, although crusting at the exit site alone does not necessarily indicate infection. Treatment can be with oral cephalosporins (gram positive) or fluoroquinolones (gram

negative). However, infections can be difficult to eradicate, and catheter removal may be required with a temporary transition to hemodialysis.
- Failure of PD fluid to drain is termed outflow failure. This may result from kinking of the catheter, constipation, or plugging of the catheter with fibrin strands. Conservative treatment should aim at resolving constipation if present and instilling heparin into the PD fluid at 500 units/L.
- Small hernias are at particularly high risk for incarceration and should be corrected surgically while the patient is temporarily treated with hemodialysis. Fluid leaks can lead to abdominal wall and genital edema and typically result from anatomic defects. Hydrothorax usually occurs on the right side and can be diagnosed by a markedly elevated glucose concentration in the pleural fluid. Pleurodesis can eliminate the potential space and permit continuation of PD.
- **Sclerosing encapsulating peritonitis** is a complication of long-term PD. The peritoneal membrane becomes thickened and entraps loops of bowel, leading to symptoms of bowel obstruction. A bloody drainage may be present. Treatment is supportive with the focus on bowel rest and surgical lysis of adhesions. A trial of immunosuppression with prednisone 10-40 mg/d may have limited benefit.
- Hyperglycemia results from the systemic absorption of glucose from the dialysis fluid. Because peritoneal uptake of insulin is unpredictable, treatment with subcutaneous insulin is preferred.

- Hyperlipidemia is common in the PD population, and treatment should be reserved for those with specific cardiac indications.
- Unlike hemodialysis, patients on PD tend to experience hypokalemia, likely due to a continuous potassium exodus in the dialysate as well as from an intracellular shift from the increased endogenous insulin production. Oral replacement is usually sufficient, either with relaxation of prior dietary restrictions or with low-dose supplementation (10-20 mEq/d of potassium chloride).
- Protein loss can be high, and the dietary protein intake should be 1.2-1.3 g/kg/d. Episodes of peritonitis can make the membrane even more susceptible to protein losses.

Transplantation

GENERAL PRINCIPLES

- Renal transplantation offers patients an improved quality of life and survival as compared to other renal replacement modalities.
- Pretransplant evaluation focuses on cardiopulmonary status, vascular sufficiency, and human lymphocyte antigen typing. Structural abnormalities of the urinary tract need to be addressed. Contraindications include most malignancies, active infection, or significant cardiopulmonary disease.
- In adult recipients, the renal allograft is placed in the extraperitoneal space, in the anterior lower abdomen. Vascular anastomosis is typically to the iliac vessels, whereas the ureter is attached to the bladder through a muscular tunnel to approximate sphincter function.
- Immunosuppression protocols vary among institutions. A typical regimen would include prednisone along with a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) and an antimetabolite (mycophenolate derivative, azathioprine, or rapamycin).
- Evaluation of allograft dysfunction frequently requires kidney biopsy. Current laboratory and radiologic tests cannot reliably distinguish acute rejection from drug toxicity, the two most common causes of a rising Cr in the transplant population. Posttransplant lymphoproliferative disease, interstitial nephritis, and infections such as cytomegalovirus, *Polyomavirus* (BK virus), and pyelonephritis may present similarly to acute allograft dysfunction and should be excluded.
- Complications and long-term management of transplant recipients are discussed further in Chapter 17, Solid Organ Transplant Medicine.

14
Treatment of Infectious Diseases

Allison L. Nazinitsky
Stephen Y. Liang
Nigar Kirmani

Principles of Therapy

GENERAL PRINCIPLES

Infections may be caused by bacteria, viruses, fungi, and parasites and can involve any organ system. When antimicrobial therapy is indicated, a number of factors reviewed in this chapter should be considered. Infectious disease consultation may assist with diagnostics, therapeutics, and long-term monitoring of side effects and drug-drug interactions. Stewardship to avoid indiscriminate use of antibiotics may combat drug resistance, avoid adverse effects, and curb excess costs.

DIAGNOSIS

- **The history and physical exam** are important, especially for diagnostic dilemmas and fever of unknown origin (FUO) cases. Eliciting exposures, travel history, and hobbies will broaden the differential diagnosis to assist with workup.
- **Gram stains** from potentially infected specimens may permit a rapid presumptive diagnosis and guide empiric antibiotic selection.
- **Aerobic, anaerobic, fungal, or acid-fast bacilli (AFB) cultures** may be performed on specimens. The microbiology laboratory should be consulted if organisms with special growth requirements are suspected to ensure appropriate transport and processing of cultures.
- **Susceptibility testing** of cultures facilitates selection of antimicrobial agents.
- **Rapid diagnostic testing**, such as polymerase chain reaction (PCR) and antigen detection, may also provide early confirmation of an infectious etiologic agent.

TREATMENT

- **Choice of initial antimicrobial therapy** Empiric therapy should be directed against the most likely pathogens and possess the narrowest spectrum.
- **Local susceptibility patterns** must be considered in selecting empiric therapy because of wide variability among communities and individual hospitals.
- Drug allergies, previous cultures, and prior antibiotic exposure should guide selection.
- **Timing for the initiation of antimicrobial therapy**
  - In acute clinical scenarios, empiric therapy should begin immediately and ideally after appropriate cultures have been obtained. Urgent therapy is indicated in febrile patients who are neutropenic or asplenic. Sepsis, meningitis, and rapidly progressive necrotizing infections should also be treated promptly with antimicrobials.
  - In clinically stable patients, one may consider withholding empiric antimicrobials, pending workup, to allow for more targeted therapy and avoid unnecessary drugs.

- **Route of administration**
  - Patients with serious infections should be given IV antimicrobial agents.
  - Oral therapy is acceptable in less urgent circumstances if adequate drug concentrations can be achieved at the site of infection.
  - IM therapy can be considered in patients without IV access or when single doses of therapy are indicated.
- **Type of therapy**
  - Bactericidal therapy is preferred over bacteriostatic regimens, especially in patients with lifethreatening infection, immunologic compromise, endocarditis, meningitis, and osteomyelitis.
  - Renal and hepatic function guide antimicrobial dosing regimens.
  - Drug interactions should always be assessed before starting treatment and may impact effectiveness of therapy.
- **Assessment of outcomes on antimicrobial therapy.** If there is concern for potential treatment failure, consider the following questions:
  - Is the isolated organism the etiologic agent?
  - Has an appropriate antimicrobial regimen been selected to cover the organism?
  - Is the concentration of antimicrobial agent adequate at the site of infection?
  - Have resistant pathogens emerged?
  - Is a persistent fever due to underlying disease, abscess formation, iatrogenic complication, drug reaction, or another process?
- **Duration of therapy**
  - Duration of therapy depends on the nature and severity of infection. Therapy should be modified in accordance with the patient's clinical course and culture results.
  - Treatment of acute uncomplicated infections should be continued until the patient has been afebrile and clinically well, usually for a minimum of 72 hours.
  - Infections at certain sites (e.g., endocarditis, septic arthritis, osteomyelitis) require prolonged therapy.

SPECIAL CONSIDERATIONS

- **Immunosuppressed hosts**
  - Examples include patients with HIV/AIDS, transplant recipients (solid organ and hematopoietic stem cell), patients undergoing chemotherapy, and patients on steroids or other immune-modulating agents for treatment of rheumatologic diseases.
  - Consider a more extensive differential diagnosis including opportunistic infections and broader empiric antimicrobial coverage.
- **Pregnancy and the postpartum patient**
  - Although no antimicrobial agent is known to be completely safe in pregnancy, the penicillins and cephalosporins are most often used. **Tetracyclines and fluoroquinolones are contraindicated.** Sulfonamides and aminoglycosides should not be used if alternative agents are available.

- Many antibiotics can be excreted in breast milk. Caution should be used in prescribing antimicrobials to breast-feeding women.

TOXIN-MEDIATED INFECTIONS

Clostridium difficile Infection

GENERAL PRINCIPLES

Frequently seen after systemic antimicrobial therapy.

DIAGNOSIS

Clinical Presentation

- Symptoms may range from mild or moderate watery diarrhea to severe and potentially fatal pseudomembranous colitis. Abdominal pain, cramping, low-grade fever, and leukocytosis are often present.
- Fulminant disease can manifest as colonic ileus or toxic megacolon leading to bowel perforation.

Differential Diagnosis

Antibiotic-associated osmotic diarrhea without *Clostridium difficile* infection should be considered and will resolve after withdrawal of the antibiotic.

Diagnostic Testing

- Diagnosis is made by detection of *C. difficile* toxin in diarrheal stool through PCR or enzyme immunoassay (EIA) or detection of *C. difficile* organisms through EIA or culture.
- Visualization of pseudomembranes on colonoscopy or sigmoidoscopy with biopsy can also be diagnostic for *C. difficile* infection.

TREATMENT

- For **mild to moderate disease**, treatment should consist of metronidazole 500 mg PO (preferred over IV) tid for 10-14 days and discontinuation of the offending antibiotic if possible (*Am J Gastroenterol 2013;108:478*; *Infect Control Hosp Epidemiol 2010; 31:431*).
- In **severe disease**, vancomycin 125-500 mg PO q6h (IV is not effective) is preferred (*Clin Infect Dis 2007;45:302*). Vancomycin should also be considered for mild to moderate disease that has failed to respond to metronidazole after 5-7 days of therapy.
- For infections complicated by ileus, toxic megacolon, or shock, surgery consultation should be obtained and the addition of IV metronidazole and intracolonic vancomycin is recommended (*Clin Infect Dis 2002;35:690*). In some cases, colectomy may be necessary.
- Endpoint of therapy is cessation of diarrhea; **do not retest stool for toxin clearance**.
- Avoid antimotility agents in severe disease.
- Recurrence is common and is treated with metronidazole or vancomycin in extended duration, pulsed, or tapered regimens. Adjunctive therapy with oral rifaximin is sometimes used (*Clin Infect Dis 2007;44:846*).

- Fidaxomicin may have an evolving role in the treatment and prevention of recurrent *C. difficile* infection (*N Engl J Med 2011;364:422*). Fecal microbiota transplantation (FMT) may also be considered given the appropriate clinical scenario at experienced centers (*J Clin Gastroenterol 2014;48:693*).

Tetanus

GENERAL PRINCIPLES

- Caused by *Clostridium tetani* toxin from wound contamination with spores.
- Tetanus is best prevented by immunization. For high-risk wounds, prophylaxis with human tetanus immunoglobulin 250 units IM is recommended (*MMWR Morb Mortal Wkly Rep 2006;55(No. RR-17):1*).

DIAGNOSIS

Classically presents with intensely painful muscle spasms and rigidity, followed by autonomic dysfunction. Symptoms often begin in the face (trismus, risus sardonicus) and neck muscles. Delirium and high fever are usually absent. Diagnosis is clinical.

TREATMENT

- Passive immunization with human tetanus immunoglobulin 3000-5000 units IM (in divided doses) to neutralize unbound toxin is warranted. Active immunization with tetanus toxoid should be given at a separate site.
- Surgical debridement of the wound is critical.
- Antibiotic therapy, usually consisting of metronidazole 500 mg IV q6-8h or penicillin G 2-4 million units IV q4-6h, for 7-10 days is recommended.
- Benzodiazepines or neuromuscular blocking agents may be used to control spasms.

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is a life-threatening systemic disease caused by exotoxin superantigens produced by *Staphylococcus aureus* or group A β-hemolytic *Streptococcus* (GABHS) tissue infections (Table 14-1).

TABLE 14-1 Treatment of Toxic Shock Syndromes

Etiology	Antibiotic Therapy	Adjunctive Therapy	Notes
Group A β-hemolytic *Streptococcus* (GABHS)	Penicillin G 4 million units IV q4h + clindamycin 900 mg IV q8h for 10-14 d	IVIG 1 g/kg on day 1, then 0.5 g/kg on days 2 and 3 *(Clin Infect Dis 2003;37:333*)	Surgical debridement is almost always indicated for necrotizing infections. Clindamycin is added to decrease toxin production.

Staphylococcus	Oxacillin 2 g IV q4h or vancomycin 1 g IV q12h + clindamycin 900 mg IV q8h for 10-14 d	IVIG as per GABHS may be useful in severe cases, but higher doses may be needed (*Clin Infect Dis 2004;38:836*)	Surgical debridement may be necessary for wounds. Tampons and other foreign bodies should be removed and avoided in future, especially if TSST-1 antibody titers are negative.

IVIG, intravenous immunoglobulin; TSST-1, toxic shock syndrome toxin-1.

Staphylococcal Toxic Shock Syndrome

GENERAL PRINCIPLES

Most often associated with colonization of surgical wounds, burns, vaginitis, or tampon use in young women. Cases are also seen after nasal packing for epistaxis. Mortality is low (<3%) in menstrual cases.

DIAGNOSIS

Clinical Presentation

Typical findings are fever, hypotension, and a macular desquamating erythroderma of the palms and soles. Vomiting, diarrhea, myalgias, weakness, shortness of breath, and altered mental status may be early signs of multiorgan failure.

Diagnostic Testing

- Blood cultures are usually negative. Creatine phosphokinase (CPK) is often elevated.
- Staphylococcal isolates can be tested for toxin production, including toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxin B and C, although results are not clinically relevant. Serum antibodies against TSST-1 may protect against future recurrences (*Clin Microbiol Rev 2013;26:422*).

TREATMENT

See Table 14-1.

Streptococcal Toxic Shock Syndrome

GENERAL PRINCIPLES

Associated with invasive GABHS infections, particularly necrotizing fasciitis or myositis (80% of cases). Mortality is much higher (30-70%) compared to staphylococcal TSS.

DIAGNOSIS

Clinical Presentation

Initial presentation is typically abrupt onset of severe diffuse or localized pain. The systemic manifestations are otherwise similar to staphylococcal TSS, but the desquamating erythroderma is much less common.

Diagnostic Testing

Blood cultures are usually positive, and antistreptolysin O (ASO) titers are elevated.

TREATMENT

See Table 14-1.

SKIN, SOFT TISSUE, AND BONE INFECTIONS

The increased incidence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) has altered the approach to management of skin and soft tissue infections (SSTIs) (*Clin Infect Dis 2014;59:e10*).

Purulent Skin and Soft Tissue Infections (Furuncles, Carbuncles, and Abscesses)

GENERAL PRINCIPLES

MRSA and methicillin-sensitive *S. aureus* (MSSA) account for 25-50% of cases.

TREATMENT

- Incision and drainage (I&D) alone is usually adequate, especially for abscesses measuring <5 cm.
- Antibiotic therapy is needed for extensive disease; systemic illness; rapid progression with associated cellulitis; comorbid diseases (diabetes mellitus); immunosuppression, location on face, hand, or genitalia; or lack of response to I&D.
- Empiric antibiotic therapy should cover CA-MRSA. Oral antibiotics include clindamycin 300-450 mg tid, trimethoprim-sulfamethoxazole (TMP-SMX) 1-2 double-strength tablets bid, doxycycline 100 mg bid, and linezolid 600 mg q12h.
- Duration of antibiotic therapy is usually 5-7 days.

Nonpurulent Skin and Soft Tissue Infections (Erysipelas and Cellulitis)

Erysipelas

GENERAL PRINCIPLES

Erysipelas appears as a painful, superficial, erythematous, sharply demarcated lesion that is usually found on lower extremities. In normal hosts, GABHS is responsible for this infection.

TREATMENT

Penicillin V 250-1000 mg PO q6h or penicillin G 1.0-2.0 million units IV q6h, depending on the severity of illness. In patients who are penicillin allergic, macrolides and clindamycin are alternatives.

Cellulitis

GENERAL PRINCIPLES

- Common organisms include β-hemolytic streptococci and *S. aureus* (MSSA and MRSA).
- Severe cellulitis is sometimes seen after exposure to fresh (*Aeromonas hydrophila*) or salt (*Vibrio vulnificus*)

water.

TREATMENT

- If streptococci or MSSA are suspected, a β-lactam antibiotic (cephalexin or dicloxacillin 500 mg PO q6h) or clindamycin can be used.
- If there is a strong concern for CA-MRSA, empiric antibiotic coverage may consist of clindamycin or linezolid. TMP-SMX can also be used in combination with a β-lactam antibiotic (e.g., cephalexin) to provide streptococcal coverage.

- Coverage for waterborne pathogens should initially consist of ceftazidime 2 g IV q8h, cefepime 2 g IV q8h, or ciprofloxacin 750 mg PO bid in combination with doxycycline 100 mg IV/PO q12h.

Complicated Skin and Soft Tissue Infections

GENERAL PRINCIPLES

Deep soft tissue infections, surgical and traumatic wound infections, large abscesses, complicated cellulitis, and infected ulcers and burns fall under this classification.

DIAGNOSIS

Cultures of abscesses and surgical debridement specimens should be obtained to guide antibiotic therapy.

TREATMENT

Patients should be hospitalized to receive IV antibiotics and undergo surgical intervention as necessary. Vancomycin 15-20 mg/kg IV q12h, linezolid 600 mg PO/IV q12h, daptomycin 4 mg/kg IV daily, clindamycin 900 mg IV q8h, and ceftaroline 600 mg IV q12h are all acceptable antibiotic options.

Infected Decubitus Ulcers and Limb-Threatening Diabetic Foot Ulcers

GENERAL PRINCIPLES

- Infections are usually polymicrobial. **Superficial swab cultures are unreliable.** Instead, deep tissue cultures obtained after wound debridement are preferred.
- Osteomyelitis is a frequent complication and should be excluded.

TREATMENT

- Wound care and debridement are important first-line therapies.
- **Mild diabetic foot infections** are usually due to *S. aureus* and streptococci, and can be treated with cephalexin or amoxicillin-clavulanate (875 mg/125 mg PO bid) (*Clin Infect Dis 2012;54:132*). If MRSA is suspected, either TMP-SMX or doxycycline is recommended.
- **Moderate to severe infections** require systemic antibiotics covering *S. aureus* (including MRSA), anaerobes, and enteric gram-negative organisms. Options include vancomycin plus a β-lactam/β-lactamase inhibitor combination, a carbapenem (ertapenem, doripenem, or meropenem), or vancomycin with metronidazole combined with either ciprofloxacin or a third-generation cephalosporin.

Necrotizing Fasciitis

GENERAL PRINCIPLES

- This is an infectious disease emergency with high mortality manifested by extensive soft tissue infection and thrombosis of the microcirculation with resulting necrosis (*Crit Care*

Med 2011;39:2156). Infection spreads quickly along fascial planes and may be associated with sepsis or TSS. Fournier gangrene is necrotizing fasciitis of the perineum.
- Bacterial etiology is either mixed (aerobic and anaerobic organisms) or monomicrobial (GABHS or *S. aureus*, including CA-MRSA).

DIAGNOSIS

Clinical Presentation

May present initially like simple cellulitis rapidly progressing to necrosis with dusky, hypoesthetic skin and bulla formation in association with severe pain. Pain out of proportion to exam should raise concern for necrotizing fasciitis.

Diagnostic Testing

- Diagnosis is clinical. High suspicion should prompt **immediate surgical exploration** where lack of resistance to probing is diagnostic.
- Cultures of operative specimens and blood should be obtained. CPK may be elevated.
- CT and plain films may demonstrate gas and fascial edema early in the disease process.

TREATMENT

- Aggressive surgical debridement is critical, along with IV antibiotics and volume support.
- Initial empiric antibiotic therapy should be broad spectrum and consist of a β-lactam/β-lactamase inhibitor, high-dose penicillin, carbapenem, or fluoroquinolone in combination with clindamycin. Vancomycin should also be added until MRSA can be excluded.
- Adjunctive hyperbaric oxygen may be useful.

Anaerobic Myonecrosis (Gas Gangrene)

GENERAL PRINCIPLES

Usually due to *Clostridium perfringens*, *Clostridium septicum*, *S. aureus*, GABHS, or other anaerobes. Distinguishing this condition from necrotizing fasciitis requires gross inspection of the involved muscle at the time of surgery.

TREATMENT

Treatment requires prompt surgical debridement and combination antimicrobial therapy with IV penicillin plus clindamycin. A third-generation cephalosporin, ciprofloxacin, or an aminoglycoside should be added until a gram-negative infection can be excluded.

Osteomyelitis

GENERAL PRINCIPLES

- Osteomyelitis is an inflammatory process caused by an infecting organism that can lead to bone destruction. It should be considered when skin or soft tissue infections overlie bone and when localized bone pain accompanies fever or sepsis.
- See Table 14-2.

TABLE 14-2 Treatment of Osteomyelitis

Etiology of Osteomyelitis	Organism	Treatment considerations
Acute hematogenous	• *Staphylococcus aureus*	• Antibiotic therapy alone may be sufficient if no foreign body present.
Vertebral	• *S. aureus* • Gram-negative bacilli • Mycobacterium tuberculosis	• Biopsy off antibiotics (preferred) to guide therapy. • Antibiotic therapy alone may be sufficient.
Associated with a contiguous focus of infection	• *S. aureus* • Gram-negative bacilli • Coagulase-negative staphylococci (surgical site infections) • Anaerobes/polymicrobial (infected sacral decubitus ulcers, diabetics)	• Diabetics and patients with peripheral vascular disease seldom are cured with antibiotics alone. Revascularization, debridement, or amputation is often required. • Long-term, suppressive antimicrobial therapy can be used if surgery is not feasible. • Hyperbaric oxygen may be a useful adjunct.
Presence of an orthopedic device	• *S. aureus* • Coagulase-negative *Staphylococcus* species	• Rarely eradicated by antimicrobials alone, and typically requires removal of the device. • If removal is impossible, the addition of rifampin 300 mg PO tid is recommended, and long-term, suppressive antimicrobial therapy may be needed.
Associated with hemoglobinopathies	• *S. aureus* • *Salmonella* species	
Chronic	• Gram-negative	• Surgical removal of sequestrum is

osteomyelitis	pathogens (necrotic sequestrum) • *S. aureus*	recommended in addition to antibiotics.
Culture-negative osteomyelitis	• Review above pathogens	• Empiric therapy should cover *S. aureus* and all other likely pathogens.

DIAGNOSIS

- Diagnosis is made by detection of exposed bone through a skin ulcer or by imaging with plain films, bone scintigraphy, or MRI (*Clin Infect Dis 2008;47:519*; *JAMA 2008;299:806*).
- Biopsy and cultures of the affected bone should be performed (prior to initiation of antimicrobials when possible) for pathogen-directed therapy.

- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually markedly elevated and can be used to monitor the response to therapy.

TREATMENT

- See Table 14-2.
- Parenteral β-lactam antibiotics (oxacillin, cefazolin) are effective against MSSA. Vancomycin, daptomycin, and linezolid are used to treat MRSA osteomyelitis. Oral agents capable of achieving reasonable bone levels include TMP-SMX, clindamycin, and doxycycline.
- Gram-negative osteomyelitis can be treated with parenteral or oral fluoroquinolones, which have excellent bone penetration and bioavailability, or with a third-generation cephalosporin.
- Cure typically requires at least 4-6 weeks of high-dose antimicrobial therapy. Parenteral therapy should be given initially; oral regimens may be considered after 2-3 weeks if the pathogen is susceptible and adequate bactericidal levels can be achieved (*Clin Infect Dis 2012;54:403*).
- If peripheral vascular disease is present, revascularization may be helpful.

CENTRAL NERVOUS SYSTEM INFECTIONS

Meningitis

GENERAL PRINCIPLES

- Meningitis (inflammation of the meninges) can be caused by bacterial, fungal, or viral infections or by noninfectious causes such as medications.
- Bacterial meningitis is a medical emergency. Therapy should not be delayed for diagnostic measures because prognosis hinges on rapid initiation of antimicrobial treatment.
- *Streptococcus pneumoniae* is the most common bacterial etiology in adults of all ages, followed by *Neisseria meningitidis*, group B *Streptococcus*, and *Haemophilus influenzae*. *Listeria monocytogenes* is more frequent in the elderly and in immunocompromised hosts (*N Engl J Med 2011;364:2016*).
- Health care-associated meningitis (after neurosurgical procedures or head trauma) is caused by staphylococci

and gram-negative bacilli.

DIAGNOSIS

Clinical Presentation

- Meningitis should be considered in any patient with fever and stiff neck or neurologic symptoms, especially if another concurrent infection or head trauma is present.
- **Aseptic meningitis** (meningitis with negative bacterial cultures) is usually milder than bacterial meningitis and may be preceded by upper respiratory symptoms or pharyngitis. Viruses, especially enteroviruses, are common causes, as is drug-induced inflammation (e.g., NSAIDs, TMP-SMX).
- Distinction between bacterial, viral, and noninfectious etiologies cannot be made clinically.

Diagnostic Testing

- Diagnosis requires a lumbar puncture with measurement of opening pressure; examination of cerebrospinal fluid (CSF) protein, glucose, and cell count with differential; and Gram stain with culture (Table 14-3). Blood cultures should always be obtained. A head CT scan before lumbar puncture is controversial but is generally not required

for immunocompetent patients who present without focal neurologic abnormalities, seizures, or diminished level of consciousness (*Clin Infect Dis 2004;39:1267*).

TABLE 14-3 Typical Cerebrospinal Fluid Findings in Meningitis

	Opening Pressure (mm H_2O)	White Cells (/μL)	Glucose (mg/dL)	Protein (mg/dL)	Laboratory Diagnosis
Normal	<180	0-5	50-75	15-40	None
Bacterial meningitis	↑	100-5000 neutrophils	<40	100-500	Gram stain, culture
Tuberculous meningitis	↑	50-300 lymphocytes	<45	50-300	Acid-fast bacilli smear, culture, polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*
Cryptococcal meningitis	↑↑	20-500 lymphocytes	<40	>45	Cryptococcal antigen, India ink stain, fungal culture
Viral meningitis	↑	10-1000 lymphocytes	Normal	50-100	Virus-specific PCR

Adapted from Tunkel A. Approach to the patient with central nervous system infection. In: Bennett JE, Dolan R, Blaser MJ, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. New York: Elsevier Churchill Livingston; 2015:1091-6.

- Typical CSF findings in **bacterial meningitis** include a neutrophilic pleocytosis, markedly elevated CSF protein, and decreased glucose level.
- In **aseptic meningitis**, a lymphocytic CSF pleocytosis is common (although neutrophils may predominate very early in the disease course). CSF PCR can detect enteroviruses, herpes simplex virus (HSV), and HIV. CSF lymphocytosis and decreased glucose level should prompt a workup for TB or fungal meningitis.
- Depending on the clinical scenario, other potentially useful CSF studies include Venereal Disease Research Laboratory (VDRL), acid-fast stain and culture, cryptococcal antigen and fungal culture, and arbovirus antibodies.

TREATMENT

- Treatment consists of supportive measures and antimicrobial therapy (*Clin Infect Dis 2004;39:1267*). Whenever acute bacterial meningitis is suspected, high-dose parenteral antimicrobial therapy should be started **immediately after lumbar puncture** (without delay for imaging). Until the etiology of the meningitis is known, an empiric regimen should be based on patient risk factors and Gram stain of the CSF.
- **If no organisms are seen**, high-dose third-generation cephalosporins (ceftriaxone 2 g IV q12h) and vancomycin 15-20 mg/kg IV q8-12h are recommended while culture results are pending.
- Ampicillin 2 g IV q4h should be added for **immunocompromised and older patients (>50 years old)** to cover *L. monocytogenes*.

- In the **postneurosurgical setting or after head or spinal trauma**, broad-spectrum coverage with high-dose vancomycin and ceftazidime or cefepime 2 g IV q8h is indicated. Empiric broad-spectrum regimens should be narrowed once culture and sensitivity data are known.
- **Dexamethasone** 0.15 mg/kg IV q6h started just prior to or with initial antibiotics and continued for 4 days reduces the risk of a poor neurologic outcome in patients with meningitis caused by ***S. pneumoniae***. Steroids have not proven to be of benefit for bacterial meningitis caused by other organisms and should be discontinued if a different pathogen is isolated (*Cochrane Database Syst Rev 2013;6:CD004405*).
- **Therapy for specific infections**
  - For ***S. pneumoniae***, initial therapy consists of ceftriaxone plus vancomycin. Vancomycin should be discontinued if the isolate is susceptible to ceftriaxone (minimum inhibitory concentration [MIC] <1.0 µg/mL). For penicillin-sensitive isolates (MIC <0.1 µg/mL), IV penicillin G 4 million units q4h can be used. Dexamethasone can be a valuable adjunct if given early in treatment.
  - For ***N. meningitidis***, high-dose ceftriaxone or cefotaxime is used. If the isolate is susceptible, penicillin can be used. Alternatives are meropenem and chloramphenicol. Patients should be placed in droplet isolation for at least the first 24 hours of treatment. Close contacts (e.g., persons living in the same household and health care workers having close contact with secretions, such as intubation) should receive prophylaxis with either ciprofloxacin 500 mg PO once; rifampin, 600 mg PO bid for 2 days; or ceftriaxone 250 mg IM. Terminal component complement deficiency (C5 through C9) should be ruled

out in patients with recurrent meningococcal infections.

- ***L. monocytogenes*** meningitis is seen in immunosuppressed adults, pregnant women, and the elderly. Treatment is with ampicillin 2 g IV q4h for at least 3 weeks. TMP-SMX (TMP 5 mg/kg IV q6h) or meropenem (2 g IV q8h) is an alternative for the penicillinallergic patient.
- **Gram-negative bacillary meningitis** is usually a complication of head trauma or neurosurgical procedures. High-dose ceftazidime or cefepime 2 g IV q8h is used for most pathogens, including *Pseudomonas aeruginosa*. High-dose ceftriaxone or cefotaxime may be used for susceptible pathogens. Alternatives include meropenem and ciprofloxacin.
- ***S. aureus*** **meningitis** is usually a result of high-grade bacteremia, direct extension from a parameningeal focus, or recent neurosurgical procedure. Vancomycin should be used initially in penicillin-allergic patients and for methicillin-resistant isolates. Oxacillin and nafcillin 2 g IV q4h are the drugs of choice for MSSA. Ceftriaxone is an alternative for MSSA. Avoid first-generation cephalosporins because they do not penetrate into the CSF.
- For **enteroviral** meningitis, the treatment is supportive care. Acyclovir, 10 mg/kg IV q8h, is used for moderate to severe **HSV meningitis**.

Encephalitis

GENERAL PRINCIPLES

Encephalitis is inflammation of the brain parenchyma, usually associated with viral infections. **HSV-1** is the most common and most important cause of sporadic infectious encephalitis. Other causes include arboviruses such as West Nile virus (WNV), enteroviruses, other herpesviruses, and rabies. Nonviral causes include *Mycobacterium tuberculosis*, syphilis, fungi, *Mycoplasma pneumoniae*, and *Bartonella henselae*. In the summer months, tick-borne illness (e.g., *Ehrlichia*, Rocky Mountain spotted fever, Lyme disease) should be considered. Noninfectious causes include vasculitis, collagen vascular disease, paraneoplastic syndromes, and acute disseminated encephalomyelitis, which can occur after an infection or immunization.

DIAGNOSIS

Clinical Presentation

Presenting complaints include fever, altered mental status, and neurologic abnormalities, particularly with personality change or seizures, usually without meningeal signs.

Diagnostic Testing

CSF analysis is important and should include PCR testing for HSV and enteroviruses and measurement of CSF and serum arbovirus antibodies. A positive PCR for HSV-1 confirms the diagnosis, but a negative PCR does not rule out HSV encephalitis. Other PCR tests (*Ehrlichia*, *Bartonella*, *Mycoplasma*, varicella-zoster virus, cytomegalovirus) may be sent, depending on clinical suspicion. The diagnosis of WNV is made by detecting IgM antibodies in the CSF. MRI is the most sensitive neuroimaging and may show temporal lobe enhancement in HSV encephalitis.

TREATMENT

Acyclovir 10 mg/kg IV q8h should be started on all patients with suspected encephalitis and continued for 14-21 days, unless HSV is definitively ruled out. Delayed initiation of therapy greatly increases the risk of

poor neurologic outcomes. Treatment of other viral causes is mainly supportive. Antibiotic therapy for presumed bacterial meningitis (see above) should be initiated if clinically indicated and discontinued once CSF cultures are negative. Doxycycline 100 mg q12h should be added if there is suspicion for tick-borne illness (*Clin Infect Dis 2008;47:303*).

Brain Abscess

GENERAL PRINCIPLES

Brain abscess in the immunocompetent host is usually bacterial in origin and a result of spread from a contiguous focus (mastoiditis, sinusitis, dental infection) or from septic emboli from endocarditis or bacteremia or related to trauma or surgery. Infection is often polymicrobial, with viridans streptococci, *S. aureus*, and anaerobes being the most common pathogens; staphylococci and gram-negative bacilli predominate after surgery. In immunocompromised hosts, etiologies include invasive fungal infection, *Nocardia*, and TB; in HIV-infected patients, toxoplasmosis is a leading consideration (*N Engl J Med 2014;371:447*).

DIAGNOSIS

- Diagnosis is radiographic, with ring-enhancing lesions seen on MRI or contrast-enhanced CT scan.
- A microbiologic etiology must be determined by aspiration, by biopsy, or at the time of surgery.

TREATMENT

Empiric therapy should cover the most likely pathogens based on the primary infection site. When no preceding infection can be found, a third-generation cephalosporin (ceftriaxone) combined with metronidazole and vancomycin is a reasonable regimen in immunocompetent hosts until culture data are available. Cefepime or ceftazidime should be substituted for ceftriaxone after neurosurgical procedures or with penetrating head trauma.

Neurosurgical consultation is imperative for drainage; cultures must be sent to enable pathogen-directed therapy. A prolonged course of antibiotic therapy is often needed, with follow-up imaging to assess improvement.

Neurocysticercosis

Neurocysticercosis should be suspected in patients from Mexico and Central and South America who present with seizures. Ingested eggs of *Taenia solium* differentiate into larvae, which disseminate to brain and other tissues and form cysts. Brain imaging reveals characteristic multiple unilocular cysts that eventually calcify. Treatment consists of anticonvulsants, albendazole or praziquantel (with steroids to decrease the inflammatory response), and/or surgery (*Lancet Neurol 2014;13:1202*).

CARDIOVASCULAR INFECTIONS

Infective Endocarditis

GENERAL PRINCIPLES

Epidemiology

- The incidence of acute bacterial endocarditis (ABE) and health care-associated endocarditis (related to IV catheters and invasive procedures) is rising (*Arch Intern Med 2009;109:463*).
- **Prosthetic valve endocarditis (PVE)** occurs in 1-4% of patients with prosthetic heart valves.

Etiology

- **Infective endocarditis (IE)** is usually caused by gram-positive cocci. *S. aureus* is the most common pathogen followed by viridans streptococci, enterococci, and coagulase-negative staphylococci.
- *Enterococcus* species cause 5-20% of cases of **subacute bacterial endocarditis (SBE)**.
- Gram-negative and fungal IE occur infrequently and are usually associated with injection drug use or prosthetic heart valves.
- Dental procedures and bacteremia from distant foci of infection are frequent seeding events.
- Early PVE (within 2 months of surgery) is typically caused by *S. aureus*, coagulase-negative staphylococci, gram-negative bacilli, and *Candida* species.
- Late-onset PVE is typically caused by *S. aureus*, coagulase-negative staphylococci, enterococci, and viridans streptococci.

Risk Factors

Structural heart disease, IV drug use, prosthetic heart valves, intravascular devices, chronic hemodialysis, and a prior history of endocarditis are predisposing factors for endocarditis.

DIAGNOSIS

The modified Duke criteria (Tables 14-4 and 14-5) for diagnosis of IE, incorporating microbiologic, pathologic, echocardiographic, and clinical findings, are widely used (*Clin Infect Dis 2000;30:633*).

Clinical Presentation

- Patients with **ABE** may present within 3-10 days of onset of infection with critical illness.
- **SBE** may present over weeks to months with constitutional symptoms (fever, malaise, anorexia), immune complex disease (nephritis, arthralgias, Osler nodes), and embolic phenomenon (renal, splenic, and cerebral infarcts; petechiae; Janeway lesions).
- **PVE** must be considered in any patient with persistent bacteremia after heart valve surgery.

TABLE 14-4 Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major Criteria

Positive blood cultures for IE

1. Two separate blood cultures with viridans streptococci, *Streptococcus gallolyticus* (formerly *bovis*), *Staphylococcus aureus*, HACEK group, or community-acquired enterococci (no primary focus)
2. Persistently positive blood cultures drawn more than 12 hours apart OR all of three or a majority of four separate blood cultures, drawn 1 hour apart

3. Single positive blood culture for *Coxiella burnetii*

Evidence of endocardial involvement

Positive echocardiogram for IE, such as:

1. Oscillating intracardiac mass on a valve or supporting structure, in the path of regurgitant jets, or on implanted materials in the absence of another anatomic explanation
2. Abscess
3. New partial dehiscence of a prosthetic valve
4. New valvular regurgitation (change in preexisting murmur not sufficient)

Minor Criteria

1. Predisposing heart condition or IV drug use
2. Fever ≥38°C (100.4°F)
3. Vascular phenomena: Arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial or conjunctival hemorrhage, Janeway lesions
4. Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. Microbiologic evidence: Positive blood culture but not meeting major criteria OR serologic evidence of infection with an organism consistent with IE

HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; IE, infective endocarditis.

Diagnostic Testing

- The most reliable diagnostic criterion for IE is persistent bacteremia in a compatible clinical setting. Three blood cultures should be taken from separate sites over at least a 1-hour period prior to empiric antimicrobial therapy. Blood cultures are positive in at least 90% of patients but can be negative if the patient has already received antibiotics.
- Echocardiography plays an important role in establishing the diagnosis of IE and determining the need for surgical intervention.
- Patients with IE and vegetations seen by transthoracic echocardiography (TTE) are at higher risk of embolism, heart failure, and valvular disruption. However, a negative TTE cannot rule out IE.
- When clinical evidence of IE exists, **transesophageal echocardiography (TEE)** improves the sensitivity of the Duke criteria, especially in patients with prosthetic heart valves.
- **Culture-negative IE** is usually encountered when prior antimicrobial therapy has been given, or rarely, with fastidious pathogens, such as nutritionally deficient streptococci (now *Abiotrophia* and *Granulicatella*), HACEK organisms, *Coxiella burnetii* (Q fever), *Bartonella*, *Brucella*, *Tropheryma whipplei* (Whipple disease), and fungi. Empiric therapy can be initiated despite negative cultures (Table 14-6).

TABLE 14-5 Classification of Infective Endocarditis (IE) by Modified Duke Criteria

Definite IE

Pathologic criteria:

Vegetation or intracardiac abscess confirmed by histology showing active endocarditis AND an associated microorganism demonstrated by culture or histology

Clinical criteria:

Two major criteria OR
One major and three minor criteria OR
Five minor criteria

Possible IE

One major and one minor criteria OR
Three minor criteria

Rejected IE

Firm alternative diagnosis OR
Resolution of manifestations with therapy for <4 days OR
No pathologic evidence at surgery or autopsy after antibiotic therapy ≤4 days

---

Adapted from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633-8.

- **HACEK** is an acronym for a group of fastidious, slow-growing, gram-negative bacteria (**H**aemophilus, **A**ctinobacillus [now **A**ggregatibacter], **C**ardiobacterium, **E**ikenella, and **K**ingella species) that have a predilection for infecting heart valves.

TREATMENT

- **High doses of IV antimicrobials for extended periods (generally 4-6 weeks) are required.**
- Quantitative antimicrobial susceptibility testing of the causative organism is essential for optimal treatment.
- **ABE** often requires empiric antimicrobial treatment before culture results become available. Initial treatment for *S. aureus* should consist of vancomycin 15 mg/kg IV q12h. Therapy should then be modified based on culture and susceptibility data. For methicillinsensitive isolates, oxacillin 2 g IV q4h is superior to vancomycin.
- **SBE** caused by susceptible organisms should be treated with penicillin, because this typically results in cure rates of >90%. Therapy can usually be delayed until culture data and susceptibilities are available.
- **PVE** requires aggressive combination therapy for at least 6 weeks or longer because of the increased risk for treatment failure and relapse. Indications for valve replacement are detailed in the following text.

Initial empiric therapy pending culture data includes the addition of rifampin to vancomycin and gentamicin to improve biofilm penetration. Oxacillin should be substituted for vancomycin if sensitive. Treatment failure or relapse is common.

- Baseline audiometry is recommended for patients who will receive 7 or more days of aminoglycoside therapy, with repeat testing weekly while on treatment or if symptoms develop.

P.432

P.433

TABLE 14-6 Treatment of Endocarditis Caused by Specific Organisms[a]

Organism	Antibiotic Regimen	Duration	Notes
Viridans streptococci			
MIC <0.12 µg/mL	◦ Penicillin G (12-18 million units IV q24h) or ceftriaxone +/- gentamicin (3 mg/kg IV in two or three divided doses) ◦ Vancomycin (15 mg/kg IV q12h) if PCN allergic	◦ 4 wk without gentamicin (2 wk total if used in combination)	◦ 2-wk course not indicated for prosthetic valves, major embolic or extended symptoms ◦ Gentamicin may be ototoxic and nephrotoxic
MIC 0.12-0.5 µg/mL	◦ Penicillin G (4 million units IV q4h) or ceftriaxone + gentamicin ◦ Vancomycin if PCN allergic and unable to desensitize to PCN	◦ 4 wk total with 2 wk of gentamicin	◦ Vancomycin monotherapy in allergic patients
MIC >0.5 µg/mL	◦ Treat as enterococcal endocarditis	◦ 4-6 wk	
Enterococcus species			
Penicillin susceptible	◦ Ampicillin 2 g IV q4h + gentamicin ◦ Vancomycin + gentamicin	◦ 4-6 wk	◦ If high-level gentamicin resistance, substitute streptomycin (15 mg/kg IV q24h IV in two divided doses based on ideal body weight) or ceftriaxone (4 g IV q24h in two divided doses)

Penicillin resistant	◦ *β-lactamase:* Ampicillin/sulbactam 3 g IV q6h + gentamicin ◦ *Intrinsically resistant:* Vancomycin + gentamicin	◦ 6 wk	
Vancomycin (VRE) and ampicillin resistant	◦ Linezolid (600 mg [IV or PO] q12h) or daptomycin ◦ Quinupristin/dalfopristin ± doxycycline	◦ ≥8 wk	◦ Consult infectious diseases specialist because VRE IE is difficult to treat
Staphylococcus species			
Native valve, MSSA (*Clin Infect Dis 2009;48:713*; *Medicine (Baltimore) 2003;82:333*)	◦ Oxacillin or nafcillin (2 g IV q4h) ◦ Cefazolin 2 g IV q8h if penicillin allergy without anaphylaxis	◦ 6 wk	◦ Initial 3-5 d gentamicin for synergy may not be beneficial. ◦ Penicillins are superior to vancomycin, and desensitization is preferred when possible.
Tricuspid valve, MSSA (IV drug user)	◦ Oxacillin + gentamicin	◦ 2 wk	◦ Avoid vancomycin
Native valve, MRSA	◦ Vancomycin or daptomycin (6 mg/kg IV q24h) (also for MSSA if anaphylactic allergy)	◦ 6 wk	◦ Linezolid used with some success
Staphylococcus species (prosthetic valve)			
MSSA/MSSE	◦ Oxacillin + rifampin (300 mg PO q8h) + gentamicin	◦ ≥6 wk total (2 wk of gentamicin)	
MRSA/MRSE	◦ Vancomycin + rifampin + gentamicin	◦ ≥6 wk total (2 wk of gentamicin)	
HACEK	◦ Ceftriaxone (2g IV	◦ 4 wk	◦ HACEK stands for

organisms and culture-negative IE	q24h) or ampicillin-sulbactam (3 g IV q6h) or ciprofloxacin (400 mg IV q12h)	*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella.*

IE, infective endocarditis; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; PCN, penicillin; VRE, vancomycinresistant *Enterococcus*.
Baseline and weekly audiometry recommended for patients receiving aminoglycosides for >7 days. Monitor aminoglycoside and vancomycin levels. Goal vancomycin trough levels are near 15-20 µg/mL.

[a]See *Circulation* 2005;111:e393.

- **Antibiotic therapy for specific organisms** (see Table 14-6)
  - ***Streptococcus pyogenes*** and ***S. pneumoniae*** should be treated with penicillin G 2-4 million units IV q4h for 4-6 weeks. Penicillin-resistant pneumococci should be treated with ceftriaxone 2 g IV q24h for 4-6 weeks. *Streptococcus bovis* bacteremia and endocarditis are associated with lower gastrointestinal (GI) tract disease, including neoplasms. Groups B and G streptococcal endocarditis may also be associated with lower intestinal pathology.
  - **Culture-negative IE** can be treated with empiric antibiotics (see Table 14-6).
  - **Coagulase-negative *Staphylococcus*** (e.g., ***Staphylococcus epidermidis***) IE primarily occurs in patients with prosthetic heart valves, although native valve endocarditis is increasing, particularly in health care settings. *Staphylococcus lugdunensis* IE is associated with a high rate of perivalvular extension and metastatic spread. A β-lactam antibiotic or vancomycin is used for treatment.
- **Response to antimicrobial therapy**
  - Clinical improvement is frequently seen within 3-10 days of initiating therapy.
  - Blood cultures should be obtained daily until clearance of bacteremia has been documented.
  - Persistent or recurrent fever usually represents extensive cardiac infection but also may be due to septic emboli, drug hypersensitivity, or subsequent nosocomial infection (*Circulation 2005;111:e393*).

Surgical Management

- For native valve endocarditis, indications for surgery include refractory heart failure; aortic or mitral regurgitation with hemodynamic evidence of elevated left ventricular enddiastolic pressure; complications such as heart block, annular or aortic abscess, fistula, or perforation; and infection with fungi or other highly resistant organisms. Recurrent emboli and sustained bacteremia on appropriate therapy are other indications.
- For PVE, indications include heart failure, valve dehiscence, increasing valve obstruction or worsening regurgitation, complications such as abscess formation, persistent bacteremia or recurrent emboli, resistant organisms, and relapsing infection (*J Am Coll Cardiol 2006;48:e1*).

SPECIAL CONSIDERATIONS

The American Heart Association recommendations for prophylaxis for IE are outlined in Table 14-7.

Myocarditis

GENERAL PRINCIPLES

- When the heart is involved in an inflammatory process, the cause is often an infectious agent. Myocarditis may occur during and after viral, rickettsial, bacterial, fungal, and parasitic infections.
- Viruses are the most frequent cause and include enteroviruses (Coxsackie B and echovirus), adenovirus, human herpesvirus 6, parvovirus B-19, and many others. Myocarditis can also be a rare complication of smallpox vaccination.

DIAGNOSIS

- Nasopharyngeal swab testing and serology to detect viral infections are rarely helpful.
- Endomyocardial biopsy for histopathology and viral PCR is the “gold standard” but is not routinely done.

TABLE 14-7 Endocarditis Prophylaxis[a]

I. Endocarditis prophylaxis is recommended for the following cardiac conditions: prosthetic valves; previous endocarditis; unrepaired congenital heart disease, including palliative shunts or conduits, repaired congenital heart disease with prosthetic material during the first 6 months after procedure, or with residual defects at or adjacent to the site of the prosthetic device; and cardiac valvulopathy in transplant recipients.

II. Regimens for dental, oral, or respiratory tract procedures (including dental extractions, periodontal or endodontic procedures, professional teeth cleaning, bronchoscopy with biopsy, rigid bronchoscopy, surgery on respiratory mucosa, tonsillectomy):

Clinical Scenario	Drug and Dosage
Standard prophylaxis	Amoxicillin 2 g PO 1 h before procedure
Unable to take PO	Ampicillin 2 g IM or IV, or cefazolin or ceftriaxone 1 g IM or IV within 30 min before procedure
Penicillin-allergic patient	Clindamycin 600 mg PO, or cephalexin 2 g PO, or clarithromycin or azithromycin 500 mg PO 1 h before procedure
Penicillin allergic and unable to take PO	Clindamycin 600 mg IV, or cefazolin or ceftriaxone 1 g IV within 30 min before procedure

III. Gastrointestinal and genitourinary procedures do not require routine use of prophylaxis. High-

risk patients infected or colonized with enterococci should receive amoxicillin, ampicillin, or vancomycin to eradicate the organism prior to urinary tract manipulation.

IV. Prophylaxis is recommended for procedures on infected skin, skin structures, or musculoskeletal tissue ONLY for patients with cardiac conditions outlined above. An antistaphylococcal penicillin or cephalosporin should be used.

---

[a]See *Circulation* 2007;116:1736.

TREATMENT

Supportive care is the mainstay of treatment. Nonsteroidal agents (NSAIDs) should be avoided. The role of IV immunoglobulin and antiviral agents in viral-mediated myocarditis remains anecdotal.

Pericarditis

GENERAL PRINCIPLES

Acute pericarditis is a syndrome caused by inflammation of the pericardium and characterized by chest pain, a pericardial friction rub, and diffuse ST-segment elevations on ECG. Viruses are the most common infectious etiology. Staphylococci, *S. pneumonia*, TB, and histoplasmosis are occasional causes (see the Tuberculosis section).

TREATMENT

The role of antiviral therapies in viral pericarditis remains unclear. NSAIDs may be used for pain. If an etiology is identified, specific treatment can be initiated.

UPPER RESPIRATORY TRACT INFECTIONS

Pharyngitis

GENERAL PRINCIPLES

Pharyngitis is commonly (>50%) caused by viruses, with infections due to group A streptococci (GABHS) and other bacteria responsible to a lesser extent. Unfortunately, 60% of adults with pharyngitis receive antibiotics (*JAMA Intern Med 2014;174:138*).

DIAGNOSIS

Clinical Presentation

Fever, cervical lymphadenopathy, tonsillar exudates, and lack of cough may or may not be present in addition to throat pain. Distinguishing bacterial from viral pharyngitis on clinical grounds alone is difficult.

Differential Diagnosis

- **Acute HIV infection** should be considered in the setting of pharyngitis with atypical lymphocytosis

and negative *Streptococcus* and Epstein-Barr virus testing.

- **Epiglottitis** should be considered in the febrile patient with severe throat pain, odynophagia, new-onset drooling, and dysphagia (see Epiglottitis section)
- Suppurative complications including **peritonsillar or retropharyngeal abscess** should be considered in the patient with severe unilateral pain, muffled voice, trismus, and dysphagia.

Diagnostic Testing

- Diagnostic testing is usually reserved for symptomatic patients with exposure to a case of streptococcal pharyngitis, those with signs of significant infection (fever, tonsillar exudates, and cervical adenopathy), patients whose symptoms persist despite symptomatic therapy, and patients with a history of rheumatic fever.
- Rapid antigen detection testing (RADT) is useful for identifying **GABHS**, which requires therapy to prevent suppurative complications and rheumatic fever. A negative test does not reliably exclude GABHS, making throat culture necessary if clinical suspicion is high.
- Serology for **Epstein-Barr virus** (e.g., heterophile agglutinin or monospot) and examination of a peripheral blood smear for atypical lymphocytes should be performed when infectious mononucleosis is suspected.

TREATMENT

- Most cases of pharyngitis are self-limited and do not require antimicrobial therapy.
- Treatment for **GABHS** is indicated with a positive culture or RADT, if the patient is at high risk for development of rheumatic fever, or if the diagnosis is strongly suspected, pending culture results. Treatment options include penicillin V 250 mg PO qid or 500 mg PO bid for 10 days, clindamycin 300-450 mg PO q6-8h for 5 days, azithromycin 500 mg PO on day 1 followed by 250 mg on days 2-5, or benzathine penicillin G 1.2 million units IM as a one-time dose (*Clin Infect Dis 2012;55:1279*).

- Gonococcal pharyngitis is treated with ceftriaxone 250 mg IM as a single dose, plus azithromycin or doxycycline.

Epiglottitis

GENERAL PRINCIPLES

H. influenzae type B, *S. pneumoniae*, *S. aureus*, and GABHS are common bacterial causes of epiglottitis, although viral and fungal pathogens may also be implicated.

DIAGNOSIS

Clinical Presentation

Fever, sore throat, odynophagia, drooling, muffled voice, and dysphagia in a patient with a normal oropharyngeal examination should prompt a clinical diagnosis of epiglottitis. Inspiratory stridor is a sign of impending respiratory compromise.

Diagnostic Testing

- Throat and blood cultures are useful in determining the etiology.
- Soft tissue lateral radiographs of the neck may show the “thumb print” sign.
- Definitive diagnosis is made by visualization of the epiglottis.

TREATMENT

Prompt treatment including hospitalization, and otolaryngologic consultation for airway management is recommended in all suspected cases. Antimicrobial therapy should include an agent that is active against *H. influenzae*, such as ceftriaxone 2 g IV q24h or cefotaxime 2 g IV q6-8h. Vancomycin or clindamycin should be added if there is concern for MRSA.

Rhinosinusitis

GENERAL PRINCIPLES

- **Acute rhinosinusitis** is most frequently caused by upper respiratory viruses. Bacterial pathogens, such as *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and anaerobes are involved in <2% of cases and should be considered only if symptoms persist for >10 days.
- **Chronic rhinosinusitis** may be caused by any of the etiologic agents responsible for acute sinusitis, as well as *S. aureus*, *Corynebacterium diphtheriae*, and many anaerobes (e.g., *Prevotella* spp., *Veillonella* spp.). Possible contributing factors include asthma, nasal polyps, allergies, or immunodeficiency.

DIAGNOSIS

Clinical Presentation

- **Acute rhinosinusitis** presents with purulent nasal discharge, nasal obstruction, facial or dental pain, and sinus tenderness with or without fever, lasting <4 weeks.
- **Chronic rhinosinusitis** is defined by symptoms lasting >12 weeks including mucopurulent drainage, nasal obstruction, facial pain or pressure, and decreased sense of smell with documented signs of inflammation.

Diagnostic Testing

- Diagnosis requires objective evidence of mucosal disease, usually with rhinoscopy and nasal endoscopy or a sinus CT. Plain films are not recommended.
- Sinus cultures can be obtained from nasal endoscopy or sinus puncture. Nasal swabs are not helpful.

TREATMENT

- The goals of medical therapy for acute and chronic rhinosinusitis are to control infection, reduce tissue edema, facilitate drainage, maintain patency of the sinus ostia, and break the pathologic cycle that leads to chronic sinusitis.
- **Acute rhinosinusitis**
  - **Symptomatic treatment** is the mainstay of therapy, including oral decongestants and analgesics with or without a short course of topical decongestant or intranasal glucocorticoid (*Otolaryngol Head Neck*

Surg 2007;137:S1).

- **Empiric antibiotic therapy** is indicated only for severe persistent symptoms (≥10 days) or failure of symptomatic therapy. First-line therapy should consist of a 5- to 7-day course of amoxicillin-clavulanate 875 mg/125 mg PO bid. Doxycycline or a respiratory fluoroquinolone (e.g., moxifloxacin, levofloxacin) may be used as alternative therapy in case of β-lactam allergy or primary treatment failure. TMP-SMX and macrolides are not recommended for empiric therapy due to high rates of resistance (*Clin Infect Dis 2012;54:e72*).

- **Chronic rhinosinusitis.** Treatment usually includes topical and/or systemic glucocorticoids; the role of antimicrobial agents is unclear. If they are used, amoxicillin-clavulanate is the first-line treatment, with clindamycin for penicillin-allergic patients. Some chronic cases may require endoscopic surgery.

Influenza Virus Infection

GENERAL PRINCIPLES

Influenza is readily transmissible and associated with outbreaks of varying severity during the winter months.

DIAGNOSIS

Clinical Presentation

Influenza virus infection causes an acute, self-limited febrile illness marked with headache, myalgias, cough, coryza, and malaise.

Diagnostic Testing

Diagnosis is usually made clinically during influenza season, with confirmation by nasopharyngeal swab for rapid antigen testing, PCR, or direct fluorescent antibody test and culture.

TREATMENT

- Treatment is usually symptomatic.
- Antiviral medications may shorten the duration of illness but must be initiated within 24-48 hours of the onset of symptoms to be effective in immunocompetent patients (*MMWR Morb Mortal Wkly Rep 2011;60(1):1*). Antiviral therapy should not be withheld

  from patients presenting >48 hours after symptom onset requiring hospitalization or at high risk for complications (see Complications section).

  - The **neuraminidase inhibitors** (oseltamivir 75 mg PO bid or zanamivir 10 mg inhaled twice a day, each for 5 days) are used in treatment and prophylaxis of influenza A and B. Peramivir, 600 mg single dose IV, has recently been approved by the U.S. Food and Drug Administration.
  - **Adamantanes** (amantadine and rimantadine, each 100 mg PO bid) are not recommended due to high rates of resistance.
  - Circulating strains change annually with varying resistance patterns to both classes of antivirals. **Treatment decisions must be based on annual resistance data**, available from the Centers for Disease Control and Preventions (CDC; *http://www.cdc.gov*).

- **Vaccination** is the most reliable prevention strategy. Annual vaccination is recommended for all individuals 6 months of age and older (*MMWR Morb Mortal Wkly Rep 2011;60(33):1128*).

COMPLICATIONS

- Adults >65 years old, residents of nursing homes and other long-term care facilities, pregnant women (and those up to 2 weeks postpartum), and patients with chronic medical conditions (e.g., pulmonary disease, cardiovascular disease, active malignancy, diabetes mellitus, chronic renal insufficiency, chronic liver disease, immunosuppression including HIV and transplantation, morbid obesity) are at greater risk of complications.
- Influenza pneumonia and secondary bacterial pneumonia are the most common complications of influenza infection.
- Viral antigenic drift and shift can cause emergence of strains with enhanced virulence or the potential for pandemic spread, requiring modified therapy or heightened infection control measures.

LOWER RESPIRATORY TRACT INFECTIONS

Acute Bronchitis

GENERAL PRINCIPLES

Acute bronchitis involves inflammation of the bronchi, most often caused by viruses such as coronavirus, rhinovirus, influenza, or parainfluenza. Uncommon causes include *M. pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*. Unfortunately, 60-90% of patients with acute bronchitis are given antibiotics (*JAMA 2014;311:2020*).

DIAGNOSIS

Clinical Presentation

Symptoms include cough with or without sputum production lasting >5 days and may be indistinguishable from an upper respiratory tract infection early on. Fever is uncommon.

Diagnostic Testing

- Diagnosis is made clinically. Sputum cultures are not recommended.
- In febrile, systemically ill, or older patients with abnormal vital signs, pneumonia should be ruled out clinically or radiographically, and diagnostic tests for influenza should be performed depending on the season and local disease trends.
- Cough lasting >2 weeks in an adult should be evaluated for pertussis with a nasopharyngeal swab for culture or PCR.

TREATMENT

- Treatment is symptomatic and should be directed toward controlling cough (dextromethorphan 15 mg PO q6h).
- Routine antimicrobial use is **not** recommended unless pertussis has been diagnosed (*Cochrane Database Syst Rev 2014;3:CD000245*).
- **Pertussis** treatment consists of clarithromycin 500 mg PO bid for 14 days or azithromycin 500 mg PO

single dose followed by 250 mg PO daily for 4 more days.

- Pertussis cases should be reported to the local health department for contact tracing and administration of postexposure prophylaxis with azithromycin when indicated.

Community-Acquired Pneumonia

GENERAL PRINCIPLES

- The predominant organism involved is *S. pneumoniae*; other bacterial etiologies are *H. influenzae* and *M. catarrhalis*. Pneumonia caused by atypical agents, such as *Legionella pneumophila*, *C. pneumoniae*, or *M. pneumoniae*, cannot be reliably distinguished clinically. Influenza and other respiratory viruses may also cause pneumonia in adults.
- CA-MRSA is an important cause of severe, necrotizing pneumonia.
- Health care-associated pneumonia (HCAP; seen in nursing home residents, clinic and hemodialysis patients seen within 30 days, and patients hospitalized within prior 90 days) is more likely to involve multidrug-resistant organisms and should be distinguished from community-acquired pneumonia (CAP).

DIAGNOSIS

Clinical Presentation

- Fever and respiratory symptoms, including cough with sputum production, dyspnea, and pleuritic chest pain, are common presenting features in immunocompetent patients. Signs include tachypnea, rales, or signs of consolidation on auscultation.
- CAP presents acutely, over a matter of hours to days. If a patient has symptoms for more than 2-3 weeks, particularly if accompanied by weight loss or night sweats, this should raise the question of an alternate diagnosis, such as mycobacterial or fungal infection.

Diagnostic Testing

- Sputum Gram stain and culture of an adequate sample and blood cultures prior to antibiotic therapy should be obtained.
- In selected patients, urine *Legionella* or pneumococcal antigen, nasopharyngeal swab for influenza or other virus detection by PCR, and respiratory samples for atypical pathogens should be sent. If there is suspicion for TB, sputum for acid-fast staining and culture should be obtained, and the patient should be placed on airborne isolation.
- CXR should be performed and may reveal lobar consolidation, interstitial infiltrates, or cavitary lesions, confirming the diagnosis.
- Fiberoptic bronchoscopy may be used for detection of less common organisms, especially in immunocompromised patients, or if the patient is not responding to adequate therapy.

TREATMENT

- All patients should be assessed for hospitalization and evaluated for severity of illness, comorbid factors, and oxygenation. Guidelines giving detailed empiric treatment

regimens have been published, with an emphasis on targeting the most likely pathogens within specific

risk groups (*Clin Infect Dis 2007;44:S27*). Antibiotics should be given as soon as CAP is diagnosed because delay leads to higher patient mortality. Antibiotic therapy should be narrowed once a specific microbiologic etiology has been identified.

- **Immunocompetent outpatients** with no recent antibiotic exposure and no comorbidities should receive a macrolide, such as azithromycin 500 mg PO single dose followed by 250 mg PO daily for 4 more days, or doxycycline 100 mg PO for at least 5 days.
- **Outpatients with recent antibiotic exposure or comorbidities** should receive respiratory fluoroquinolone (e.g., moxifloxacin) monotherapy or a macrolide (azithromycin or clarithromycin) with high-dose amoxicillin 1 g PO q8h for at least 5 days.
- **Hospitalized patients** should be treated with ceftriaxone 1 g IV daily or cefotaxime 1 g IV q8h PLUS a macrolide (azithromycin or clarithromycin), OR monotherapy with a respiratory fluoroquinolone. Duration of therapy should be at least 5 days but is typically longer, because the patient should be afebrile for >48 hours with clinical improvement prior to discontinuation.
- In **critically ill patients**, the addition of azithromycin or a respiratory fluoroquinolone to a β-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) is necessary to provide coverage for *L. pneumophila*. CA-MRSA coverage with vancomycin or linezolid should also be considered. If *P. aeruginosa* is a concern, an antipseudomonal β-lactam (cefepime, piperacillin-tazobactam, meropenem, imipenem) in combination with an antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin) is recommended. Once *Pseudomonas* has been isolated and antibiotic susceptibilities are available, monotherapy is an option.
- **Thoracentesis** of pleural effusions should be performed, with analysis of pH, cell count, Gram stain and bacterial culture, protein, and lactate dehydrogenase (see Chapter 10, Pulmonary Diseases). Empyemas should be drained.

Lung Abscess

GENERAL PRINCIPLES

Lung abscess typically results from aspiration of oral flora. Polymicrobial infections are common and involve oral anaerobes (*Prevotella* spp., *Peptostreptococcus*, *Fusobacterium*, *Bacteroides* spp., and *Actinomyces* spp.) (*Clin Infect Dis 2005;40:923*). Microaerophilic streptococci (*Streptococcus milleri*), enteric gram-negative bacilli (*Klebsiella pneumoniae*), and *S. aureus*, including CA-MRSA, are less frequent causes. Risk factors include periodontal disease and conditions that predispose patients to aspiration of oropharyngeal contents (alcohol intoxication, seizures, stroke).

DIAGNOSIS

Clinical Presentation

Infections are indolent and may be reminiscent of pulmonary TB, with dyspnea, fever, chills, night sweats, weight loss, and cough productive of putrid or blood-streaked sputum for several weeks.

Diagnostic Testing

CXR is sensitive and typically reveals infiltrates with cavitation and air-fluid levels in dependent areas of the lung, such as the lower lobes or the posterior segments of the upper lobes. Chest CT can provide additional anatomic detail. Respiratory isolation and sputum testing for TB should be performed on all patients with cavitary lung lesions.

TREATMENT

- Antibiotic therapy should consist of clindamycin or a β-lactam/β-lactamase inhibitor (ampicillin-sulbactam, piperacillin-tazobactam, amoxicillin-clavulanate) or a carbapenem (ertapenem). For MRSA cavitary lung lesions, linezolid or vancomycin should be used. Metronidazole monotherapy is ineffective and should be combined with penicillin.
- Percutaneous drainage or surgical resection is rarely necessary and should be reserved for antibiotic-refractory disease, usually involving large abscesses (>6 cm) or infections with resistant organisms.

Tuberculosis

GENERAL PRINCIPLES

- TB infects >2 billion people and is a leading infectious cause of deaths worldwide. In the United States, cases fell to 3.0 per 100,000 in 2013. Most US cases occur in foreign-born individuals and result from reactivation of prior infection (*MMWR Morb Mortal Wkly Rep 2014;63:229*). Multidrug-resistant TB has increased among immigrants from Southeast Asia, sub-Saharan Africa, the Indian subcontinent, and Central America. Extensively drug-resistant TB is becoming increasingly prevalent in sub-Saharan Africa.
- High risk of TB exposure occurs in household contacts, prisoners, the homeless, IV drug abusers, and immigrants from high-prevalence countries. Persons at highest risk for progression include those with impaired immunity, such as HIV infection, silicosis, diabetes mellitus, chronic renal insufficiency, malignancy, malnutrition, and immunosuppressive medications, including therapy with tumor necrosis factor (TNF) antagonists (*Ann Rheum Dis 2013; 72:37*).
- Latent TB infection (LTBI) occurs when someone has been exposed to TB but has no signs, symptoms, or radiographic evidence of current active disease. Untreated, approximately 5% of persons with LTBI develop active TB disease within 2 years of infection. TB disease develops in an additional 5% of persons with LTBI over their remaining life span. Adequate treatment of LTBI can substantially reduce the risk of disease (*Am J Respir Crit Care Med 2014;190:1044*).

DIAGNOSIS

Clinical Presentation

- The most frequent clinical presentation is pulmonary disease. Symptoms are often indolent and may include cough, hemoptysis, dyspnea, fever, night sweats, weight loss, or fatigue. Misdiagnosis and treatment with a fluoroquinolone for presumed CAP can lead to treatment delay and fluoroquinolone resistance (*Int J Infect Dis 2011;15(3):e211*).
- Extrapulmonary disease can present as cervical lymphadenopathy, genitourinary disease, osteomyelitis, miliary dissemination, meningitis, peritonitis, or pericarditis.

Diagnostic Testing

- CXR may reveal focal infiltrates, nodules, cavitary lesions, miliary disease, pleural effusions, or hilar/mediastinal lymphadenopathy. Reactivation disease classically involves the upper lobes.
- Three sputum specimens should be sent for AFB smears and cultures. A diagnosis of active TB is made with a positive AFB smear along with a positive nucleic acid amplification (NAA) test for *M. tuberculosis* complex, which is confirmed on culture. Nontuberculous mycobacteria (NTM) may be positive on smear but negative on NAA test.

- *M. tuberculosis* can take several weeks to grow in culture, so if the clinical suspicion is high, presumptive therapy even with negative smears may be indicated until cultures are negative.
- Drug susceptibility testing should be performed on all initial isolates and on isolates obtained from patients who do not respond to standard therapy. Rapid detection of rifampin resistance, which correlates with multidrug-resistant TB, is possible with molecular techniques (Cepheid Gene Xpert MTB/RIF). Genetic testing on direct specimens is also available for selected cases through the CDC (molecular detection of drug resistance).
- Latent TB may be diagnosed by a positive tuberculin skin test (TST) or interferon-γ release assay. Criteria for a **positive TST** are based on the **maximum diameter of induration** (not erythema):
  - **5-mm induration** is considered positive in patients with HIV infection, close contacts of a known case of TB, patients with CXRs indicative of healed TB, and individuals with organ transplantation or other immunosuppression (TNF-α inhibitors, chemotherapy, steroids).
  - **10-mm induration** is considered positive in immigrants from high-prevalence areas (Asia, Africa, Latin America, Eastern Europe), prisoners, the homeless, IV drug users, nursing home residents, patients with chronic medical illnesses (silicosis, diabetes, hemodialysis, leukemia, lymphoma, malnutrition), and those who have frequent contact with these groups (e.g., health care workers, prison guards).
  - **15-mm induration** is considered positive for otherwise healthy individuals at low risk for TB.

TREATMENT

Active Tuberculosis

- If a patient is hospitalized, he or she should be put on airborne isolation in a **negativepressure room** with use of N95 masks (*MMWR Morb Mortal Wkly Rep 2003;52(RR-11):1*).
- The local health department should be notified of all cases of TB so that contacts can be identified and directly observed therapy (DOT) administered when the patient is discharged. DOT is essential to ensure adherence and prevent emergence of drug resistance.
- **Multidrug anti-TB treatment regimens** are required because drug resistance develops when a single drug is administered. Extended therapy is necessary because of the prolonged generation time of mycobacteria.
- **Initial therapy** (the first 8 weeks) of uncomplicated pulmonary TB should consist of four drugs (RIPE): **rifampin** (**RIF**, 10 mg/kg; maximum, 600 mg PO daily), **isoniazid** (**INH** 5 mg/kg; maximum, 300 mg PO daily), **pyrazinamide** (**PZA**, 15-25 mg/kg; maximum, 2 g PO daily), and **ethambutol** (**EMB**, 15-25 mg/kg PO daily). Pyridoxine (vitamin B_6) 25-50 mg PO daily should be used with INH to prevent sensory neuropathy. If the isolate proves to be **fully susceptible** to INH and RIF, then EMB can be dropped and INH, RIF, and PZA continued to complete this initial phase.
- **Continuation therapy** consists of 16 weeks of INH and RIF to reach a standard total of 6 months of therapy for pulmonary TB. Patients at high risk for relapse (cavitary pulmonary disease or positive TB cultures after 2 months of therapy) should be treated for an additional 28 weeks beyond the 8-week initial phase, for a total of 9 months.
- After at least 2 weeks of daily therapy, intermittent drug administration (two or three times per week at adjusted doses) is effective and facilitates DOT.
- Patients with HIV with CD4 counts <100/μL must receive therapy at least three times weekly.

- If **INH resistance** is documented, INH should be discontinued and RIF, PZA, and EMB continued for the remaining duration of therapy. Organisms resistant only to INH can be effectively treated with a 6-month regimen if the standard four-drug regimen was started initially.

- Therapy for **multidrug-resistant TB** has been less well studied, and consultation with an expert in the treatment of TB is strongly recommended.
- **Extrapulmonary disease** in adults can be treated in the same manner as pulmonary disease, with 6- to 9-month regimens. Central nervous system (CNS) TB should be treated for 12 months.
- **Pregnant women** should not receive PZA and should be treated with a 9-month regimen. INH, RIF, and EMB, with pyridoxine, should be administered during the initial 8-week phase, until susceptibilities are known, with continuation of INH and RIF for the remainder of therapy.
- **Glucocorticoids** remain controversial in the management of TB but have been used in combination with antituberculous drugs to treat life-threatening complications such as pericarditis (*Circulation 2005;112:3608*) and meningitis (*N Engl J Med 2004;351:1741*). Prednisone 1 mg/kg (maximum, 60 mg) PO daily or dexamethasone 12 mg IV daily is tapered over several weeks.

Latent Tuberculosis

- Chemoprophylaxis for LTBI should be administered only after active disease has been ruled out by clinical assessment, CXR, and sputum collection.
- Risk factors for progression include a TST conversion within 2 years of a previously negative TST; a history of untreated TB or CXR evidence of previous fibrotic disease (calcified granulomas in the absence of fibrosis do not confer increased risk); patients with HIV infection, diabetes mellitus, end-stage renal disease, hematologic or lymphoreticular malignancy, chronic malnutrition, or silicosis or who are receiving immunosuppressive therapy; and household members and other close contacts of patients with active disease who have a reactive TST.
- Persons with advanced **HIV** infection or other severely immunocompromised states (e.g., transplant) who have had known contact with a patient with active TB should be treated for LTBI regardless of the TST.
- INH 300 mg PO daily for 9 months should be administered to persons with LTBI who have risk factors for progression to active TB disease, regardless of age.
- INH 900 mg PO plus rifapentine 900 mg PO (with dose adjustment for patients <50 kg) once weekly for 12 weeks is a newer regimen of shorter duration. It should be given by DOT to ensure compliance and monitor adverse effects (*N Engl J Med 2011;365:2155*).

Monitoring

- **Response to therapy.** Patients with initial positive sputum AFB smears should submit sputum for AFB smear and culture every 1-2 weeks until AFB smears become negative. Sputum should then be obtained monthly until two consecutive negative cultures are documented. Conversion of cultures from positive to negative is the most reliable indicator of response to treatment. Continued symptoms or persistently positive cultures after 3 months of treatment should raise the suspicion of drug resistance or nonadherence and prompt referral to an expert in the treatment of TB.
- **Adverse reactions.** Most patients should have a baseline laboratory evaluation at the start of therapy that includes hepatic enzymes, bilirubin, complete blood count (CBC), and serum creatinine. Routine laboratory monitoring for patients with normal baseline values is probably unnecessary except in the setting of HIV (particularly if receiving concurrent antiretroviral therapy), alcohol abuse, chronic liver disease, or pregnancy. Monthly clinical evaluations with specific inquiries about

symptoms of drug toxicity are essential. Patients taking EMB should be tested monthly for visual acuity and red-green color perception.

- Referral to the public health department is recommended to ensure adherence by DOT and to monitor for medication-related complications.

GASTROINTESTINAL AND ABDOMINAL INFECTIONS

- Intra-abdominal infections can be classified as uncomplicated or complicated. Uncomplicated intra-abdominal infections include acute uncomplicated diverticulitis or colitis; involvement is limited to intramural inflammation. Complicated intra-abdominal infections extend beyond the initial organ, causing peritonitis or abscess formation.
- Iatrogenic infections may be complicated due to presence of multidrug-resistant organisms.
- Infections are typically polymicrobial with enteric gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella* spp.), *Enterococcus* spp., and anaerobes such as *Bacteroides* spp.
- Empiric antibiotic therapy should consist of a β-lactam/β-lactamase inhibitor, fluoroquinolone, or third-generation cephalosporin plus metronidazole (Table 14-8).
- A carbapenem should be considered in severe disease or if extended-spectrum β-lactamase-producing organisms are suspected.
- Empiric antifungal coverage is usually not indicated unless yeast is seen on Gram stain or grown in culture.
- Abscess drainage or surgical resection may be necessary for source control (*Clin Infect Dis 2010;50:133*).

Peritonitis

GENERAL PRINCIPLES

- **Primary** or **spontaneous bacterial peritonitis (SBP)** is a common complication of cirrhosis and ascites. *M. tuberculosis* and *Neisseria gonorrhoeae* (Fitz-Hugh-Curtis syndrome in women)

also occasionally cause primary peritonitis (see Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Syndrome, and Acquired Immunodeficiency Syndrome).

TABLE 14-8 Empiric Therapy Examples for Intra-Abdominal Infections

Oral Regimens

- Amoxicillin/clavulanate 875 mg/125 mg PO q12h
- Ciprofloxacin 500-750 mg PO q12h + metronidazole 500 mg PO q8h
- Moxifloxacin 400 mg PO q24h

Parenteral Regimens

No concern for *Pseudomonas aeruginosa*

- Ampicillin/sulbactam 3 g IV q6h
- Ceftriaxone 1-2 g IV q24h + metronidazole 500 mg IV q8h
- Ertapenem 1 g IV q24h
- Tigecycline 100 mg IV × 1 dose then 50 mg IV q12h

Confirmed or concern for *P. aeruginosa*

- Piperacillin/tazobactam 4.5 g IV q6h
- Cefepime 1-2 g IV q8h + metronidazole 500 mg IV q8h
- Ciprofloxacin 400 mg IV q8-12h + metronidazole 500 mg IV q8h
- Meropenem or imipenem

Concern for vancomycin-resistant *Enterococcus spp.*

- Add linezolid 600 mg PO/IV q12h or daptomycin 6-8 mg/kg IV q24h to above regimens

Concern for yeast

- Add echinocandin (e.g., micafungin 100 mg IV q24h) or fluconazole 400 mg PO/IV q24h to above regimens

---

- **Secondary peritonitis** may be caused by a perforated viscus in the GI or genitourinary (GU) tract or contiguous spread from a visceral infection, usually resulting in an *acute* surgical abdomen.
- Peritonitis related to **peritoneal dialysis** is addressed in Chapter 13, Renal Diseases.

DIAGNOSIS

Clinical Presentation

SBP may present without signs or symptoms typical for infection. SBP should be ruled out with a diagnostic paracentesis in patients admitted with cirrhosis and ascites presenting with GI bleeding, encephalopathy, acute kidney injury, or other decompensation of liver disease (*Gut 2012;61:297*). Patients with secondary peritonitis may appear acutely ill with abdominal tenderness and peritoneal signs.

Diagnostic Testing

- Send ascites fluid for culture (directly inoculate culture bottles at bedside), cell count, and differential. **SBP** is diagnosed when ascites fluid has >250 neutrophils.
- Diagnosis of **secondary peritonitis** is made clinically, supplemented by blood culture (positive 20-30%) and imaging to evaluate for free air (perforation) or other source of infection.

TREATMENT

- SBP treatment duration is 7 days but should be extended to 2 weeks if bacteremia is present. First-line treatment typically includes either a third-generation cephalosporin (e.g., cefotaxime 2 g IV q8h) or a fluoroquinolone (e.g., ciprofloxacin 400 mg IV q12h). Administration of IV albumin on days 1 and 3 of

treatment may improve survival (*N Engl J Med 1999;341(6):403*). If a repeat paracentesis reveals <250 polymorphonuclear leukocytes (PMNs) and cultures remain negative, treatment may be shortened to 5 days. **SBP prophylaxis** should be initiated after the first episode of SBP or after variceal bleeding.

- **Secondary peritonitis** may require surgical intervention in the setting of perforation or intra-abdominal abscess formation. Percutaneous drainage of abscess may be preferable to surgical drainage. Antibiotics are often continued until imaging demonstrates resolution of the abscess.
- Treatment of chronic TB peritonitis is the same as that of pulmonary TB.

Hepatobiliary Infections

GENERAL PRINCIPLES

- **Acute cholecystitis** is typically preceded by biliary colic associated with cholelithiasis and characteristically presents with fever, right upper quadrant (RUQ) tenderness with Murphy sign, and vomiting. Acalculous cholecystitis occurs in 5-10% of cases. Organisms usually consist of normal gut flora. Leukocytosis and mild elevations of bilirubin, transaminases, and alkaline phosphatase are possible.
- **Ascending cholangitis** is a sometimes fulminant infectious complication of an obstructed common bile duct, often following pancreatitis or cholecystitis.

DIAGNOSIS

Clinical Presentation

Tenderness and guarding of the RUQ is a common sign of a hepatobiliary infection. **Murphy sign** can be elicited on physical exam to evaluate for cholecystitis. Ascending cholangitis presents as the **Charcot triad** of fever, RUQ pain, and jaundice. **Reynolds pentad** adds symptoms of confusion and hypotension and warrants rapid intervention. Bacteremia and shock are common.

Diagnostic Testing

- Liver function test (LFT) abnormalities are often severe.
- Diagnosis of biliary tract infections is usually made by imaging, with ultrasonography being the primary modality. Technetium-99m-hydroxy iminodiacetic acid scanning and CT scanning may also be useful (*N Engl J Med 2008;358(26):2804*).
- Endoscopic retrograde cholangiopancreatography (ERCP) allows for diagnosis as well as therapeutic intervention in the case of common bile duct obstruction and should be considered in patients with common bile duct dilation, jaundice, or LFT abnormalities.

TREATMENT

- Management of **acute cholecystitis** includes parenteral fluids, restricted PO intake, analgesia, and surgery. Advanced age, severe disease, or complications such as gallbladder ischemia or perforation, peritonitis, or bacteremia mandate broad-spectrum antibiotics (see Table 14-8). Immediate surgery is usually necessary for severe disease, but surgery may be delayed up to 6 weeks if there is an initial response to medical therapy (*Br J Surg 2010;97(2):141-50*). After cholecystectomy, perioperative antibiotics may be discontinued (*JAMA 2014;312(2):145-54*).
- The mainstay of therapy for **ascending cholangitis** is aggressive supportive care, including broad-

spectrum antibiotics (see Table 14-8) and surgical or endoscopic decompression and drainage. Development of an abscess is a complication requiring surgical drainage.

OTHER INFECTIONS

- **Infectious diarrhea** (see Chapter 18, Gastrointestinal Diseases)
- **Viral hepatitis** (see Chapter 19, Liver Diseases)
- ***Helicobacter pylori***-associated disease (see Chapter 18, Gastrointestinal Diseases)

GENITOURINARY INFECTIONS

- The spectrum of GU tract infections varies from uncomplicated to complicated depending on host factors and underlying conditions. Diagnostic and therapeutic approaches to adult GU infections are determined by gender-specific anatomic differences, prior antimicrobial exposures, and the presence of medical devices. Infections are primarily caused by Enterobacteriaceae (*E. coli*, *Proteus mirabilis*, and *K. pneumoniae*) and *Staphylococcus saprophyticus*.
- Workup typically includes a urinalysis and microscopic examination of a fresh, unspun, clean-voided or catheterized urine specimen. Pyuria (positive leukocyte esterase or more than eight leukocytes per high-power field) or bacteriuria (positive nitrites or more than one organism per oil-immersion field) suggests active infection. A urine Gram stain can be helpful in guiding initial antimicrobial choices. Quantitative culture often yields >10^5 bacteria/mL, but colony counts as low as 10^2-10^4 bacteria/mL may indicate infection in women with acute dysuria.

Asymptomatic bacteriuria

- Asymptomatic bacteriuria is defined as the isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection.
- **Asymptomatic bacteriuria is of limited clinical significance except in pregnant women or patients undergoing urologic surgery**. Pregnant women should have screening urine culture near the end of the first trimester and be treated if positive. Treatment is not recommended for asymptomatic bacteriuria in elderly, institutionalized patients, spinal cord injury patients, or catheterized patients when the catheter remains in place (*Clin Infect Dis 2005;40:643-54*).

Cystitis

Uncomplicated cystitis is defined as infection of the bladder or lower urinary tract in otherwise healthy, nonpregnant adult women. Complicated cystitis is defined based on several risk factors including anatomic abnormality, immunosuppression, pregnancy, indwelling catheters, or unusual pathogens. Recurrent cystitis may be seen in women and is usually due to reinfection rather than recurrence.

DIAGNOSIS

Clinical Presentation

- Lower urinary tract infection (UTI) is diagnosed based on clinical history of dysuria, urgency, or urinary frequency associated with urinalysis abnormalities of pyuria and bacteriuria and urine culture. Fever is more likely to be seen if there is associated pyelonephritis.

- Dysuria without pyuria in sexually active patients warrants consideration of sexually transmitted infection.

Diagnostic Testing

- **Acute uncomplicated cystitis in women.** A pretreatment urine culture is recommended for diabetics, patients who are symptomatic for >7 days, individuals with recurrent UTI, women who use a contraceptive diaphragm, and individuals older than 65 years.
- **Sterile pyuria.** Patients who have taken antimicrobials may have negative cultures. Differential diagnosis includes chronic interstitial nephritis, interstitial cystitis, or infection with atypical organisms including *Chlamydia trachomatis*, *Ureaplasma urealyticum*, or less frequently, *N. gonorrhoeae.* Specific cultures of the endocervix for sexually transmitted infections should be performed. Rare cases of TB can present with sterile pyuria as well.

TREATMENT

- See Tables 14-9 and 14-10 for details.
- **Acute uncomplicated cystitis in women.** A 3-day course of empiric antibiotic therapy is recommended for symptomatic women with pyuria. Therapy should be extended to 7 days in pregnant patients and diabetics. Posttreatment urine culture may be indicated in certain circumstances. Foreign bodies including stents and catheters should be removed (*JAMA 2014;312(16):1677-84*).
- **Recurrent cystitis in women** may be challenging to manage. Risk factors include frequency of intercourse and spermicide use in young women and urologic abnormalities like incontinence and cystocele in older women (*JAMA 2014;311(8):844-54*). Relapses with the original infecting organism that occur within 2 weeks of cessation of therapy should be treated for 2 weeks and may indicate a urologic abnormality.

TABLE 14-9 Empiric Therapy for Urinary Tract Infections

Disease	Empiric Therapy	Notes
Simple cystitis		
Women (*Clin Infect Dis 2011*; *52:e103*; *JAMA 2014; 312(16):1677*; *Cochrane Database Syst Rev 2011;19: CD002256*)	*First line:* ◦ TMP-SMX ◦ Nitrofurantoin ◦ Fosfomycin *Alternative:* ◦ FQ *Pregnancy:* ◦ Nitrofurantoin ◦ Cephalexin ◦ Cefuroxime axetil	◦ Choose antibiotics based on local susceptibility patterns. ◦ Usually treat for 3 d. Extend therapy to 7 d for diabetics and older patients. ◦ Fosfomycin and β-lactams have lower efficacy than other agents; avoid if early pyelonephritis is suspected. ◦ Treat asymptomatic bacteriuria in pregnancy.
Men	*First line:*	◦ Treat 7-14 days.

(*J Antimicrob Chemother 2000;46 (suppl 1):23*)	◦ TMP-SMX ◦ FQ	◦ Avoid nitrofurantoin and β-lactam in men due to low tissue concentrations. ◦ Consider urologic evaluation for recurrent disease or pyelonephritis.
Pyelonephritis, complicated UTI (*Clin Infect Dis 2011;52:e103*)	*Outpatient, mild-moderate illness:* ◦ FQ *Inpatient, severe illness:* ◦ FQ ◦ Aminoglycoside ◦ β-lactam/β-lactamase inhibitor[a] ◦ Third- or fourthgeneration cephalosporin[b]	◦ Consider IV until afebrile followed by outpatient oral therapy in stable patients to complete 10-14 d. ◦ Can consider shortening if complicating factor is resolved (i.e., removal of stone). ◦ Do not use FQ in pregnancy.
Recurrent cystitis (*JAMA 2014; 311(8):844*; *Clin Infect Dis 2014;58:147*)	*Postcoital prophylaxis:* TMP-SMX SS × 1 or ciprofloxacin 250 mg × 1 or nitrofurantoin 100 mg × 1 *Continuous prophylaxis:* TMP-SMX 0.5 SS qday or every other day × 6 months or nitrofurantoin 50-100 mg qhs × 6 months *Intermittent self-treatment:* TMP-SMX DS PO bid × 3 d or ciprofloxacin 250 mg PO bid × 3 d	◦ Cranberry juice, topical vaginal estrogen in postmenopausal women, and methenamine hippurate may have a role in preventing recurrent UTI.
Candiduria (*Clin Infect Dis 2004;38:161*)	*Candida albicans:* ◦ Fluconazole 100-200 mg PO qday *Critically ill or nonalbicans species:* ◦ Amphotericin B	◦ Remove catheter if present. ◦ Consider treatment if symptoms with pyuria, hardware, pregnancy, neutropenia, renal allografts, prior to GU surgery, or risk of dissemination.

DS, double strength; FQ, fluoroquinolone; GU, genitourinary; SS, single strength; TMP, trimethoprim; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

[a]β-lactam/β-lactamase inhibitors: ampicillin/sulbactam 1.5-3 g IV q6h, piperacillin/tazobactam 3.75-4.5 g IV q6h.

[b]Third- or fourth-generation cephalosporins include ceftriaxone 1-2 g IV q24h (third-generation) or cefepime 1 g IV q8h (fourth-generation).

TABLE 14-10 Dosing Examples for Urinary Tract Infections

Class	Oral (less severe)	Parenteral (more severe)
Folate inhibitors	○ TMP-SMX DS 160 mg/800 mg PO q12h ○ Trimethoprim 100 mg PO q12h	N/A
Fluoroquinolone	○ Ciprofloxacin 250-500 mg PO q12h ○ Levofloxacin 250-750 mg PO daily	○ Ciprofloxacin 400 mg IV q12h ○ Levofloxacin 250-750 mg IV qday
β-Lactam/β-lactamase inhibitor	○ Amoxicillin-clavulanate 500 mg/125 mg PO bid-tid	○ Ampicillin-sulbactam 1.5-3 g IV q6h ○ Piperacillin-tazobactam 3.375-4.5 g IV q6h
Cephalosporins	○ Cephalexin 200-500 mg PO qid ○ Cefpodoxime-proxetil 100 mg PO bid	○ Cefazolin 1 g IV q8h ○ Ceftriaxone 1 g IV qday ○ Cefepime 1 g IV q8h
Carbapenems	N/A	○ Ertapenem 1 g IV q8h ○ Imipenem 500 mg IV q6h ○ Meropenem 1 g IV q8h
Aminoglycoside	N/A	○ Gentamicin 5 mg/kg qday
Fosfomycin[a]	○ Fosfomycin 3 g PO once	N/A
Nitrofurantoin[a]	○ Nitrofurantoin 100 mg PO bid	N/A

DS, double strength; N/A, not applicable; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Uncomplicated cystitis.

- Prophylaxis may be considered for patients with frequent reinfection using continuous, postcoital, or self-initiated antibiotics. Cranberry pills and estrogen therapy may also have a role in prevention (*Clin Infect Dis 2014;58:147-60*).
- Dysuria without pyuria in sexually active patients warrants consideration of sexually transmitted infection.

Consider **empiric treatment** for *C. trachomatis* and *U. urealyticum* with doxycycline 100 mg PO bid for 7 days or azithromycin 1 g PO in a single dose.

Genitourinary Infections in Men

CYSTITIS

Cystitis is uncommon in young men. Risk factors include urologic abnormality, anal intercourse, and lack of circumcision. Pyuria may be present due to sexually transmitted infections. Urologic studies are appropriate when no underlying risk factor is identified, when treatment fails, in the event of recurrent infections, or when pyelonephritis occurs.

PROSTATITIS

- **Acute prostatitis** is often a severe systemic illness characterized by fever, chills, dysuria, and a boggy, tender prostate on examination. Diagnosis is usually obvious by physical exam and urine Gram stain and culture. Prostatic massage is not necessary or recommended to diagnose acute prostatitis. Enteric gram-negative organisms are the usual causative organisms.
- **Chronic prostatitis** can manifest vaguely as low back pain; perineal, testicular, or penile pain; dysuria; ejaculatory pain; recurrent UTIs with the same organism; or hematospermia. Physical exam is usually unrevealing. Prostatitis is frequently abacterial; diagnosis requires identification of organisms by quantitative urine cultures before and after prostatic massage (*Tech Urol 1997;3:38*). Causative organisms are the same as for acute prostatitis. Transrectal ultrasound is only helpful if abscess is suspected.

Treatment

- **Acute bacterial prostatitis** should be treated with a 2- to 4-week course of either ciprofloxacin 500 mg PO bid or TMP-SMX 160 mg/800 mg (double-strength) PO bid.
- Culture-positive **chronic bacterial prostatitis** should receive prolonged therapy (for at least 6 weeks with a fluoroquinolone or 3 months with TMP-SMX).

EPIDIDYMITIS

Epididymitis presents as a unilateral scrotal ache with swollen and tender epididymis on exam. Causative organisms are usually *N. gonorrhoeae* or *C. trachomatis* in sexually active young men and gram-negative enteric organisms in older men. Diagnosis and therapy should be directed according to this epidemiology, with ceftriaxone and doxycycline in young men and TMP-SMX or ciprofloxacin in men older than 35 years.

Catheter-Associated Urinary Tract Infection

- Pyuria and bacteriuria are inevitable in patients with chronic indwelling catheters and should not be treated in absence of symptoms (unless there are complicating factors, as mentioned previously). Aseptic technique during insertion of a catheter is of utmost importance for prevention as well as prompt removal of the catheter when no longer needed.

- Symptomatic catheter-associated UTIs should be managed with removal or exchange of the catheter, collection of blood and urine cultures, and treatment with 7-10 days of antibiotic therapy (*Clin Infect Dis 2010;50:625*).

- Candiduria should be initially treated with catheter removal and should not be treated unless the patient is immunocompromised and at high risk for candidemia.

Pyelonephritis

DIAGNOSIS

Clinical Presentation

Patients present with fever, flank pain, and lower UTI symptoms due to ascending infection from the lower urinary tract.

Diagnostic Testing

- Urine specimens characteristically demonstrate significant bacteriuria, pyuria, red blood cells (RBCs), and occasional leukocyte casts.
- Diagnosis should include urine culture in all patients. Blood cultures should be obtained in those who are hospitalized because bacteremia may be present in 15-20% of cases. The causative agents are typically Enterobacteriaceae such as *E. coli* or *Proteus* spp. No further tests are usually needed for initial workup, but the presence of other organisms may suggest an anatomic abnormality or immune compromise.

TREATMENT

- See Tables 14-9 and 14-10 for details.
- Patients with **mild to moderate illness** who are able to take oral medication can typically be treated in the outpatient setting. Patients with more **severe illness** and pregnant patients should be treated initially with IV therapy. Nausea and vomiting may necessitate IV antibiotics until the patient can tolerate PO antibiotics.

SPECIAL CONSIDERATIONS

Evaluation for anatomic abnormalities should be done for patients who do not respond to initial empiric treatment within 48 hours. Ultrasonography, CT scan, or IV pyelogram may show presence of a renal abscess or renal calculi, which may require more invasive management for source control.

SYSTEMIC MYCOSES AND ATYPICALS

- Clinical presentations are protean and not pathogen specific. The systemic mycoses should be considered in normal hosts with unexplained chronic pulmonary pathology, chronic meningitis, lytic bone lesions, chronic skin lesions, FUO, or cytopenias. In immunocompromised patients, the development of new pulmonary, cutaneous, funduscopic, or head and neck signs and symptoms or persistent unexplained fever should prompt consideration of these pathogens
- The mycoses can often be identified by taking into account epidemiologic clues (many are geographically restricted), site of infection, inflammatory response, and microscopic fungal appearance. These infections can be complex and difficult to treat, and infectious disease consultation is recommended. Antifungal agents have variable doses depending on severity of infection and may vary based on renal and hepatic function. There are

significant drug-drug interactions between azole antifungals and many medications including antirejection drugs. Loading doses of azole antifungals may be recommended in certain circumstances. Because treatment may be prolonged for weeks to months, it is recommended to check therapeutic levels of several antifungals to minimize toxicity. Levels may be checked for flucytosine, itraconazole, posaconazole, and voriconazole. For details on treatment of fungal pathogens, *Nocardia*, and *Actinomyces*, see Table 14-11.

Candidiasis

GENERAL PRINCIPLES

Candida species are the most common cause of invasive fungal infections in humans. Infections ranging from uncomplicated mucosal disease to life-threatening invasive disease affecting any organ can occur (*Clin Infect Dis 2009;48:503*). Infections are often associated with concurrent antibiotic use, contraceptive use, immunosuppressant and cytotoxic therapy, and indwelling foreign bodies. Mucocutaneous disease may resolve after elimination of the causative condition (e.g., antibiotic therapy) or may persist and progress in the setting of immunosuppressive conditions. Serious complications, such as candidemia leading to skin lesions, ocular disease, endocarditis, and osteomyelitis, can occur.

DIAGNOSIS

Diagnosis of **mucocutaneous candidiasis** is usually based on clinical findings but can be confirmed by a potassium hydroxide preparation of exudates. Cultures can be obtained in refractory cases to exclude the presence of non-*Candida albicans* species. **Invasive candidiasis** is diagnosed by positive cultures of blood or tissue.

TREATMENT

- See Table 14-11.
- Also see the Catheter-Related Bloodstream Infections section under Health Care-Associated Infections.

Cryptococcosis

GENERAL PRINCIPLES

Cryptococcus neoformans is a ubiquitous yeast associated with soil and pigeon excrement. Disease is principally meningeal (headache and mental status changes) and pulmonary (ranging from asymptomatic nodular disease to fulminant respiratory failure). Skin lesions can also be seen. Significant infections are usually opportunistic.

DIAGNOSIS

Diagnosis requires detection of encapsulated yeast in tissue or body fluids (India ink stain) with confirmation by culture. The latex agglutination test for cryptococcal antigen in serum or CSF is helpful, and a positive serum antigen titer is highly suggestive of disseminated disease. Lumbar puncture is necessary in persons with systemic disease to exclude coexistent CNS involvement. Always measure opening pressure, because elevated opening pressure (>25 cm H_2O) has poor prognostic implications and must be managed, usually with serial lumbar punctures or with a lumbar drain.

TABLE 14-11 Treatment of Fungal Infections, *Nocardia*, and *Actinomyces*

Pathogen and Therapy	Additional Comments
Candida spp. (*Clin Infect Dis 2009;48:503*) *Mucosal* • Thrush: Clotrimazole troche or nystatin suspension × 7-14 d • Esophageal: Fluc 14-21 d • Vaginal: Topical azole × 3-7 d or Fluc 150 mg PO once • Frequent recurrence: Fluc 150 mg/wk × 6 mo *Invasive* • *Candida albicans* candidemia: Fluc × 14 d • Nonalbicans species: Echinocandin or Ampho × 14 d • Osteomyelitis: Fluc × 6-12 mo	• *Prophylaxis*: May be beneficial in select patients with solid organ transplant, chemotherapy-induced neutropenia, or stem cell transplants. • *Candidemia*: Treat from first negative blood culture. Perform ophthalmologic exam to rule out endophthalmitis. Catheters must be removed. • *Complicated infection*: Duration may be extended if metastatic foci present or continued neutropenia.
Cryptococcus neoformans (*Clin Infect Dis 2010;50:291*) *Nonmeningeal or Mild-Moderate Disease* • Immunocompetent/immunosuppressed: Fluc 400 mg PO/IV q24h × 6-12 mo *Meningitis or Moderate-Severe Disease* • Immunosuppressed: Ampho + 5-FC × 2 wk, then Fluc 400 mg PO q24h × 8 wk, then Fluc 200 mg q24h × 6-12 mo • Immunocompetent: Same as immunosuppressed except induction for 4-6 wk	• Perform LP to rule out meningitis. • HIV: Initiate HAART 2-10 wk after starting Tx. Continue Fluc 200 mg PO qd for at least 12 mo and until CD4 count ≥100 for 6 mo. • Check baseline CSF opening pressure. If ≥25 cm of CSF, reduce by 50% (up to 30 mL). Perform daily serial LPs if pressure elevated.
Histoplasma capsulatum (*Clin Infect Dis 2007;45:807*) *Pulmonary* • Acute, mild-moderate: Observation. May Tx if symptoms >1 mo • Acute, moderately severe to severe: Ampho for 1-2 wk or until clinically improved, then Itra for 12 wk • Chronic cavitary: Itra for 12-24 mo *Progressive disseminated histoplasmosis (PDH)* • Mild-moderate: Itra for 12 mo • Moderately severe to severe: Ampho for 1-2 wk or until clinically improved, then Itra for 12 mo	• Steroids may be considered for respiratory distress, hypoxemia, or severe mediastinal lymphadenitis. • HIV: Itra 200 mg PO qday ppx in areas of high endemicity if CD4 count <150. • PDH: Check urine antigen levels during/after Tx to monitor for relapse.
Blastomyces dermatitidis (Clin Infect Dis 2008;46:1801) *Pulmonary or Disseminated Extrapulmonary*	• For CNS disease, Itra or Vori can be used instead of Fluc.

- Mild to moderate: Itra for 6-12 mo
- Moderately severe to severe: Ampho for 1-2 wk or until clinically improved, then Itra for 6-12 mo
- Immunosuppressed: Treat as severe disease for 12 mo

Suppression: Itra lifelong if continued immunosuppression *CNS:* Ampho for 4-6 wk then Fluc 800 mg PO q24h for 12 mo

Coccidioides immitis (*Clin Infect Dis 2005;41:1217*)
Pulmonary

- Uncomplicated pneumonia, asymptomatic pulmonary nodule: May not need Tx. If Tx, Fluc 400 mg PO q24h for 3-6 mo
- Diffuse pneumonia: Ampho for 1-2 wk or until clinically improved, then Fluc 400 mg PO qday for 12 mo

Disseminated/Extrapulmonary

- Nonmeningeal: Fluc 400-800 mg IV/PO q24h
- Meningeal: Fluc +/- intrathecal Ampho; continue Fluc lifelong

- Can follow serum CF titers during/after treatment. Rising titers suggest recurrence.
- Consider surgery if pulmonary cavitary disease >2 yr or rupture.
- HIV: Continue Tx until CD4 count ≥250, lifelong if meningitis.
- Hydrocephalus may require shunt for decompression.

Sporothrix (*Clin Infect Dis 2007;45:1255*)
Lymphocutaneous/Cutaneous: Itra × 3-6 mo *Severe Systemic*

- Pulmonary/disseminated/osteoarticular: Ampho for 1-2 wk or until clinically improved, then Itra for 12 mo
- Meningeal: Ampho for 4-6 wk then Itra for 12 mo

- If no initial response, can use higher doses of Itra or add topical saturated solution of potassium iodide.

Aspergillus (*Clin Infect Dis 2008;46:327*; *N Engl J Med 2009;360:1870*)
Pulmonary Aspergilloma: Surgical resection or arterial embolization in cases of severe hemoptysis
Invasive Pulmonary Aspergillosis: Vori for at least 6-12 wk until lesions resolve and immunosuppression resolves
Invasive Sinonasal Aspergillosis: Ampho or Vori. Surgical debridement may be adjunctive for cure
Allergic Bronchopulmonary Aspergillosis: Itra or intermittent steroids may decrease exacerbations.
Prophylaxis: Posa in high-risk patients may be considered

- Ampho to cover mucormycosis as initial therapy for sinus disease pending confirmation of diagnosis.
- If immunosuppression recurs, may need to restart ppx or Tx.

Mucormycosis (*Clin Infect Dis 2012;54:1629*)
Cutaneous, Rhinocerebral: Aggressive surgical resection and debridement with clean margins followed by Ampho at upper dose range until improvement

- Mortality is very high in immunosuppressed patients with disseminated disease.
- Echinocandins may be beneficial when

Pulmonary: Ampho	added to Ampho for initial induction therapy.
Nocardia (*Clin Infect Dis 2007;44:1307*; *Clin Infect Dis 1996;6:891*) *Cutaneous:* TMP-SMX *Severe Infection (including CNS):* Induction regimen typically includes two or three drugs including TMP-SMX or imipenem for 4-6 wk with stepdown to oral therapy for 6-12 mo *Suppression/prophylaxis:* TMP-SMX	• TMP-SMX is drug of choice but typically combined with other agents depending on disease manifestation. • Await susceptibility results to narrow treatment.
Actinomyces Penicillin G 18-24 million units IV per day × 4-6 wk then penicillin VK 1 g PO tid × 6-12 mo	• Surgery or drainage may be helpful in some cases. • Clindamycin or doxycycline can be used if penicillin allergy

5-FC, flucytosine; Ampho, amphotericin; CF, complement fixation; CNS, central nervous system; CSF, cerebrospinal fluid; Fluc, fluconazole; HAART, highly active antiretroviral therapy; Itra, Itraconazole; LP, lumbar puncture; Posa, posaconazole; ppx, prophylaxis; TMP-SMX, trimethoprim-sulfamethoxazole; Tx, treatment; Vori, voriconazole.

P.455
P.456
P.457

TREATMENT

Treatment is dependent on the patient's immune function and site of infection (see Table 14-11).
Management of elevated intracranial pressure is critical.

Histoplasmosis

GENERAL PRINCIPLES

Histoplasma capsulatum is more prevalent in the Ohio and Mississippi River Valleys of the United States and in Latin America and grows in soil contaminated by bat or bird droppings.

DIAGNOSIS

- Clinical manifestations are extremely varied, including acute flu-like or chronic granulomatous pulmonary disease or fulminant multiorgan failure in the immunocompromised patient.
- Diagnosis is based on culture or histopathology, antigen assay (urine, blood, or CSF), or complement fixation (CF) assay (≥1:16 or fourfold rise). Urine antigen assay is good for detecting disseminated disease and is helpful in following response to therapy.

TREATMENT

See Table 14-11.

Blastomycosis

GENERAL PRINCIPLES

Blastomyces dermatitidis is endemic in the upper midwestern, south central, and southeastern United States. This organism commonly disseminates, even in immunocompetent patients, and tends to affect the lungs, skin, bone, and GU tract. Aggressive pulmonary and CNS disease can occur in both immunocompromised and immunocompetent patients.

DIAGNOSIS

Diagnosis is based on culture, histopathology, or antigen assay. Serologic studies cross-react with tests for *Histoplasma* and *Cryptococcus* species and are unreliable for diagnosis but can be used to assess early response to therapy when positive.

TREATMENT

See Table 14-11.

Coccidioidomycosis

GENERAL PRINCIPLES

- *Coccidioides immitis* is endemic to the southwestern United States and Central America.
- Disease is usually a self-limited pulmonary syndrome. Less common manifestations are chronic pulmonary illness and disseminated disease, which can affect the meninges, bones, joints, and skin. Risk factors for development of severe or disseminated disease include immunocompromising conditions, African American or Filipino ethnicity, diabetes, and pregnancy.

DIAGNOSIS

- Diagnosis requires culture, histopathology, or positive CF serology.
- Serum CF titer of 1:16 or greater suggests extrathoracic dissemination.
- **Lumbar puncture** should be performed for culture and CF to rule out CNS involvement in persons with severe, rapidly progressive, or disseminated disease.
- **Skin testing** should only be used for epidemiologic purposes to evaluate exposure.

TREATMENT

See Table 14-11.

Aspergillosis

GENERAL PRINCIPLES

- *Aspergillus* species are ubiquitous environmental fungi that cause a broad spectrum of disease, usually affecting the respiratory system and sinuses.
- **Pulmonary aspergilloma.** Pulmonary aspergilloma occurs in the setting of preexisting bullous lung disease and can be easily recognized by characteristic radiographic presentation and *Aspergillus* serology.
- **Invasive aspergillosis (IA).** IA is a serious condition associated with vascular invasion, thrombosis, and ischemic infarction of involved tissues and progressive disease after hematogenous dissemination. IA is usually seen in severely immunocompromised patients, and clinical features vary by predisposing host characteristics.
- **Allergic bronchopulmonary aspergillosis (ABPA).** ABPA is a chronic relapsing and remitting respiratory syndrome associated with colonization with *Aspergillus*.

DIAGNOSIS

- Diagnosis can be very difficult given the varied manifestations of IA, and a high index of suspicion should be applied to patients with prolonged severe immunosuppression.
- Radiographic findings can be highly suggestive, if not diagnostic, of pulmonary IA, particularly the halo-crescent sign on CT in immunosuppressed patients.
- The diagnosis can be confirmed with characteristic histologic evidence of involved tissue. Fungal culture has a low yield.
- The galactomannan assay can support a diagnosis of IA and can be followed prospectively in at-risk patients (*Clin Infect Dis 2004;39:797*). Sensitivity is higher when performed on respiratory secretions as compared to serum (*Am J Respir Crit Care Med 2008;177:27*).

TREATMENT

See Table 14-11.

Sporotrichosis

GENERAL PRINCIPLES

Sporothrix schenckii is a globally endemic fungus that causes disease following traumatic inoculation with soil or plant material; most cases are vocational. Infection can also be associated with spread from infected cats or other digging animals (*Clin Infect Dis 2007;45:1255*).

DIAGNOSIS

Clinical Presentation

Lymphocutaneous disease is the usual manifestation with localization to skin and soft tissues. Pulmonary and disseminated forms of the infection are rarely seen from inhalation of the fungus.

Diagnostic Testing

Diagnosis requires culture or histopathologic demonstration of yeast in tissue or body fluids.

TREATMENT

See Table 14-11.

Mucormycosis

GENERAL PRINCIPLES

The Zygomycetes are a class of fungi that includes Mucorales, Mortierellales, and Entomophthorales. The Mucorales order contains the genera most commonly involved in human disease. These include *Mucor* spp., *Rhizopus* spp., and *Cunninghamella* spp. Disease manifestations may vary from head and neck, pulmonary, GI, and cutaneous disease to disseminated infection with angioinvasion and multiorgan infarction. Risk factors include immunosuppression, iron overload, high-dose glucocorticoid therapy, and diabetes with or without ketoacidosis.

DIAGNOSIS

- Clinical manifestations vary depending on which organ is affected. Invasive mucormycosis is devastating with rapid development of tissue necrosis from vascular invasion and thrombosis (*Lancet Infect Dis 2011;11:301*).
- Diagnosis requires tissue culture and silver stain with care to avoid disrupting fungal architecture.
- Head CT or MRI is helpful in head and neck disease to identify involved structures.
- Sinus endoscopy should be performed if there is concern for invasive fungal sinusitis.

TREATMENT

See Table 14-11.

Nocardiosis

GENERAL PRINCIPLES

Nocardia is a ubiquitous group of aerobic gram-positive branching filamentous bacteria that causes severe local and disseminated disease in the setting of impaired cell-mediated immunity (*Clin Infect Dis 2007;44:1307*). Typical infection tends to be pulmonary infiltrate, abscess, or empyema, but dissemination is common and tends to favor CNS infection, causing abscess.

DIAGNOSIS

- Clinical presentation can be acute, subacute, or chronic pneumonia.
- Chest imaging can reveal a variety of findings such as infiltrates, nodules, pleural effusions, or cavities (*Infection 2010;38:89*).
- Diagnosis requires sputum or tissue Gram stain and culture (including AFB), often needing multiple samples because yields are low.

- Look for CNS disease with brain MRI in patients with pulmonary disease.

TREATMENT

See Table 14-11.

Actinomycosis

GENERAL PRINCIPLES

Actinomyces is a microaerophilic gram-positive bacillus that usually causes oropharyngeal, pulmonary, and GI disease. Classic infections are chronic, indurated soft tissue lesions associated with draining fistulae that pass through tissue planes. Unlike *Nocardia*, infection is not limited to immunocompromised hosts.

DIAGNOSIS

Clinical presentation varies depending on what site is affected. Orocervicofacial infection is the most common form. Rare sites include the CNS and bones. Diagnosis is made by histopathology or observation of "sulfur granules" in drainage (*BMJ 2011; 343:d6099*).

TREATMENT

See Table 14-11.

Atypical (Nontuberculous) Mycobacteria

- NTM are ubiquitous environmental organisms that cause a spectrum of disease involving the lungs, skin, soft tissue, and lymph nodes. Susceptibility testing and infectious disease consultation are recommended to guide treatment.
- ***Mycobacterium avium***, ***Mycobacterium kansasii*** (see Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome).
- ***Mycobacterium fortuitum***, ***Mycobacterium marinum***, ***Mycobacterium ulcerans***, ***Mycobacterium haemophilum***, and ***Mycobacterium scrofulaceum*** cause a spectrum of chronic progressive disease of soft tissue and bone.
- ***Mycobacterium leprae*** is typically classified separately from the other NTM because of its potential for human-to-human transmission.

TICK-BORNE INFECTIONS

Tick-borne infections (TBIs) are common during the summer months in many areas of the United States; prevalence of specific diseases depends on the local population of vector ticks and animal reservoirs. Coinfection with multiple TBIs can occur and should be considered

when patients present with overlapping syndromes. Risk should be assessed by outdoor activity in endemic regions rather than the report of a tick bite, which often goes unnoticed.

Lyme Borreliosis (Lyme Disease)

GENERAL PRINCIPLES

Lyme borreliosis is the most common vector-borne disease in the United States and is a systemic illness of variable severity caused by the spirochete *Borrelia burgdorferi*. It is seen in endemic regions, including northeastern coastal states, the upper Midwest, and northern California. Prophylactic doxycycline 200 mg PO (single dose) may reduce the risk of Lyme disease in endemic areas following a bite by a nymph-stage deer tick (*N Engl J Med 2001;345:79*).

DIAGNOSIS

Clinical Presentation

Lyme disease has three distinct clinical stages, which start after an incubation period of 7-10 days:

- Stage 1 (early local disease) is characterized by erythema migrans, a slowly expanding macular rash >5 cm in diameter, often with central clearing, and by mild constitutional symptoms.
- Stage 2 (early disseminated disease) occurs within several weeks to months and includes multiple erythema migrans lesions, neurologic symptoms (e.g., seventh cranial nerve palsy, meningoencephalitis), cardiac symptoms (atrioventricular block, myopericarditis), and asymmetric oligoarticular arthritis.
- Stage 3 (late disease) occurs after months to years and includes chronic dermatitis, neurologic disease, and asymmetric monoarticular or oligoarticular arthritis. Chronic fatigue is not seen more frequently in patients with Lyme borreliosis than in control subjects.

Diagnostic Testing

Diagnosis rests on clinical suspicion in the appropriate setting but can be supported by two-tiered serologic testing (screening enzyme-linked immunosorbent assay [ELISA] followed by Western blot) with acute and convalescent serologies.

TREATMENT

- Treatment depends on stage and severity of disease (*Clin Infect Dis 2006;43:1089*). Oral therapy (doxycycline 100 mg PO bid, amoxicillin 500 mg PO tid, or cefuroxime axetil 500 mg PO bid for 10-21 days) is used for early localized or disseminated disease without neurologic or cardiac involvement. The same agents, given for 28 days, are recommended for late Lyme disease. Doxycycline has the added benefit of covering potential coinfection with ehrlichiosis.
- Parenteral therapy (e.g., ceftriaxone 2 g IV daily, cefotaxime 2 g IV q8h, penicillin G 3-4 million units IV q4h) for 14-28 days should be used for severe neurologic or cardiac disease, regardless of stage.

Rocky Mountain Spotted Fever

GENERAL PRINCIPLES

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii* after a tick bite. Endemic regions are east of the Rocky Mountains.

DIAGNOSIS

Clinical signs include fever, headache, and myalgias, followed 1-5 days later by a petechial rash starting on the distal extremities that may be faint and difficult to detect. Initial diagnosis leading to presumptive

treatment should be based on the clinical syndrome, but skin biopsy and acute and convalescent serologies can provide additional support.

TREATMENT

Antibiotic treatment of choice is doxycycline 100 mg q12h IV or PO for 7 days or until afebrile for 2 days. Chloramphenicol is an alternative (*Lancet Infect Dis 2007;7:724*).

OUTCOME/PROGNOSIS

Death can occur when treatment is delayed.

Ehrlichiosis and Anaplasmosis

GENERAL PRINCIPLES

Ehrlichiosis and anaplasmosis are systemic TBIs caused by intracellular pathogens of the closely related *Ehrlichia* and *Anaplasma* genera. Two similar syndromes are recognized:

- **Human monocytic ehrlichiosis** (HME), caused by *Ehrlichia chaffeensis*, is endemic in south and south central United States.
- **Human granulocytic anaplasmosis** (HGA, formerly HGE), caused by *Anaplasma phagocytophilum*, is found in the same regions as Lyme borreliosis due to a shared tick vector.

DIAGNOSIS

Clinical Presentation

Clinical onset of illness usually occurs 1 week after tick exposure with fever, headache, and myalgias. Rash is only occasionally seen. Severe disease can result in respiratory failure, renal insufficiency, and neurologic decompensation. Leukopenia, thrombocytopenia, and elevated liver transaminases are the hallmarks of moderately severe disease.

Diagnostic Testing

- Diagnosis can be made by identification of morulae in circulating monocytes (HME) or granulocytes (HGA), which is uncommon but diagnostic in the appropriate clinical setting. Confirmation is by acute and convalescent serologies.
- PCR of blood or other fluids is rapidly becoming the test of choice (*Clin Infect Dis 2007;45:S45*).

TREATMENT

Prompt initiation of treatment with antimicrobials is likely to improve prognosis in severe disease. The drugs of choice are doxycycline 100 mg PO or IV q12h or tetracycline 25 mg/kg/d PO divided qid for 7-14 days. Rifampin dosed at 300 mg PO q12h for 7-10 days is an alternative treatment and is recommended only for patients with contraindications to doxycycline or tetracycline therapy (*Clin Infect Dis 2007;45:S45*).

Tularemia

GENERAL PRINCIPLES

Tularemia is caused by the gram-negative bacteria *Francisella tularensis* and is endemic to south central United States. It is transmitted by tick bite, by exposure to infected animals (particularly rabbits), or by exposure to infectious aerosol. *F. tularensis* is one of the most infectious pathogenic bacteria known. Inoculation or inhalation of as little as 10 organisms is adequate to cause disease. It is considered to be a dangerous potential biologic weapon due to its extreme infectivity, ease of dissemination, and capacity to cause illness and subsequent death (*JAMA 2001;285:2763*).

DIAGNOSIS

Clinical Presentation

Fever and malaise occur 2-5 days after exposure. The clinical presentation depends on the inoculation site and route of exposure. Painful regional lymphadenitis with (ulceroglandular) or without (glandular) a skin ulcer is the most common finding. Oculoglandular disease can occur. Systemic (typhoidal) and pneumonic diseases are more likely to be severe, with high mortality if not treated promptly.

Diagnostic Testing

Diagnosis can be confirmed by culture of blood, sputum, or pleural fluid but can lack sensitivity. The microbiology laboratory must be alerted promptly of culture specimens from patients with suspected tularemia to allow for use of advanced biohazard precautions. Acute and convalescent serologic studies provide a retrospective diagnosis.

TREATMENT

Treatment of choice is streptomycin 1 g IM q12h for 10 days; however, gentamicin 5 mg/kg IV divided q8h is nearly as effective and easier to administer. Doxycycline 100 mg PO/IV q12h for 14-21 days is an oral alternative but is more likely to result in relapse. Ciprofloxacin 500-750 mg PO bid for 14-21 days may also be effective (*JAMA 2001;285:2763*).

Babesiosis

GENERAL PRINCIPLES

Babesiosis is a malaria-like illness and is caused by the intraerythrocytic parasite *Babesia microti* after a tick bite. It is endemic in the same regions as Lyme borreliosis, with which patients may be co-infected.

DIAGNOSIS

- Clinical disease ranges from subclinical to severe, with fever, chills, myalgias, and headache. Hemolytic anemia may also be present.
- Diagnosis is made by visualization of the parasite in erythrocytes on thin blood smears. Serology and PCR may be available in certain laboratories.

TREATMENT

- Treatment may be necessary for moderate or severe disease, especially in asplenic patients.

- Atovaquone 750 mg PO bid plus azithromycin 500 mg PO on day 1, then 250 mg daily for 7-10 days, is the first choice for immunocompetent hosts. Clindamycin 600 mg IV q8h plus quinine 650 mg PO q8h for 7-10 days should be considered for lifethreatening disease. Exchange transfusions may also be needed.
- Longer duration of therapy may be necessary in patients with persistent symptoms or until parasitemia has cleared (*Clin Infect Dis 2006;43:1089*).

MOSQUITO-BORNE INFECTIONS

Arboviral Meningoencephalitis

GENERAL PRINCIPLES

Arboviral meningoencephalitis can be caused by multiple viral agents, which vary by geographic area (e.g., WNV, Eastern and Western equine encephalitis, La Crosse encephalitis, St. Louis encephalitis). In addition to mosquitoes, transmission can occur from blood transfusion, organ transplant, and breast feeding. Infections usually occur in the summer months, and most are subclinical.

DIAGNOSIS

Clinical Presentation

Symptomatic cases of WNV infection range from a mild febrile illness to aseptic meningitis, fulminant encephalitis, or a poliomyelitis-like presentation with flaccid paralysis. Long-term neurologic sequelae are common with severe disease.

Diagnostic Testing

Diagnosis is usually clinical or by acute and convalescent serologic studies. Specific IgM antibody detection in CSF is diagnostic for acute WNV.

TREATMENT

Treatment for arboviral meningoencephalitides is mostly supportive. Interferon α-2b may reduce neurologic sequelae in cases of St. Louis encephalitis (*Clin Infect Dis 2008; 47:303*).

Malaria

GENERAL PRINCIPLES

- Malaria is a systemic parasitic disease that is endemic to most of the tropical and subtropical world. Several species of the parasite exist.
- Travel advice and appropriate chemoprophylaxis regimens are available from the CDC at *http://www.cdc.gov/travel/*.

DIAGNOSIS

Clinical Presentation

The onset of illness may occur within weeks or up to 6-12 months after infection with fever, headache, myalgias, and fatigue. Malaria is sometimes characterized by triphasic, periodic (every 48 hours for

Plasmodium ovale and *Plasmodium vivax*) paroxysms of rigors followed by high fever with headache, cough, and nausea, then culminating in profuse sweating. *Plasmodium falciparum* malaria, the most severe form, is a potential medical emergency. Complicated, or severe, falciparum malaria is diagnosed in the setting of hyperparasitemia (>5%), cerebral malaria, hypoglycemia, lactic acidosis, renal failure, acute respiratory distress syndrome, or coagulopathy.

Diagnostic Testing

- Malaria should be suspected and excluded in all persons with fever who have traveled to an endemic area within the previous year.
- Diagnosis is made by visualization of parasites on Giemsa-stained thick blood smears. Smears should be obtained during febrile episodes to maximize parasite yield.
- Rapid diagnostic tests targeting antigens common to all *Plasmodium* species as well those specific to *P. falciparum* are available but should be confirmed with microscopy.

TREATMENT

- Treatment is dependent on the type of malaria, severity, and risk of chloroquine resistance where the infection was acquired. Updated information on geographic locations of chloroquine resistance and recommended treatment regimens from the CDC can be found at *http://www.cdc.gov/travel/* and *http://www.cdc.gov/malaria*.
- **Uncomplicated malaria (*P. falciparum, P. ovale, P. vivax, Plasmodium malariae, and Plasmodium knowlesi*)** from **chloroquine-sensitive areas:** Chloroquine 600 mg base PO single dose followed by 300 mg base PO at 6 hours, 24 hours, and 48 hours.
- **Uncomplicated *P. falciparum*** from **chloroquine-resistant areas** and ***P. vivax* from Australia, Indonesia, or South America:** Quinine sulfate 542 mg base PO tid plus doxycycline 100 mg PO bid for 7 days. Alternatively, can use atovaquone-proguanil (250 mg atovaquone/100 mg proguanil) four tablets daily for 3 days.
- ***P. ovale* or *P. vivax*:** Add primaquine phosphate 30 mg base PO daily for 14 days to above regimens to prevent relapse. Rule out glucose-6-phosphate dehydrogenase deficiency before initiating primaquine.
- **Complicated severe malaria (most commonly *P. falciparum*):** Quinidine gluconate 6.25 mg base/kg loading dose IV over 1-2 hours followed by 0.0125 base/kg/min as a continuous infusion plus doxycycline 100 mg PO/IV every 12 hours for at least 24 hours or until parasitemia is <1%, at which time complete treatment with oral quinine sulfate and doxycycline as previously described. IV artesunate is available in the United States on emergency request through the CDC Malaria Branch (*http://www.cdc.gov/malaria/*). Exchange transfusion may also be considered when *P. falciparum* parasitemia exceeds 15%, although the benefit has not been proven.

ZOONOSES

Avian and Swine Influenza (see the Emerging Infections and Bioterrorism section)

Anthrax (see the Emerging Infections and Bioterrorism section)

Plague (see the Emerging Infections and Bioterrorism section)

Cat-Scratch Disease (Bartonellosis)

GENERAL PRINCIPLES

Bartonellosis is caused by the bacterium *B. henselae*. It is usually self-limiting.

DIAGNOSIS

Clinical presentation usually consists of a few papulopustular lesions appearing 3-30 days after a cat bite or scratch, followed by regional lymphadenitis (usually cervical or axillary) and mild constitutional symptoms. Atypical presentations include oculoglandular disease, encephalopathy, arthritis, FUO, and culture-negative endocarditis. Diagnosis is made by exclusion of other causes of lymphadenitis and by detection of antibodies to *B. henselae* or PCR of infected tissue, skin, or pus.

TREATMENT

Localized disease spontaneously resolves in 2-4 months without treatment. If antimicrobial therapy is prescribed, azithromycin 500 mg PO single dose followed by 250 mg PO for 4 more days is recommended. Needle aspiration of suppurative lymph nodes may provide symptomatic relief. Culture-negative endocarditis has been discussed in the Cardiovascular Infections section (*Clin Infect Dis 2005;41:1373*).

Leptospirosis

GENERAL PRINCIPLES

- Leptospirosis is an acute febrile illness with varying presentations caused by *Leptospira interrogans*, a ubiquitous pathogen of wild and domestic mammals, reptiles, and amphibians. Symptom onset is 5-14 days after contact with infected animals or water contaminated with their urine.
- **Anicteric leptospirosis**, which accounts for most cases, is a biphasic illness that starts with influenza-like symptoms and proceeds to conjunctival suffusion and aseptic meningitis after a brief defervescent period.
- A minority of cases progress directly to **Weil disease (icteric leptospirosis)**, with multiorgan failure manifested by severe jaundice, uremia, and hemorrhagic pneumonitis.

DIAGNOSIS

Diagnosis is confirmed by specific cultures of urine or blood, PCR, or paired serologic studies.

TREATMENT

Therapy for anicteric disease, which can shorten the duration of illness, is doxycycline 100 mg PO bid or amoxicillin 500 mg PO q6h for 7 days. Penicillin G 1.5 million units IV q4-6h or a third-generation cephalosporin is used for treatment of severe disease, during which a Jarisch-Herxheimer reaction is possible (*Clin Microbiol Rev 2001;14:296*).

Brucellosis

GENERAL PRINCIPLES

Brucellosis is a protean systemic infection caused by members of the *Brucella* genus of gram-negative

coccobacilli. Infection is usually preceded by direct contact with body fluids of livestock animals, by eating unpasteurized dairy foods, or by inhalation of infected aerosolized particles.

DIAGNOSIS

Clinical Presentation

Symptoms are initially nonspecific but usually include constitutional symptoms such as fever and perspiration. Fever can be spiking and accompanied by rigors but can also be relapsing and protracted. Malodorous perspiration is almost pathognomonic. Physical exam may be nonrevealing, although lymphadenopathy, hepatomegaly, or splenomegaly may be present. Complications within every organ system can occur (e.g., diarrhea, arthritis, meningitis, endocarditis, pneumonia, hepatitis).

Diagnostic Testing

Diagnosis is confirmed by isolation of the organism from blood or tissue culture. Serology may also be used, but cross-reactivity may exist with other bacteria.

TREATMENT

Antimicrobial treatment is doxycycline 100 mg PO bid for 6 weeks with streptomycin 15 mg/kg IM for 2-3 weeks. Gentamicin for 5-7 days or rifampin for 6 weeks may be alternatives to streptomycin (*N Engl J Med 2005;352:2325*).

BITE WOUNDS

Animal Bites

GENERAL PRINCIPLES

Management includes copious irrigation, culturing visibly infected wounds, and obtaining imaging to exclude fracture, foreign body, or joint space involvement. Most wounds should not be sutured unless they are on the face and have been thoroughly irrigated. Wound elevation should be encouraged.

TREATMENT

- Antimicrobial therapy is given to treat overt infection and as prophylaxis for high-risk bite wounds based on severity (e.g., moderate to severe), location (e.g., hands, genitalia, near joints), bite source (e.g., cats), immune status (e.g., diabetes mellitus, asplenia, immunosuppression), and type of injury (e.g., puncture, crush injury). Tetanus toxoid should be administered if the patient has been previously vaccinated but has not received a booster in the last 5 years.
- Prophylactic antibiotic therapy with amoxicillin-clavulanate 875 mg/125 mg PO bid for 3-5 days should usually be administered, unless the bite is trivial. Antibiotics are most

effective for patients presenting >8 hours after the injury (*Arch Emerg Med 1989;6:251*; *Lancet Infect Dis 2009;9:439*).

SPECIAL CONSIDERATIONS

- **Dog bites:** Normal oral flora includes *Pasteurella multocida*, streptococci, staphylococci, and

Capnocytophaga canimorsus. Dog bites comprise 80% of animal bites, but only 5% of such bites become infected. For infected dog bite wounds, amoxicillin-clavulanate, or clindamycin plus ciprofloxacin, is effective.

- **Cat bites:** Normal oral flora includes *P. multocida* and *S. aureus*. Because more than 80% of cat bites become infected, prophylaxis with amoxicillin-clavulanate should be routinely provided. Cephalosporins should not be used. Bartonellosis can also develop after a cat bite.
- **Wild animal bites:** The need for rabies vaccination should be determined (see the following text). For most animal bites, amoxicillin-clavulanate is a good choice for prophylaxis and empiric treatment. Monkey bites should be treated with acyclovir because of the risk of *Herpesvirus simiae* (B virus).
- **Rabies**
  - Rabies causes an invariably fatal neurologic disease classically manifesting with hydrophobia, aerophobia, pharyngeal spasm, seizures, and coma.
  - The need for rabies vaccination and immunoglobulin prophylaxis (see Appendix A, Immunizations and Postexposure Therapies) should be determined after any animal bite. Risk of rabies depends on the animal species and geographic location. In the United States, most recent indigenous cases have been associated with bats, whereas dog bites account for the vast majority of human cases in the developing world.
  - Regardless of species, if the animal is rabid or suspected to be rabid, the human diploid vaccine and rabies immunoglobulin should be administered immediately. Bites by domestic animals rarely require prophylaxis unless the condition of the animal is unknown. Public health authorities should be consulted to determine whether prophylaxis is recommended for other types of animal bites.
  - A single case of survival after symptom onset using an aggressive coma-inducing regimen has been reported (*N Engl J Med 2005;352:2508*).

Human Bites

- Human bites, particularly clenched-fist injuries, are prone to infection and other complications. The normal oral flora of humans includes viridans streptococci, staphylococci, *Bacteroides* spp., *Fusobacterium* spp., peptostreptococci, and *Eikenella corrodens*.
- **Prophylaxis** with amoxicillin-clavulanate 875 mg/125 mg PO bid for 5 days is recommended for uninfected wounds.
- Infected wounds may require **parenteral therapy**, such as ampicillin-sulbactam 1.5 g IV q6h, cefoxitin 2 g IV q8h, or ticarcillin-clavulanate 3.1 g IV q6h for 1-2 weeks. Therapy should be extended to 4-6 weeks if osteomyelitis is present.

HEALTH CARE-ASSOCIATED INFECTIONS

Health care-associated infections (HAIs) substantially contribute to morbidity, mortality, and excess health care costs. Efforts to control and prevent the spread of HAIs require an institutional assessment of resources, priorities, and commitment to infection control practices (see Appendix B, Infection Control and Isolation Recommendations).

Catheter-Related Bloodstream Infections

GENERAL PRINCIPLES

- *S. aureus*, *S. epidermidis* (coagulase-negative staphylococci), aerobic gram-negative species, and *Candida* spp. are the most common organisms associated with catheter-related bloodstream infections (CRBSIs) (*Clin Infect Dis 2009;49:1*).
- Subclavian central venous catheters (CVCs) are associated with lower CRBSI rates than internal jugular CVCs, whereas femoral CVCs have the highest rates and should be removed within 72 hours of placement.
- Strategies for decreasing the incidence of CRBSIs include proper hand hygiene, skin antisepsis using an alcohol-based chlorhexidine solution, maximal sterile barrier precautions during insertion, strict adherence to aseptic technique, and removal of nonessential CVCs as soon as possible (*Infect Control Hosp Epidemiol 2014;35:753*). Subcutaneous tunneling and use of antiseptic-impregnated CVCs may further reduce the incidence of CRBSIs. Routine exchange of CVCs over guide wire is not recommended.

DIAGNOSIS

Clinical Presentation

CRBSIs should be suspected in any febrile patient with a CVC. Clinical findings that increase the suspicion of CRBSIs include local inflammation or phlebitis at the CVC insertion site, sepsis, endophthalmitis, lack of another source of bacteremia, and resolution of fever after catheter removal.

Diagnostic Testing

- Diagnosis is established by obtaining two or more blood cultures from both the CVC and a peripheral vein prior to initiation of antibiotics.
- Repeat blood cultures should be obtained after starting antibiotic therapy to demonstrate clearance of bacteremia.
- TEE is recommended to rule out endocarditis if the patient has an implantable cardiac pacemaker or defibrillator, a prosthetic heart valve, persistent bacteremia or fungemia, or persistent fever >3 days after initiation of appropriate antibiotic therapy and catheter removal, or if *S. aureus* is involved and <4 weeks of therapy is being considered.

TREATMENT

- Host factors, including comorbidities, severity of illness, multidrug-resistant colonization, prior infections, and current antimicrobial agents, are important considerations when selecting an antimicrobial regimen. Management guidelines are available from the Infectious Diseases Society of America (*Clin Infect Dis 2009;49:1*).
- **Empiric therapy**
  - Vancomycin 15-20 mg/kg IV q12h is appropriate for empiric therapy because a majority of CRBSIs are caused by staphylococci. The dose should be adjusted to achieve a vancomycin trough between 15-20 µg/mL.
  - Gram-negative bacilli, including *Pseudomonas*, should be covered broadly until species identification and susceptibilities are known. Fourth-generation cephalosporins (e.g., cefepime), carbapenems, or a β-lactam/β-lactamase inhibitor combined with or without an aminoglycoside are potential options.
  - The recommended duration of therapy depends on whether the infection is complicated or uncomplicated, beginning from the date of the first negative blood culture or removal of the infected CVC, whichever came later.

- **Pathogen-specific therapy:** Once the pathogen has been identified, antimicrobial therapy should be narrowed to the most effective regimen.
  - ***S. aureus*: MSSA** CRBSIs should be treated with oxacillin 2 g IV q4h or cefazolin 1-2 g IV q8h. First-line therapy for **MRSA** is vancomycin 15-20 mg/kg IV q12h with a target vancomycin trough between 15-20 µg/mL. Linezolid 600 mg PO or IV q12h or daptomycin 6 mg/kg IV daily are alternatives. Routine use of gentamicin for synergy in *S. aureus* bacteremia is not recommended (*Clin Infect Dis 2009;48:722*). TEE should be considered to evaluate for endocarditis. The recommended duration of therapy is generally 4-6 weeks. A 2-week course is acceptable for uncomplicated MRSA bacteremia, as defined by a negative TEE, negative blood cultures, and defervescence within 72 hours of starting effective therapy, absence of prosthetic material (e.g., pacemaker, valve), and no evidence of metastatic infection (*Clin Infect Dis 2011;52:1*).
  - ***S. epidermidis* (coagulase-negative staphylococci)** CRBSI is treated similarly to MRSA, with vancomycin being the drug of choice in most cases. Duration of therapy is 7 days after CVC removal or 14 days if the CVC is retained.
  - Sensitive ***Enterococcus*** CRBSI should be treated with ampicillin. Vancomycin should be used in the setting of ampicillin resistance. Vancomycin-resistant enterococci may require therapy with daptomycin or linezolid. Duration of treatment should be 7-14 days.
  - Therapy against **gram-negative bacilli** should be guided by antibiotic susceptibility testing. Duration may range from 7-14 days.
  - **Candidemia** should be treated with an echinocandin (e.g., micafungin 100 mg IV daily) in cases of moderate to severe illness pending species identification, after which therapy can be tailored. Fluconazole 400 mg IV or PO daily may be appropriate for stable patients who have not had any recent azole exposure. Duration of antifungal treatment should be for 14 days after the last positive blood culture (*Clin Infect Dis 2009;48:503*). A dilated ophthalmologic examination is advised to look for *Candida* endophthalmitis.
- **CVC removal** is always preferable. At a minimum, it is recommended that CVCs be removed in the following situations:
  - Any CRBSI involving *S. aureus*, most gram-negative bacilli, or *Candida* spp.
  - Insertion site or tunnel site infection (pus or significant inflammation at the site)
  - Immunocompromised patients with fever, neutropenia, and hemodynamic instability (e.g., sepsis)
- Antibiotic lock therapy in combination with an extended course of antibiotics may be an option in certain situations where CVC salvage is absolutely necessary.

Hospital- and Ventilator-Associated Pneumonia

GENERAL PRINCIPLES

The most frequent pathogens are gram-negative bacilli and *S. aureus*.

DIAGNOSIS

Clinical Presentation

- Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring ≥48 hours after admission that was not incubating at the time of admission.

- Ventilator-associated pneumonia (VAP) is defined as HAP developing after >48-72 hours of endotracheal intubation and mechanical ventilation.
- In addition to new or progressive pulmonary infiltrate, patients may present with fever, purulent respiratory secretions, tachypnea, and hypoxia.

Diagnostic Testing

Diagnosis is made by clinical criteria as well as microbiologic testing. Optimal specimens are uncontaminated sterile body fluids (pleural or blood), bronchoscopy aspirates (cultured quantitatively), or aspirates from endotracheal tubes. Fiberoptic bronchoscopy may be diagnostic (quantitative cultures) and therapeutic (reexpansion of lung segment).

TREATMENT

- Initial empiric antimicrobial therapy should cover common health care-acquired pathogens, particularly *P. aeruginosa* and MRSA. Targeted therapy should be based on culture results and in vitro sensitivity testing (*Am J Respir Crit Care Med 2005;171:388*; *Clin Infect Dis 2010;51(S1):S42*).
- Empyemas require drainage.

Methicillin-Resistant *Staphylococcus aureus* Infections

GENERAL PRINCIPLES

MRSA infection should be distinguished from MRSA colonization, especially when isolated from nonsterile sites such as sputum. Contact precautions are indicated.

TREATMENT

- First-line therapy for most MRSA infections is vancomycin (dosed to therapeutic trough levels). Alternative agents include linezolid 600 mg IV or PO q12h, daptomycin 6 mg/kg IV q24h, ceftaroline, and telavancin. Daptomycin should not be used to treat pneumonia due to inactivation by pulmonary surfactant.
- Eradication of MRSA nasal carriage can sometimes be achieved with a 5-day course of twice-daily intranasal mupirocin. Other regimens include chlorhexidine soap products, bleach baths, and oral antibiotic treatment with TMP-SMX with or without rifampin. However, mupirocin resistance can develop, and carriage often recurs. Eradication efforts should target patients with recurrent MRSA infections.

Vancomycin-Resistant *Enterococcus* Infections

GENERAL PRINCIPLES

Vancomycin-resistant *Enterococcus* (VRE) infection should be distinguished from VRE colonization. Most VRE-related lower UTIs can be treated with nitrofurantoin, ampicillin, ciprofloxacin, or other agents that achieve high urinary concentrations. Contact precautions are indicated. Eradication of enteric VRE colonization has been attempted without success.

TREATMENT

The majority of patients with VRE bloodstream infections are treated with linezolid, daptomycin, or quinupristin/dalfopristin.

Multidrug-Resistant Gram-Negative Infections

GENERAL PRINCIPLES

Highly resistant gram-negative organisms (e.g., *Acinetobacter*, *Klebsiella*, and *Pseudomonas* species) have become increasingly common causes of HAI. Contact precautions are indicated.

TREATMENT

Antimicrobial choices are often limited. Options include broad-spectrum agents such as β-lactam/β-lactamase inhibitor combinations, carbapenems, tigecycline, and polymyxins. Infectious disease consultation is recommended for complicated multidrug-resistant infections.

EMERGING INFECTIONS AND BIOTERRORISM

- Changing patterns in human behavior and demographics, natural phenomena, and microbial evolution continually introduce new pathogens to human contact, leading to the introduction and spread of new or previously rare diseases. Included in this category are several highly fatal and easily produced microorganisms, which have the potential to be used as agents of bioterrorism and produce substantial illness in large populations via an aerosol route of exposure. Most of the likely diseases are rare, so a high index of suspicion is necessary to identify the first few cases.
- A bioterrorism-related outbreak should be considered if an unusually large number of patients present simultaneously with a respiratory, GI, or febrile rash syndrome; if several otherwise healthy patients present with unusually severe disease; or if an unusual pathogen for the region is isolated.

Anthrax

GENERAL PRINCIPLES

Spores from the gram-positive *Bacillus anthracis* germinate at the site of entry into the body, causing cutaneous, GI, or inhalational anthrax.

DIAGNOSIS

Clinical Presentation

- Natural transmission can occur through butchering and eating infected animals, usually resulting in cutaneous or GI disease.
- **Cutaneous anthrax** (“woolsorter's disease”) is characterized by a painless black eschar with surrounding tissue edema.
- **GI anthrax** can present with nausea, vomiting, abdominal pain, ascites, and hemorrhage related to necrotic mucosal ulcers.
- **Inhalational anthrax** (45% case-fatality rate) may result from inadvertent aerosolization of spores from contaminated animal products (e.g., wool or animal hides) or an intentional release (*JAMA 2001;286:2549*). Infection presents initially with an influenza-like illness, GI symptoms, or both, followed

by fulminant respiratory distress and multiorgan failure.

Diagnostic Testing

Diagnosis of inhalational disease is suggested by a widened mediastinum without infiltrates on CXR and confirmed by blood culture and PCR. Notify local infection control and public health department immediately for confirmed cases.

TREATMENT

- Treatment with immediate antibiotic initiation on first suspicion of inhalational anthrax reduces mortality. Empiric therapy is ciprofloxacin 400 mg IV q12h *or* doxycycline 100 mg IV q12h *and* one or two other antibiotics that are active against *B. anthracis* (e.g., penicillin, clindamycin, vancomycin) (*JAMA 2002;287:2236*). Oral therapy with

ciprofloxacin 500 mg PO bid *or* doxycycline 100 mg PO bid *and* one other active agent should be started after improvement and continued for 60 days to reduce the risk of delayed spore germination.
- Uncomplicated cutaneous anthrax can be treated with oral ciprofloxacin 500 mg bid *or* doxycycline 100 mg bid for the same duration. GI anthrax should be treated the same as inhalational disease.
- Postexposure prophylaxis for individuals at risk for inhalational anthrax consists of oral ciprofloxacin 500 mg bid for 60 days after exposure. Doxycycline and amoxicillin are alternatives if the strain proves susceptible.

Smallpox

GENERAL PRINCIPLES

- The variola virus that causes smallpox is easily transmitted person to person through respiratory droplets and carries a case-fatality rate of 25-30%.
- Smallpox, as a naturally occurring disease, was declared eradicated in 1979. However, remaining viral stocks pose a potential bioterrorism threat to unimmunized populations.

DIAGNOSIS

Clinical Presentation

High fever, myalgias, low back pain, and headache appear 7-17 days after exposure, followed by a distinctive rash 3-5 days later. Lesions progress through stages of macules, deep vesicles, pustules, scabs, and permanent pitting scars. The rash starts on the face and distal extremities, including palms and soles, with relative sparing of the trunk, and all lesions in one area are in the same stage of development. These features help to distinguish smallpox from chickenpox (varicella).

Diagnostic Testing

Diagnosis is primarily clinical but can be confirmed by electron microscopy and PCR of pustule fluid at reference laboratories. Notify local infection control, public health departments, and the CDC immediately. Treat all diagnostic samples as highly infectious.

TREATMENT

- Treatment consists of supportive care. No specific antiviral treatment is currently available, although several investigational drugs are in development.
- All suspected cases must be placed in contact and airborne isolation; patients remain infectious until all scabs have separated from the skin.
- Postexposure prophylaxis with live vaccinia virus vaccine within 3 days of exposure offers near-complete protection for responders but is associated with uncommon severe adverse reactions. Progressive vaccinia, eczema vaccinatum, and severe cases of generalized vaccinia can be treated with vaccinia immunoglobulin.

Plague

GENERAL PRINCIPLES

- Plague is caused by the gram-negative bacillus *Yersinia pestis*.
- Naturally acquired plague occurs rarely in the southwestern United States after exposure to infected animals (e.g., through scratches, bites, direct handling, inhalation of aerosolized respiratory secretions) and via rodent flea bites.

DIAGNOSIS

Clinical Presentation

There are three forms of plague.

- **Bubonic:** Local painful lymphadenitis (bubo) and fever (14% case-fatality rate).
- **Septicemic:** Can cause peripheral necrosis and disseminated intravascular coagulation (DIC) ("black death"). Usually from progression of bubonic disease (30-50% case-fatality rate).
- **Pneumonic:** Severe pneumonia with hemoptysis preceded by initial influenza-like illness (57% case-fatality rate, nearing 100% when treatment is delayed). Pneumonic disease can be transmitted from person to person and would be expected after inhalation of aerosolized *Y. pestis*.

Diagnostic Testing

Diagnosis is confirmed by isolation of *Y. pestis* from blood, sputum, or CSF. Treat all diagnostic samples as highly infectious. Notify local infection control and public health departments immediately.

TREATMENT

- Treatment should start at first suspicion of plague because rapid initiation of antibiotics improves survival. Agents of choice are streptomycin 1 g IM q12h; gentamicin 5 mg/kg IV/IM q24h *or* a 2 mg/kg loading dose and then 1.7 mg/kg IV/IM q8h, with appropriate monitoring of drug levels; or doxycycline 100 mg PO/IV bid. Alternatives include ciprofloxacin and chloramphenicol. Oral therapy can be started after clinical improvement, for a total course of 10-14 days.
- Postexposure prophylaxis is indicated after unprotected face-to-face contact with patients with known or suspected pneumonic plague and consists of doxycycline 100 mg PO bid or ciprofloxacin 500 mg PO bid for 7 days.

Botulism

GENERAL PRINCIPLES

- Botulism results from intoxication with botulinum toxin, produced by the anaerobic gram-positive bacillus *Clostridium botulinum*.
- Modes of acquisition include ingestion of the neurotoxin from improperly canned food and contamination of wounds with *C. botulinum* from the soil. Inhalational botulism could result from an intentional release of aerosolized toxin.
- Mortality is low when botulism is recognized early but may be very high in the setting of mass exposure and limited access to mechanical ventilation equipment.

DIAGNOSIS

- The classic triad consists of an absence of fever, clear sensorium, and symmetric descending flaccid paralysis with cranial nerve involvement, beginning with ptosis, diplopia, and dysarthria, and progressing to loss of gag reflex and diaphragmatic function with respiratory failure, followed by diffuse skeletal muscle paralysis. Sensation remains intact. Paralysis can last from weeks to months.
- Diagnosis is confirmed by detection of toxin in serum. Notify local infection control and public health departments.

TREATMENT

- Treatment is primarily supportive and may require mechanical ventilation in the setting of respiratory failure. Wound botulism requires extensive surgical debridement.
- Further progression of paralysis can be halted by early administration of botulinum antitoxin, available through the state public health department or the CDC. Antitoxin is reserved only for cases where there is a high suspicion for botulism based on clinical presentation and exposure history. Routine postexposure prophylaxis with antitoxin is not recommended because of the high incidence (10%) of hypersensitivity reactions and limited supply.

Viral Hemorrhagic Fever

GENERAL PRINCIPLES

- This syndrome is caused by many different RNA viruses, including filoviruses (Ebola and Marburg), flaviviruses (dengue, yellow fever), bunyaviruses (hantaviruses, Congo-Crimean hemorrhagic fever [CCHF], Rift Valley fever [RVF]), and arenaviruses (South American hemorrhagic fevers, Lassa fever).
- All of these viruses cause sporadic disease in endemic areas, and most can be transmitted as an aerosol or contact with infected body fluids. A recent multinational epidemic of Ebola virus disease (EVD) in West Africa demonstrates that sustained human-to-human transmission is also possible in vulnerable populations (*N Engl J Med 2014;371:1481*).
- Case-fatality rates are variable but can be as high as 90% for EVD in resource-limited settings.

DIAGNOSIS

Clinical Presentation

- Early symptoms include fevers, myalgias, and malaise, with varying severity and symptomatology depending on the virus, but all can severely disrupt vascular permeability and cause DIC. Thrombocytopenia, leukopenia, and hepatitis are common.
- Vomiting and severe diarrhea leading to significant dehydration and mortality, as evidenced by the West African EVD epidemic, can also be a prominent feature (*N Engl J Med 2014;371:2092*; *N Engl J Med 2015;372:40*).

Diagnostic Testing

- Diagnosis requires consideration of epidemiology and patient risk factors, especially travel to endemic areas.
- Serology performed by reference laboratories can confirm diagnosis. Notify local infection control and public health departments immediately.

TREATMENT

- Treatment is primarily supportive with attention to infection control.
- Ribavirin (2 g IV × 1, then 1 g q6h × 4 d, then 500 mg q8h × 6 d) has been used for CCHF, Lassa, and RVF (*JAMA 2002;287:2391*; *J Antimicrob Chemother 2011; 66:1215*).
- Exposed contacts should monitor temperature twice daily for 3 weeks. Postexposure prophylaxis with oral ribavirin can be administered to febrile CCHF, Lassa, and RVF contacts.

Severe Acute Respiratory Syndrome

GENERAL PRINCIPLES

- Severe acute respiratory syndrome (SARS) is a fulminant febrile influenza-like respiratory illness that progresses to pneumonia and acute respiratory distress syndrome (ARDS) (*JAMA 2003;290:374*) and is caused by SARS-associated coronavirus (SARS-CoV).
- SARS should be considered in clusters of cases of undiagnosed febrile illness, particularly in the setting of travel to mainland China, Hong Kong, or Taiwan within 10 days of symptom onset.

DIAGNOSIS

Diagnosis is confirmed by acute or convalescent SARS-CoV serum antibodies or PCR of clinical specimens (e.g., respiratory tract, stool, serum) by the CDC.

TREATMENT

Treatment is primarily supportive. Interferon and high-dose steroids have also been used.

Middle East Respiratory Syndrome

GENERAL PRINCIPLES

- Middle East respiratory syndrome (MERS) manifests primarily as a febrile respiratory illness with pneumonia and ARDS (*Ann Intern Med 2014;160:389*) and is caused by MERS coronavirus (MERS-CoV). Milder and asymptomatic infections are also possible (*Lancet Infect Dis 2013;13:752*; *N Engl J Med 2015;372:846*).
- Most cases have been reported in countries in and near the Arabian Peninsula. MERS should be considered in individuals with febrile respiratory illness who have traveled to this region within the past 14 days.

DIAGNOSIS

Diagnosis is confirmed by PCR of clinical specimens obtained from the lower respiratory tract, nasopharynx, or serum by the CDC.

TREATMENT

Treatment is primarily supportive. Interferon and ribavirin have also been used.

Pandemic, Avian, and Swine Influenza

- Genetic reassortment can result in influenza strains that were previously confined to avian and swine hosts gaining human infectivity, causing severe disease and/or rapid spread through human populations.
- Infection control measures and close communication with public health authorities are critical when pandemic strains are circulating. Each new strain may have different virulence, affected age ranges, clinical presentation, and antiviral susceptibilities. Following updated, local data during an outbreak is essential.

Chikungunya

GENERAL PRINCIPLES

- Chikungunya virus is an arthropod-borne alphavirus that is transmitted to humans by the bite of an infected *Aedes* mosquito. It is endemic to West Africa, but infections have been reported in Europe, the Caribbean, and North America (*Clin Infect Dis 2009;49:942*).
- The only way to prevent the virus is to minimize mosquito exposure. No vaccine is currently available.

DIAGNOSIS

Clinical Presentation

Fever and malaise are the earliest symptoms progressing to polyarthralgia that begins about 2-5 days after the onset of the fever. Multiple joints are involved and typically include the joints of the hands, wrists, and ankles. Pain may be disabling and can cause immobilization. Maculopapular rash may appear. Following acute illness, some patients may experience relapsing joint pain even 6 months after the infection.

Diagnostic Testing

Serology is the primary tool for diagnosis. PCR has high sensitivity and specificity within the first 5 days of symptoms.

TREATMENT

Supportive care with anti-inflammatory agents.

15
Antimicrobials

David J. Ritchie

Matthew P. Crotty

Nigar Kirmani

Empiric antimicrobial therapy should be initiated based on expected pathogens for a given infection. As microbial resistance is increasing among many pathogens, a review of institutional as well as local, regional, national, and global susceptibility trends can assist in the development of empiric therapy regimens. Antimicrobial therapy should be modified, if possible, based on results of culture and sensitivity testing to agent(s) that have the narrowest spectrum possible. In some cases, shorter durations of therapy have been shown to be as effective as traditionally longer courses. Attention should be paid to the possibility of switching from parenteral to oral therapy where possible, as many oral agents have excellent bioavailability. Several antibiotics have major drug interactions or require alternate dosing in renal or hepatic insufficiency, or both. For antiretroviral, antiparasitic, and antihepatitis agents, see Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome; Chapter 14, Treatment of Infectious Diseases; and Chapter 19, Liver Diseases, respectively.

ANTIBACTERIAL AGENTS

Penicillins

GENERAL PRINCIPLES

- Penicillins (PCNs) irreversibly bind PCN-binding proteins in the bacterial cell wall, causing osmotic rupture and death. These agents have a diminished role today because of acquired resistance in many bacterial species through alterations in PCN-binding proteins or expression of hydrolytic enzymes.
- PCNs remain among the drugs of choice for syphilis and infections caused by PCN-sensitive streptococci, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Listeria monocytogenes*, *Pasteurella multocida*, and *Actinomyces*.

TREATMENT

- **Aqueous PCN G** (2-5 million units IV q4h or 12-30 million units daily by continuous infusion) is the IV preparation of PCN G and the drug of choice for most PCN-susceptible streptococcal infections and neurosyphilis.
- **Procaine PCN G** is an IM repository form of PCN G that can be used as an alternative treatment for neurosyphilis at a dose of 2.4 million units IM daily in combination with probenecid 500 mg PO qid for 10-14 days.
- **Benzathine PCN** is a long-acting IM repository form of PCN G that is commonly used for treating early latent syphilis (<1 year duration [one dose, 2.4 million units IM]) and late latent syphilis (unknown duration or >1 year [2.4 million units IM weekly for three doses]). It is occasionally given for group A streptococcal pharyngitis and prophylaxis after acute rheumatic fever.
- **PCN V** (250-500 mg PO q6h) is an oral formulation of PCN that is typically used to treat group A streptococcal pharyngitis.

- **Ampicillin** (1-3 g IV q4-6h) is the drug of choice for treatment of infections caused by susceptible *Enterococcus* species or *L. monocytogenes*. Oral ampicillin (250-500 mg PO q6h)

may be used for uncomplicated sinusitis, pharyngitis, otitis media, and urinary tract infections (UTIs), but amoxicillin is generally preferred.

- **Ampicillin/sulbactam** (1.5-3.0 g IV q6h) combines ampicillin with the β-lactamase inhibitor sulbactam, thereby extending the spectrum to include MSSA, anaerobes, and many Enterobacteriaceae. The sulbactam component also has unique activity against some strains of *Acinetobacter*. The agent is effective for upper and lower respiratory tract infections; genitourinary tract infections; and abdominal, pelvic, and polymicrobial soft tissue infections, including those due to human or animal bites.
- **Amoxicillin** (250-1000 mg PO q8h, 875 mg PO q12h, or 775 mg extended-release q24h) is an oral antibiotic similar to ampicillin that is commonly used for uncomplicated sinusitis, pharyngitis, otitis media, community-acquired pneumonia, and UTIs.
- **Amoxicillin/clavulanic acid** (875 mg PO q12h, 500 mg PO q8h, 90 mg/kg/d divided q12h [Augmentin ES-600 suspension], or 2000 mg PO q12h [Augmentin XR]) is an oral antibiotic similar to ampicillin/sulbactam that combines amoxicillin with the β-lactamase inhibitor clavulanate. It is useful for treating complicated sinusitis and otitis media and for prophylaxis of human or animal bites after appropriate local treatment.
- **Nafcillin and oxacillin** (1-2 g IV q4-6h) are penicillinase-resistant synthetic PCNs that are drugs of choice for treating MSSA infections. Dose reduction should be considered in decompensated liver disease.
- **Dicloxacillin** (250-500 mg PO q6h) is an oral antibiotic with a spectrum of activity similar to that of nafcillin and oxacillin, which is typically used to treat localized skin infections.
- **Piperacillin/tazobactam** (3.375 g IV q6h or the higher dose of 4.5 g IV q6h for *Pseudomonas*) combines piperacillin with the β-lactamase inhibitor tazobactam. This combination is active against most Enterobacteriaceae, Pseudomonas, MSSA, ampicillin-sensitive enterococci, and anaerobes, making it useful for intra-abdominal and complicated polymicrobial soft tissue infections. The addition of an aminoglycoside should be considered for treatment of serious infections caused by *Pseudomonas aeruginosa* or for nosocomial pneumonia.

SPECIAL CONSIDERATIONS

Adverse events: All PCN derivatives have been rarely associated with anaphylaxis, interstitial nephritis, anemia, and leukopenia. Prolonged high-dose therapy (>2 weeks) is typically monitored with weekly serum creatinine and complete blood count (CBC). Liver function tests (LFTs) are also monitored with oxacillin/nafcillin, as these agents can cause hepatitis. All patients should be asked about PCN, cephalosporin, or carbapenem allergies. These agents should not be used in patients with a reported serious PCN allergy without prior skin testing or desensitization, or both.

Cephalosporins

GENERAL PRINCIPLES

- Cephalosporins exert their bactericidal effect by interfering with cell wall synthesis by the same mechanism as PCNs.

- These agents are clinically useful because of their broad spectrum of activity and low toxicity profile. All cephalosporins are devoid of clinically significant activity against enterococci when used alone. Within this class, only ceftaroline is active against methicillin-resistant *S. aureus* (MRSA).

TREATMENT

- **First-generation cephalosporins** have activity against staphylococci, streptococci, *Escherichia coli*, and many *Klebsiella* and *Proteus* species. These agents have limited activity against other enteric gram-negative bacilli and anaerobes. **Cefazolin** (1-2 g IV/IM q8h) is the most commonly used parenteral preparation, and **cephalexin** (250-500 mg PO q6h) and **cefadroxil** (500 mg to 1 g PO q12h) are oral preparations. These agents are commonly used for treating skin/soft tissue infections, UTIs, and minor MSSA infections and for surgical prophylaxis (cefazolin).
- **Second-generation cephalosporins** have expanded coverage against enteric gram-negative rods and can be divided into above-the-diaphragm and below-the-diaphragm agents.
  - **Cefuroxime** (1.5 g IV/IM q8h) is useful for treatment of infections above the diaphragm. This agent has reasonable antistaphylococcal and antistreptococcal activity in addition to an extended spectrum against gram-negative aerobes and can be used for skin/soft tissue infections, complicated UTIs, and some community-acquired respiratory tract infections. It does not reliably cover *Bacteroides fragilis*.
  - **Cefuroxime axetil** (250-500 mg PO q12h), **cefprozil** (250-500 mg PO q12h), and **cefaclor** (250-500 mg PO q12h) are oral second-generation cephalosporins typically used for bronchitis, sinusitis, otitis media, UTIs, local soft tissue infections, and oral step-down therapy for pneumonia or cellulitis responsive to parenteral cephalosporins.
  - **Cefoxitin** (1-2 g IV q4-8h) and **cefotetan** (1-2 g IV q12h) are useful for treatment of infections below the diaphragm. These agents have reasonable activity against gram negatives and anaerobes, including *B. fragilis*, and are commonly used for intra-abdominal or gynecologic surgical prophylaxis and infections, including diverticulitis and pelvic inflammatory disease.
- **Third-generation cephalosporins** have broad coverage against aerobic gram-negative bacilli and retain significant activity against streptococci and MSSA. They have moderate anaerobic activity, but generally not against *B. fragilis*. Ceftazidime is the only third-generation cephalosporin that is useful for treating serious *P. aeruginosa* infections. Some of these agents have substantial central nervous system (CNS) penetration and are useful in treating meningitis (see Chapter 14, Treatment of Infectious Diseases). Third-generation cephalosporins are not reliable for the treatment of serious infections caused by organisms producing AmpC β-lactamases regardless of the results of susceptibility testing. These pathogens should be treated empirically with carbapenems, cefepime, or fluoroquinolones.
  - **Ceftriaxone** (1-2 g IV/IM q12-24h) and **cefotaxime** (1-2 g IV/IM q4-12h) are very similar in spectrum and efficacy. They can be used as empiric therapy for pyelonephritis, urosepsis, pneumonia, intra-abdominal infections (combined with metronidazole), gonorrhea, and meningitis. They can also be used for osteomyelitis, septic arthritis, endocarditis, and soft tissue infections caused by susceptible organisms. An emerging therapy is **ceftriaxone** 2 g IV q12h in combination with ampicillin IV for treatment of ampicillin-sensitive *Enterococcus faecalis* endocarditis when aminoglycosides need to be avoided.
  - **Cefpodoxime proxetil** (100-400 mg PO q12h), **cefdinir** (300 mg PO q12h), **ceftibuten** (400 mg PO q24h), and **cefditoren pivoxil** (200-400 mg PO q12h) are oral third-generation cephalosporins useful for the treatment of bronchitis and complicated sinusitis, otitis media, and UTIs. These agents can also

be used as step-down therapy for community-acquired pneumonia. **Cefixime** (400 mg PO once) is no longer recommended as a first-line therapy for gonorrhea but may be used as alternative therapy for gonorrhea with close 7-day test-of-cure follow-up.

- **Ceftazidime** (1-2 g IV/IM q8h) may be used for treatment of infections caused by susceptible strains of *P. aeruginosa*.

- **The fourth-generation cephalosporin cefepime** (500 mg to 2 g IV/IM q8-12h) has excellent aerobic gram-negative coverage, including *P. aeruginosa* and other bacteria producing AmpC β-lactamases. Its gram-positive activity is similar to that of ceftriaxone and cefotaxime. **Cefepime** is routinely used for empiric therapy in febrile neutropenic patients. It also has a prominent role in treating infections caused by antibiotic-resistant gram-negative bacteria and some infections involving both gram-negative and gram-positive aerobes in most sites. Anti-anaerobic coverage should be added where anaerobes are suspected.
- **Ceftaroline** (600 mg IV q12h) is a cephalosporin with anti-MRSA activity that is US Food and Drug Administration (FDA) approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. **Ceftaroline's** unique MRSA activity is due to its affinity for PCN binding protein 2a (PBP2a), the same cell wall component that renders MRSA resistant to all other β-lactams. **Ceftaroline** has similar activity to ceftriaxone against gram-negative pathogens, with virtually no activity against *Pseudomonas* spp., *Acinetobacter*, and other organisms producing AmpC β-lactamase, extended-spectrum β-lactamase (ESBL), or *Klebsiella pneumoniae* carbapenemase (KPC). Like all other cephalosporins, it is relatively inactive against *Enterococcus* spp.
- **Ceftolozane-tazobactam** (1 g ceftolozane/0.5 g tazobactam IV q8 h) is a combination product consisting of a cephalosporin and a β-lactamase inhibitor. This agent is FDA approved for treatment of complicated intra-abdominal infections and complicated UTIs (cUTIs), including pyelonephritis. Ceftolozane-tazobactam has activity against many gram-negative bacteria, including some *P. aeruginosa* that are resistant to antipseudomonal carbapenems, antipseudomonal cephalosporins, and piperacillin-tazobactam. Ceftolozane-tazobactam is also active against some ESBL-producing organisms.
- **Ceftazidime-avibactam** (2 g ceftazidime/0.5 g avibactam IV q8h) is a combination product consisting of ceftazidime plus the novel β-lactamase inhibitor avibactam. This agent is FDA approved for treatment of cUTIs and complicated intra-abdominal infections. Ceftazidime-avibactam is active against gram-negative bacteria, including some *P. aeruginosa* that are resistant to other antipseudomonal β-lactams. This agent is also active against ESBL- and AmpC-producing strains and possesses unique activity against KPC-producing Enterobacteriaceae (but not against metallo-β-lactamases).

SPECIAL CONSIDERATIONS

Adverse events: All cephalosporins have been rarely associated with anaphylaxis, interstitial nephritis, anemia, and leukopenia. **PCN-allergic patients have a 5-10% incidence of a cross-hypersensitivity reaction to cephalosporins.** These agents should not be used in a patient with a reported severe PCN allergy (i.e., anaphylaxis, hives) without prior skin testing or desensitization, or both. Prolonged therapy (>2 weeks) is typically monitored with a weekly serum creatinine and CBC. Due to its biliary elimination, ceftriaxone may cause biliary sludging. Cefepime has been associated with CNS side effects, including delirium and seizures.

Monobactams

GENERAL PRINCIPLES

- **Aztreonam** (1-2 g IV/IM q6-12h) is a monobactam that is active only against aerobic gram-negative bacteria, including *P. aeruginosa*.
- It is useful in patients with known serious β-lactam allergy because there is no apparent cross-reactivity.

- Aztreonam is also available in an inhalational dosage form (75 mg inhaled q8h for 28 days) to improve respiratory symptoms in cystic fibrosis patients infected with *P. aeruginosa.*

Carbapenems

GENERAL PRINCIPLES

- **Imipenem** (500 mg to 1 g IV/IM q6-8h), **meropenem** (1-2 g IV q8h or 500 mg IV q6h), **doripenem** (500 mg IV q8h), and **ertapenem** (1 g IV q24h) are the currently available carbapenems.
- Carbapenems exert their bactericidal effect by interfering with cell wall synthesis, similar to PCNs and cephalosporins, and are active against most gram-positive and gram-negative bacteria, including anaerobes. They are among the antibiotics of choice for infections caused by organisms producing AmpC or ESBLs.

TREATMENT

- Carbapenems are important agents for treatment of many antibiotic-resistant bacterial infections at most body sites. These agents are commonly used for severe polymicrobial infections, including Fournier's gangrene, intra-abdominal catastrophes, and sepsis in immunocompromised hosts.
- Notable bacteria that are **resistant** to carbapenems include ampicillin-resistant enterococci, MRSA, *Stenotrophomonas*, and KPC- and metallo-β-lactamase-producing gram-negative organisms. In addition, ertapenem does not provide reliable coverage against *P. aeruginosa*, *Acinetobacter*, or enterococci; therefore, imipenem, doripenem, or meropenem would be preferred for empiric treatment of nosocomial infections when these pathogens are suspected. **Meropenem** is the preferred carbapenem for treatment of CNS infections.

SPECIAL CONSIDERATIONS

- **Adverse events:** Carbapenems can precipitate seizure activity, especially in older patients, individuals with renal insufficiency, and patients with preexisting seizure disorders or other CNS pathology. Carbapenems should be avoided in these patients unless no reasonable alternative therapy is available. Like cephalosporins, carbapenems have been rarely associated with anaphylaxis, interstitial nephritis, anemia, and leukopenia.
- **Patients who are allergic to PCNs/cephalosporins may have a cross-hypersensitivity reaction to carbapenems**, and these agents should not be used in a patient with a reported severe PCN allergy without prior skin testing, desensitization, or both. Prolonged therapy (>2 weeks) is typically monitored with a weekly serum creatinine, LFTs, and CBC.

Aminoglycosides

GENERAL PRINCIPLES

- Aminoglycosides exert their bactericidal effect by binding to the bacterial ribosome, causing misreading during translation of bacterial messenger RNA into proteins. These drugs are often used in combination with cell wall-active agents (i.e., β-lactams and vancomycin) for treatment of severe infections caused by gram-positive and gram-negative aerobes.

- Aminoglycosides tend to be synergistic with cell wall-active antibiotics such as PCNs, cephalosporins, and vancomycin. However, they do not have activity against anaerobes, and their activity is impaired in the low pH/low oxygen environment of abscesses. Cross-resistance among aminoglycosides is common, and in cases of serious infections, susceptibility testing with each aminoglycoside is recommended. Use of these antibiotics is limited by significant nephrotoxicity and ototoxicity.

TREATMENT

- Traditional dosing of aminoglycosides involves daily divided dosing with the upper end of the dosing range reserved for life-threatening infections. Peak and trough concentrations should be obtained with the third or fourth dose and then every 3-4 days, along with regular serum creatinine monitoring. **Increasing serum creatinine or peak/troughs out of the acceptable range requires immediate attention.**
- **Extended-interval dosing of aminoglycosides** is an alternative method of administration and is more convenient than traditional dosing for most indications. Extended-interval doses are provided in the following specific drug sections. A drug concentration is obtained 6-14 hours after the first dose, and a nomogram (Figure 15-1) is consulted to determine the subsequent dosing interval. Monitoring includes obtaining a drug concentration 6-14 hours after the dosage at least every week and a serum creatinine at least three times a week. In patients who are not responding to therapy, a 12-hour concentration should be checked, and if that concentration is undetectable, extended-interval dosing should be abandoned in favor of traditional dosing.
- For **obese patients** (actual weight >20% above ideal body weight [IBW]), an obese dosing weight (IBW + 0.4 × [actual body weight − IBW]) should be used for determining doses for both traditional and extended-interval methods. Traditional dosing, rather than extended-interval dosing, should be used for patients with endocarditis, burns that cover more than 20% of the body, anasarca, and creatinine clearance (CrCl) of <30 mL/min.
- **Gentamicin and tobramycin** traditional dosing is administered with an initial loading dose of 2 mg/kg IV (2-3 mg/kg in the critically ill), followed by 1.0-1.7 mg/kg IV q8h (peak, 4-10 μg/mL; trough, <1-2 μg/mL). Extended-interval dosing is administered with an initial loading dose of 5 mg/kg, with the subsequent dosing interval determined by a nomogram (see Figure 15-1). Tobramycin is also available as an inhaled agent for adjunctive therapy for patients with cystic fibrosis or bronchiectasis complicated by *P. aeruginosa* infection (300 mg inhalation q12h).
- **Amikacin** has an additional unique role for mycobacterial and *Nocardia* infections. Traditional dosing is an initial loading dose of 5.0-7.5 mg/kg IV (7.5-9.0 mg/kg in the critically ill), followed by 5 mg/kg IV q8h or 7.5 mg/kg IV q12h (peak, 20-35 μg/mL; trough, <10 μg/mL). Extended-interval dosing is 15 mg/kg, with the subsequent dosing interval determined by a nomogram (see Figure 15-1).

SPECIAL CONSIDERATIONS

- **Nephrotoxicity** is the major adverse effect of aminoglycosides. Nephrotoxicity is reversible when detected early but can be permanent, especially in patients with tenuous renal function due to other medical conditions. Aminoglycosides should be used cautiously or avoided, if possible, in patients with decompensated kidney disease. Concomitant administration of aminoglycosides with other known nephrotoxic agents (i.e., amphotericin B formulations, foscarnet, NSAIDs, pentamidine, polymyxins, cidofovir, and cisplatin) should be avoided if possible.

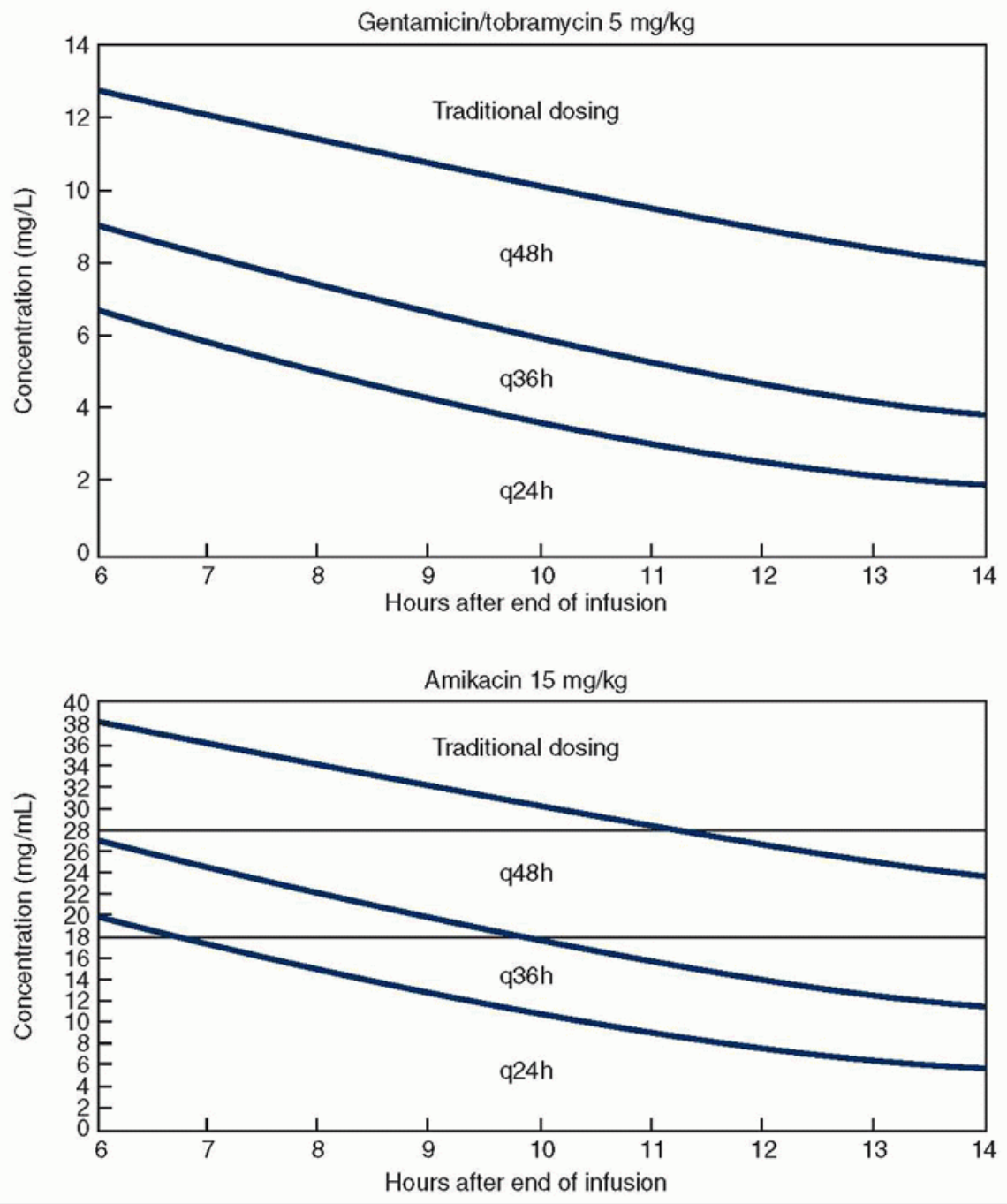


Figure 15-1. Nomograms for extended-interval aminoglycoside dosing. (Adapted from Bailey TC, Little JR, Littenberg B, et al. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;24:786-95.)

- **Ototoxicity** (vestibular or cochlear) is another possible adverse event that necessitates baseline and weekly hearing tests with extended therapy (>14 days).

Vancomycin

GENERAL PRINCIPLES

- **Vancomycin** (15 mg/kg IV q12h; up to 30 mg/kg IV q12h for meningitis) is a glycopeptide antibiotic that interferes with cell wall synthesis by binding to d-alanyl-d-alanine precursors that are critical for peptidoglycan cross-linking in most gram-positive bacterial cell walls. Vancomycin is bactericidal for staphylococci but bacteriostatic for enterococci.

P.485

- Vancomycin-resistant *Enterococcus faecium* (VRE) and vancomycin intermediately resistant *S. aureus* (VISA) present increasing treatment challenges for clinicians. Vancomycin-resistant *S. aureus* has been reported but remains rare.

TREATMENT

- Indications for use are listed in Table 15-1.
- The **goal trough** concentration is 15-20 µg/mL for treatment of serious infections.

SPECIAL CONSIDERATIONS

- Vancomycin is typically administered by slow IV infusion over at least 1 hour per gram dose. More rapid infusion rates can cause the **red man syndrome**, which is a histamine-mediated reaction that is typically manifested by flushing and redness of the upper body.
- **Adverse events.** Nephrotoxicity, neutropenia, thrombocytopenia, and rash may also occur.

Fluoroquinolones

GENERAL PRINCIPLES

- Fluoroquinolones exert their bactericidal effect by inhibiting bacterial DNA gyrase and topoisomerase function, which are critical for DNA replication. In general, these antibiotics are well absorbed orally, with serum concentrations that approach those of parenteral administration.
- Concomitant administration with aluminum- or magnesium-containing antacids, sucralfate, bismuth, oral iron, oral calcium, and oral zinc preparations can markedly impair absorption of all orally administered fluoroquinolones.

TREATMENT

- **Ciprofloxacin** (250-750 mg PO q12h. 500 mg PO q24h [Cipro XR], or 200-400 mg IV q8-12h) and **ofloxacin** (200-400 mg IV or PO q12h) are active against gram-negative aerobes including many AmpC β-lactamase-producing pathogens. These agents are commonly used for UTIs, pyelonephritis, infectious diarrhea, prostatitis, and intra-abdominal infections (with metronidazole). Ciprofloxacin is the most active quinolone against *P. aeruginosa* and is the quinolone of choice for serious infections with

P.486

that pathogen. However, ciprofloxacin has relatively poor activity against gram-positive pathogens and anaerobes and should not be used as empiric monotherapy for community-acquired pneumonia, skin and soft tissue infections, or intra-abdominal infections. Oral and IV ciprofloxacin give similar maximum serum levels at their respective doses, thus, oral therapy is appropriate unless contraindicated.

TABLE 15-1 Indications for Vancomycin Use

Treatment of serious infections caused by documented or suspected methicillin-resistant *Staphylococcus aureus* (MRSA)
Treatment of serious infections caused by ampicillin-resistant, vancomycin-sensitive enterococci
Treatment of serious infections caused by gram-positive bacteria in patients who are allergic to other appropriate therapies
Oral treatment of severe *Clostridium difficile* colitis
Surgical prophylaxis for placement of prosthetic devices at institutions with known high rates of MRSA or in patients who are known to be colonized with MRSA
Empiric use in suspected gram-positive meningitis until an organism has been identified and sensitivities confirmed

- **Levofloxacin** (250-750 mg PO or IV q24h), **moxifloxacin** (400 mg PO/IV q24h daily), and **gemifloxacin** (320 mg PO q24h daily) have improved coverage of streptococci but generally less gram-negative activity than ciprofloxacin (except levofloxacin, which does cover *P. aeruginosa*). Moxifloxacin may be used as monotherapy of intra-abdominal or skin and soft tissue infections due to its anti-anaerobic activity, although resistance among *B. fragilis* is increasing. Each of these agents is useful for treatment of sinusitis, bronchitis, community-acquired pneumonia, and UTIs (except moxifloxacin, which is only minimally eliminated in the urine). Some of these agents have activity against mycobacteria and have a potential role in treating drug-resistant TB and atypical mycobacterial infections. Levofloxacin may be used as an alternative for treatment of chlamydial urethritis.

SPECIAL CONSIDERATIONS

- **Adverse events** include nausea, CNS disturbances (headache, restlessness, and dizziness, especially in the elderly), rash, and phototoxicity. These agents can cause prolongation of the QT_c interval and should not be used in patients who are receiving class I or class III antiarrhythmics, in patients with known electrolyte or conduction abnormalities, or in those who are taking other medications that prolong the QT_c interval or induce bradycardia. These agents should also be used with caution in the elderly, in whom asymptomatic conduction disturbances are more common. Fluoroquinolones should not be routinely used in patients younger than 18 years or in pregnant or lactating women due to the risk of arthropathy in pediatric patients. They may also cause tendinitis or tendon rupture, especially of the Achilles tendon, particularly in elderly. An increase in the international normalized ratio (INR) may occur when used concurrently with warfarin.
- **This class of antimicrobials has major drug interactions.** Before initiating use of these agents, it is necessary to review concomitant medications.

Macrolide and Lincosamide Antibiotics

GENERAL PRINCIPLES

- Macrolide and lincosamide antibiotics are bacteriostatic agents that block protein synthesis in bacteria by binding to the 50S subunit of the bacterial ribosome.

- This class of antibiotics has activity against gram-positive cocci, including streptococci and staphylococci, and some upper respiratory gram-negative bacteria, but minimal activity against enteric gram-negative rods.

TREATMENT

- Macrolides are commonly used to treat pharyngitis, otitis media, sinusitis, and bronchitis, especially in PCN-allergic patients, and are among the drugs of choice for treating *Legionella*, *Chlamydia*, and *Mycoplasma* infections. Azithromycin and clarithromycin can be used as monotherapy for outpatient community-acquired pneumonia and have a unique role in the treatment and prophylaxis against *Mycobacterium avium* complex (MAC) infections. Many PCN-resistant strains of pneumococci are also resistant to macrolides.

- **Clarithromycin** (250-500 mg PO q12h or 1000 mg XL PO q24h) has enhanced activity against some respiratory pathogens (especially *Haemophilus*). It is commonly used to treat bronchitis, sinusitis, otitis media, pharyngitis, soft tissue infections, and community-acquired pneumonia. It has a prominent role in treating MAC infection and is an important component of regimens used to eradicate *Helicobacter pylori* (see Chapter 18, Gastrointestinal Diseases).
- **Azithromycin** (500 mg PO for 1 day, then 250 mg PO q24h for 4 days; 500 mg PO q24h for 3 days; 2000-mg microspheres PO for one dose; 500 mg IV q24h) has a similar spectrum of activity as clarithromycin and is commonly used to treat bronchitis, sinusitis, otitis media, pharyngitis, soft tissue infections, and community-acquired pneumonia. It has a prominent role in MAC prophylaxis (1200 mg PO every week) and treatment (500-600 mg PO q24h) in HIV patients. It is also commonly used to treat *Chlamydia trachomatis* infections (1 g PO single dose). A major advantage of azithromycin is that it does not have the numerous drug interactions seen with erythromycin and clarithromycin.
- **Clindamycin** (150-450 mg PO q6-8h or 600-900 mg IV q8h) is chemically classified as a lincosamide (related to macrolides), with activity against staphylococci and streptococci, as well as anaerobes, including *B. fragilis*. It has excellent oral bioavailability (90%) and penetrates well into the bone and abscess cavities. It is also used for treatment of aspiration pneumonia and lung abscesses. Clindamycin has activity against most community-associated strains of MRSA and has emerged as a treatment option for skin and soft tissue infections caused by this organism. Clindamycin may be used as a second agent in combination therapy for invasive streptococcal and clostridial infections to decrease toxin production. It may also be used for treatment of suspected anaerobic infections of the head and neck (peritonsillar or retropharyngeal abscesses, necrotizing fasciitis), although metronidazole is used more commonly for intra-abdominal infections (clindamycin has less reliable activity against *B. fragilis*). Clindamycin has additional uses, including treatment of babesiosis (in combination with quinine), toxoplasmosis (in combination with pyrimethamine), and *Pneumocystis jirovecii* pneumonia (in combination with primaquine).

SPECIAL CONSIDERATIONS

Adverse events: Macrolides and clindamycin are associated with nausea, abdominal cramping, and LFT abnormalities. Liver function profiles should be checked intermittently during extended therapy. Hypersensitivity reactions with prominent skin rash are more common with clindamycin, as is pseudomembranous colitis secondary to *Clostridium difficile*. Clarithromycin and azithromycin may cause QT_c interval prolongation. **Clarithromycin has major drug interactions** caused by inhibition of the cytochrome P450 system.

Sulfonamides and Trimethoprim

GENERAL PRINCIPLES

Sulfadiazine, sulfamethoxazole, and trimethoprim slowly kill bacteria by inhibiting folic acid metabolism. This class of antibiotics is most commonly used for uncomplicated UTIs, sinusitis, and otitis media. Some sulfonamide-containing agents also have unique roles in the treatment of *P. jirovecii, Nocardia*, *Toxoplasma*, and *Stenotrophomonas* infections.

TREATMENT

- **Trimethoprim** (100 mg PO q12h) is occasionally used as monotherapy for treatment of UTIs. Trimethoprim is more often used in the combination preparations/regimens outlined in the following sections. Trimethoprim in combination with dapsone is an alternate therapy for mild *P. jirovecii* pneumonia.

- **Trimethoprim/sulfamethoxazole** is a combination antibiotic (IV or PO) with a 1:5 ratio of trimethoprim to sulfamethoxazole. The IV preparation is dosed at 5 mg/kg IV q8h (based on the trimethoprim component) for serious infections. The oral preparations (160 mg trimethoprim/800 mg sulfamethoxazole per double-strength [DS] tablet) are extensively bioavailable, with similar drug concentrations obtained with IV and PO formulations. Both components have excellent tissue penetration, including bone, prostate, and CNS. The combination has a broad spectrum of activity but typically does not inhibit *P. aeruginosa*, anaerobes, or group A streptococci. It is the therapy of choice for *P. jirovecii* pneumonia, *Stenotrophomonas maltophilia*, *Tropheryma whipplei*, and *Nocardia* infections. It is commonly used for treating sinusitis, otitis media, bronchitis, prostatitis, and UTIs (one DS tab PO q12h). Trimethoprim/sulfamethoxazole is active against the majority of community-associated strains of MRSA and is widely used for uncomplicated cases of skin and soft tissue infections caused by this organism (often two DS tabs PO q12h). It is used as *P. jirovecii* pneumonia prophylaxis (one DS tab PO twice a week, three times a week, or single-strength or DS daily) in HIV-infected patients, solid organ transplant patients, bone marrow transplant patients, and patients receiving fludarabine. IV therapy is routinely converted to the PO equivalent for patients who require prolonged therapy.
- For serious infections, such as *Nocardia* brain abscesses, it may be useful to monitor drug levels with sulfamethoxazole peaks (100-150 µg/mL) and troughs (50-100 µg/mL) occasionally during the course of therapy and adjust the dose accordingly. In patients with renal insufficiency, doses can be adjusted by following trimethoprim peaks (5-10 µg/mL). Prolonged therapy can cause bone marrow suppression, possibly requiring treatment with leucovorin (5-10 mg PO q24h) until cell counts normalize.
- **Sulfadiazine** (1.0-1.5 g PO q6h) in combination with pyrimethamine (200 mg PO followed by 50-75 mg PO q24h) and leucovorin (10-20 mg PO q24h) is the regimen of choice for toxoplasmosis. Sulfadiazine is also occasionally used to treat *Nocardia* infections.

SPECIAL CONSIDERATIONS

Adverse events: These drugs are associated with cholestatic jaundice, bone marrow suppression, hyperkalemia (with trimethoprim/sulfamethoxazole), interstitial nephritis, “false” elevations in serum creatinine, and severe hypersensitivity reactions (Stevens-Johnson syndrome/erythema multiforme). Nausea is common with higher doses. **All patients should be asked whether they are allergic to “sulfa**

drugs," and specific commercial names should be mentioned (e.g., Bactrim or Septra).

Tetracyclines

GENERAL PRINCIPLES

- Tetracyclines are bacteriostatic antibiotics that bind to the 30S ribosomal subunit and block protein synthesis.
- These agents have unique roles in the treatment of *Rickettsia*, *Ehrlichia*, *Chlamydia*, and *Mycoplasma* infections. They are used as therapy for most tick-borne infections and Lyme disease-related arthritis, alternate therapy for syphilis, and therapy for *P. multocida* infections in PCN-allergic patients. Minocycline and doxycycline also have activity against some multidrug-resistant gram-negative pathogens and may be used in this setting based on results of susceptibility testing.

TREATMENT

- **Tetracycline** (250-500 mg PO q6h) is commonly used for severe acne and in some *H. pylori* eradication regimens. It can also be used for treatment of acute Lyme borreliosis,

P.489

  Rocky Mountain spotted fever, ehrlichiosis, psittacosis, *Mycoplasma* pneumonia, *Chlamydia* pneumonia, and chlamydial infections of the eye or genitourinary tract, but these infections are generally treated with doxycycline or other antibiotics. Aluminum-and magnesium-containing antacids and preparations that contain oral calcium, oral iron, or other cations can significantly impair oral absorption of tetracycline and should be avoided within 2 hours of each dose.
- **Doxycycline** (100 mg PO/IV q12h) is the most commonly used tetracycline and is standard therapy for *C. trachomatis*, Rocky Mountain spotted fever, ehrlichiosis, and psittacosis. This agent also has a role for malaria prophylaxis and for treatment of community-acquired pneumonia. It also has utility in the treatment of uncomplicated skin and skin structure infections caused by community-associated MRSA.
- **Minocycline** (200 mg IV/PO, then 100 mg IV/PO q12h) is similar to doxycycline in its spectrum of activity and clinical indications. Among the tetracyclines, minocycline is most likely to provide coverage against *Acinetobacter*. Minocycline is second-line therapy for pulmonary nocardiosis and cervicofacial actinomycosis.

SPECIAL CONSIDERATIONS

Adverse events: Nausea and photosensitivity are common side effects, so patients should be warned about direct sun exposure. Rarely, these medications are associated with pseudotumor cerebri. **They should not routinely be given to children or to pregnant or lactating women** because they can cause tooth enamel discoloration in the developing fetus and young children. Minocycline is associated with vestibular disturbances.

ANTIMICROBIAL AGENTS, MISCELLANEOUS

Colistin and Polymyxin B

GENERAL PRINCIPLES

- **Colistimethate sodium** (colistin; 2.5-5 mg/kg/d IV divided q12h) and **polymyxin B** (15,000-25,000 units/kg/d

IV divided q12h) are bactericidal polypeptide antibiotics that kill gram-negative bacteria by disrupting the cell membrane. These drugs have roles in the treatment of multidrug-resistant gram-negative bacilli but are inactive against *Proteus*, *Providencia*, and *Serratia*.

- **These medications should only be given under the guidance of an experienced clinician**, because parenteral therapy has significant CNS side effects and potential nephrotoxicity. Inhaled colistin (75-150 mg q12h given by nebulizer) is better tolerated than the IV formulation, generally causing only mild upper airway irritation, and has some efficacy as adjunctive therapy for *P. aeruginosa* or *Acinetobacter* pulmonary infections.

SPECIAL CONSIDERATIONS

Adverse events with parenteral therapy include paresthesias, slurred speech, peripheral numbness, tingling, and significant dose-dependent nephrotoxicity. The dosage should be carefully reduced in patients with renal insufficiency, because overdosage in this setting can result in neuromuscular blockade and apnea. Serum creatinine should be monitored daily early in therapy and then at a regular interval for the duration of therapy. **Concomitant use with aminoglycosides, other known nephrotoxins, or neuromuscular blockers should be avoided if at all possible.**

Dalbavancin

GENERAL PRINCIPLES

Dalbavancin (1000 mg IV on day 1 and 500 mg IV on day 8 to complete the course of therapy) is a long-acting lipoglycopeptide (terminal half-life of 346 hours) that inhibits cell wall biosynthesis and demonstrates concentration-dependent bactericidal activity. Dalbavancin has activity against many gram-positive aerobic bacteria, including staphylococci (including MRSA) and streptococci, and is FDA approved for acute bacterial skin and skin structure infections.

SPECIAL CONSIDERATIONS

Adverse events include nausea, diarrhea, vomiting, headache, insomnia, dizziness, and pruritus. In clinical trials, more dalbavancin-treated patients had alanine aminotransferase elevation greater than three times the upper limit of normal than patients treated with a comparative agent. Abnormalities in other liver tests occurred with a similar frequency in both groups.

Daptomycin

GENERAL PRINCIPLES

Daptomycin (4 mg/kg IV q24h for skin and skin structure infections; 6-8 mg/kg IV q24h for bloodstream infections) is a cyclic lipopeptide. The drug exhibits rapid bactericidal activity against a wide variety of gram-positive bacteria, including enterococci, staphylococci, and streptococci. Daptomycin is FDA approved for treatment of complicated skin and skin structure infections as well as *S. aureus* bacteremia and right-sided endocarditis. The drug should not be used to treat primary lung infections due to its decreased activity in the presence of pulmonary surfactant. Nonsusceptibility to daptomycin can develop, making it imperative that susceptibility of isolates be verified.

SPECIAL CONSIDERATIONS

Adverse events include gastrointestinal (GI) disturbances, injection site reactions, elevated LFTs, eosinophilic pneumonitis, and elevated creatine phosphokinase. Serum creatine phosphokinase should be monitored at baseline and weekly, because daptomycin has been associated with skeletal muscle effects, including rhabdomyolysis. Patients should also be monitored for signs of muscle weakness and pain, and the drug should be discontinued if these symptoms develop in conjunction with marked creatine phosphokinase elevations (5-10 times the upper limit of normal with symptoms or 10 times the upper limit of normal without symptoms). Consideration should also be given to avoiding concomitant use of daptomycin and 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors due to the potential increased risk of myopathy.

Fosfomycin

GENERAL PRINCIPLES

- **Fosfomycin** (3-g sachet dissolved in cold water PO once) is a bactericidal oral antibiotic that kills bacteria by inhibiting an early step in cell wall synthesis. It has a spectrum of

activity that includes most urinary tract pathogens, including *P. aeruginosa*, *Enterobacter* spp., and enterococci (including VRE), and some multidrug-resistant gram-negative bacteria.

- It is most useful for treating uncomplicated UTIs in women with susceptible strains of *E. coli* or *E. faecalis*. The single-dose sachet formulation should not be routinely used to treat pyelonephritis or systemic infections.

SPECIAL CONSIDERATIONS

Adverse events include diarrhea. It should not be taken with metoclopramide, which interferes with fosfomycin absorption.

Oxazolidinones

GENERAL PRINCIPLES

- Oxazolidinones block assembly of bacterial ribosomes and inhibit protein synthesis.
- **Linezolid** (600 mg IV/PO q12h) IV and oral formulations produce equivalent serum concentrations, and the drug has potent activity against gram-positive bacteria, including drug-resistant enterococci, staphylococci, and streptococci. However, it has no meaningful activity against Enterobacteriaceae.
- Linezolid is useful for serious infections with VRE, as an alternative to vancomycin for treatment of MRSA infections, for patients with an indication for vancomycin therapy who are intolerant of that medication, and as oral therapy of MRSA infections when IV access is unavailable. Linezolid is not FDA approved for catheter-related bloodstream or catheter-site infections. Resistance can develop to this antibiotic, and it is imperative that organism susceptibility is verified.
- **Tedizolid** (200 mg PO/IV q24h) is an oxazolidinone antibiotic that is FDA approved for treating acute bacterial skin and skin structure infections. Tedizolid phosphate is a prodrug that is rapidly converted in vivo to the active moiety, tedizolid, which inhibits bacterial protein synthesis. Tedizolid has activity against staphylococci (including MRSA), streptococci, and enterococci (including some strains resistant to vancomycin).

SPECIAL CONSIDERATIONS

- **Adverse events** associated with linezolid include diarrhea, nausea, and headache. Thrombocytopenia occurs frequently in patients who receive more than 2 weeks of therapy, and serial platelet count monitoring is indicated. A CBC should be checked every week during prolonged therapy with this agent. Prolonged therapy has also been associated with peripheral and optic neuropathy. Lactic acidosis may also rarely occur.
- Linezolid has **several important drug interactions**. It is a mild monoamine oxidase inhibitor, and patients should be advised not to take selective serotonin reuptake inhibitors or other antidepressants, fentanyl, or meperidine while on linezolid to avoid the serotonin syndrome. Ideally, patients should be off antidepressants for at least a week before initiating linezolid. Over-the-counter cold remedies that contain pseudoephedrine or phenylpropanolamine should also be avoided, because coadministration with linezolid can elevate blood pressure. Linezolid does not require dose adjustments for renal or hepatic dysfunction.
- **Adverse events** associated with tedizolid include nausea, diarrhea, vomiting, headache, and dizziness. Tedizolid phosphate has primarily been studied as a 6-day regimen. Whether tedizolid is less prone to adverse effects characteristic of linezolid, such as

hematologic disturbances and peripheral and optic neuropathy, if used beyond 6 days, is uncertain. Tedizolid phosphate appears less likely to inhibit monoamine oxidase as compared to linezolid; however, patients on serotonergic agents were excluded from tedizolid phase III acute bacterial skin and skin structure infection clinical trials.

Metronidazole

GENERAL PRINCIPLES

- Metronidazole (250-750 mg PO/IV q6-12h) is only active against anaerobic bacteria and some protozoa. The drug exerts its bactericidal effect through accumulation of toxic metabolites that interfere with multiple biologic processes. It has excellent tissue penetration, including abscess cavities, bone, and the CNS.
- It has greater activity against gram-negative than gram-positive anaerobes but is active against *Clostridium perfringens* and *C. difficile*. It is the treatment of choice as monotherapy for mild to moderate *C. difficile* colitis as well as bacterial vaginosis and can be used in combination with other antibiotics to treat intra-abdominal infections and brain abscesses. Protozoal infections that are routinely treated with metronidazole include *Giardia*, *Entamoeba histolytica*, and *Trichomonas vaginalis*. A dose reduction may be warranted for patients with decompensated liver disease.

SPECIAL CONSIDERATIONS

Adverse events include nausea, dysgeusia, disulfiram-like reactions to alcohol, and mild CNS disturbances (headache, restlessness). Rarely, metronidazole causes peripheral neuropathy and seizures.

Nitrofurantoin

GENERAL PRINCIPLES

- **Nitrofurantoin** (50-100 mg PO macrocrystals q6h or 100 mg PO dual-release formulation q12h for 5-7 days)

is a bactericidal oral antibiotic that is useful for uncomplicated UTIs except those caused by *Proteus*, *P. aeruginosa*, or *Serratia*. The drug is metabolized by bacteria into toxic intermediates that inhibit multiple bacterial processes. It has had a modest resurgence in use, as it is frequently effective for uncomplicated VRE UTIs.

- Although it was commonly used in the past for UTI prophylaxis, this practice should be avoided, because prolonged therapy is associated with chronic pulmonary syndromes that can be fatal. Nitrofurantoin should not be used for pyelonephritis or any other systemic infections and should be avoided in patients with renal dysfunction.

SPECIAL CONSIDERATIONS

Adverse events: Nausea is the most common adverse effect, and the drug should be taken with food to minimize this problem. Patients should be warned that their urine may become brown secondary to the medication. Neurotoxicity, hepatotoxicity, and pulmonary fibrosis may also rarely occur with nitrofurantoin. Furthermore, it should not be used in patients with CrCl <60 mL/min because the risk for development of treatment-associated adverse effects is increased. It should not be given with probenecid, because this combination decreases the concentration of nitrofurantoin in the urine.

Oritavancin

GENERAL PRINCIPLES

Oritavancin (1200 mg IV administered once to complete therapy) is a long-acting lipoglycopeptide (terminal half-life, 245 hours) that inhibits cell wall biosynthesis through multiple mechanisms and demonstrates concentration-dependent bactericidal activity. Oritavancin has activity against many gram-positive aerobic bacteria, including staphylococci (including MRSA) and streptococci, as well as some enterococci (including some strains resistant to vancomycin).

SPECIAL CONSIDERATIONS

Adverse events include nausea, diarrhea, vomiting, headache, insomnia, dizziness, and pruritus. Elevations of hepatic enzymes did not occur significantly more frequently in patients treated with oritavancin compared to vancomycin in phase III trials.

Quinupristin/Dalfopristin

GENERAL PRINCIPLES

- **Quinupristin/dalfopristin** (7.5 mg/kg IV q8h) is the first FDA-approved drug in the streptogramin class.
- This agent has activity against antibiotic-resistant gram-positive organisms, especially VRE, MRSA, and antibiotic-resistant strains of *Streptococcus pneumoniae*. It has some activity against gram-negative upper respiratory pathogens (*Haemophilus* and *Moraxella*) and anaerobes, but more appropriate antibiotics are available to treat these infections. Quinupristin/dalfopristin is bacteriostatic for enterococci and can be used for treatment of serious infections with VRE (only *E. faecium* because it is inactive against *E. faecalis*).

SPECIAL CONSIDERATIONS

Adverse events include arthralgias and myalgias, which occur frequently and can necessitate

discontinuation of therapy. IV site pain and thrombophlebitis are common when the drug is administered through a peripheral vein. It has also been associated with elevated LFTs and, because it is primarily cleared by hepatic metabolism, patients with significant hepatic impairment require a dose adjustment. Quinupristin/dalfopristin is similar to clarithromycin with regard to drug interactions.

Telavancin

GENERAL PRINCIPLES

Telavancin (7.5-10 mg/kg q24-48h, based on CrCl) is a new lipoglycopeptide antibiotic that is FDA approved for treatment of hospital-acquired and ventilator-associated bacterial pneumonia caused by *S. aureus* and for complicated skin and skin structure infections. Telavancin is broadly active against gram-positive bacteria, including MRSA, VISA, heteroresistant VISA (hVISA), daptomycin- and linezolid-resistant *S. aureus*, streptococci, vancomycin-sensitive enterococci, and some gram-positive anaerobes. The agent is not active against gram-negative bacteria, vancomycin-resistant *S. aureus*, and VRE.

SPECIAL CONSIDERATIONS

Adverse events include nausea, vomiting, metallic or soapy taste, foamy urine, and nephrotoxicity (which necessitates serial monitoring of serum creatinine). Prehydration with normal saline may mitigate the nephrotoxicity observed with the use of this drug. Telavancin can also cause a minor prolongation of the QT_c interval. Women of childbearing potential require a negative serum pregnancy test prior to receiving telavancin due to teratogenic effects noted in animals.

Tigecycline

GENERAL PRINCIPLES

Tigecycline (100 mg IV loading dose, then 50 mg IV q12h) is the only FDA-approved antibiotic in the class of glycylcyclines. Its mechanism of action is similar to that of tetracyclines by inhibiting the translation of bacterial proteins through binding to the 30S ribosome. The addition of the glycyl side chain expands its activity against bacterial pathogens that are normally resistant to tetracycline and minocycline. It has a broad spectrum of bactericidal activity against gram-positive, gram-negative, and anaerobic bacteria except *P. aeruginosa* and some *Proteus* isolates. It is currently FDA approved for treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia. Additionally, it may be used for treatment of some other tissue infections due to susceptible strains of VRE and some multidrug-resistant gram-negative bacteria. Due to low achievable blood concentrations, tigecycline should not be used to treat primary bacteremia.

SPECIAL CONSIDERATIONS

Adverse events: Nausea and vomiting are the most common adverse events. Tigecycline has not been studied in patients younger than 18 years and is contraindicated in pregnant and lactating women. Because it has a similar structure to tetracyclines, photosensitivity, tooth discoloration, and, rarely, pseudotumor cerebri may occur. Pancreatitis may also occur.

ANTIMYCOBACTERIAL AGENTS

Effective therapy of *Mycobacterium tuberculosis* (MTB) infections requires combination chemotherapy designed to prevent the emergence of resistant organisms and maximize efficacy. Increased resistance to conventional antituberculous agents has led to the use of more complex regimens and has made susceptibility testing an integral part of TB management (see Chapter 14, Treatment of Infectious Diseases).

Isoniazid

GENERAL PRINCIPLES

Isoniazid (INH; 300 mg PO q24h) exerts bactericidal effects on susceptible mycobacteria by interfering with the synthesis of lipid components of the mycobacterial cell wall. INH is a component of nearly all treatment regimens and can be given twice a week in directly observed therapy (15 mg/kg/dose; 900 mg maximum). INH remains the drug of choice for treatment of latent TB infection (300 mg PO q24h for 9 months).

SPECIAL CONSIDERATIONS

Adverse events include elevations in liver transaminases (20%). This effect can be idiosyncratic but is usually seen in the setting of advanced age, underlying liver disease, or concomitant consumption of alcohol, and may be potentiated by rifampin. Transaminase elevations to greater than threefold the upper limit of the normal range necessitate holding therapy. Patients with known liver dysfunction should have weekly LFTs during the initial stage of therapy. INH also antagonizes vitamin B_6 metabolism and potentially can cause a peripheral neuropathy. This can be avoided or minimized by coadministration of pyridoxine, 25-50 mg PO daily, especially in the elderly, in pregnant women, and in patients with diabetes, renal failure, alcoholism, and seizure disorders.

Rifamycins

GENERAL PRINCIPLES

Rifamycins exert bactericidal activity on susceptible mycobacteria by inhibiting DNA-dependent RNA polymerase, thereby halting transcription.

- **Rifampin** (600 mg PO q24h or twice a week) is an integral component of most TB treatment regimens. It is also active against many gram-positive and gram-negative bacteria. Rifampin is used as adjunctive therapy in staphylococcal prosthetic valve endocarditis (300 mg PO q8h), for prophylaxis of close contacts of patients with infection caused by *Neisseria meningitidis* (600 mg PO q12h), and as adjunctive treatment of bone and joint infections associated with prosthetic material or devices. The drug is well absorbed orally and is widely distributed throughout the body including the cerebrospinal fluid (CSF).
- **Rifabutin** (300 mg PO q24h) is primarily used to treat TB and MAC infections in HIV-positive patients who are receiving highly active antiretroviral therapy, because it has fewer drug-drug interactions and less deleterious effects on protease inhibitor metabolism than does rifampin (see Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome).

SPECIAL CONSIDERATIONS

Adverse events: Patients should be warned about reddish-orange discoloration of body fluids, and contact lenses should not be worn during treatment. Rash, GI disturbances, hematologic disturbances, hepatitis, and interstitial nephritis can occur. Uveitis has also been associated with rifabutin. **This class of antibiotics has major drug interactions.**

Pyrazinamide

GENERAL PRINCIPLES

- **Pyrazinamide** (15-30 mg/kg PO q24h [maximum, 2 g] or 50-75 mg/kg PO twice a week [maximum, 4 g/dose]) kills mycobacteria replicating in macrophages by an unknown disruption of membrane transport.
- It is well absorbed orally and widely distributed throughout the body, including the CSF. Pyrazinamide is typically used for the first 2 months of therapy.

SPECIAL CONSIDERATIONS

Adverse events include hyperuricemia and hepatitis.

Ethambutol

GENERAL PRINCIPLES

- **Ethambutol** (15-25 mg/kg PO q24h or 50-75 mg/kg PO twice a week; maximum, 2.4 g/dose) is bacteriostatic and inhibits arabinosyl transferase (involved in cell wall synthesis).
- Doses should be reduced in the presence of renal dysfunction.

SPECIAL CONSIDERATIONS

Adverse events may include optic neuritis, which manifests as decreased red-green color perception, decreased visual acuity, or visual field deficits. Baseline and monthly visual examinations should be performed during therapy. Renal function should also be carefully monitored because drug accumulation in the setting of renal insufficiency can increase risk of ocular effects.

Streptomycin

Streptomycin is an aminoglycoside that can be used as a substitute for ethambutol and for drug-resistant MTB. It does not adequately penetrate the CNS and should not be used for TB meningitis.

ANTIVIRAL AGENTS

Current antiviral agents only suppress viral replication. Viral containment or elimination requires an intact host immune response. Anti-HIV agents will be discussed in Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome.

Anti-Influenza Agents (Neuraminidase Inhibitors)

Zanamivir, oseltamivir, and peramivir block influenza A and B neuraminidases. Neuraminidase activity is necessary for successful viral egress and release from infected cells. These drugs have shown modest activity in clinical trials, with a 1- to 2-day improvement in symptoms in patients who are treated within 48 hours of the onset of influenza symptoms. At the onset of each influenza season, a consultation with local health department officials is recommended to determine the most effective antiviral agent. Although oseltamivir and zanamivir are effective for prophylaxis of influenza, annual influenza vaccination remains the most effective method for prophylaxis in all high-risk patients and health care workers (see Appendix A, Immunizations and Postexposure

Therapies).

- **Zanamivir** (10 mg [two inhalations] q12h for 5 days, started within 48 hours of the onset of symptoms) is an inhaled neuraminidase inhibitor that is active against influenza A and B. It is indicated for treatment of uncomplicated acute influenza infection in adults and children 7 years of age or older who have been symptomatic for <48 hours. The drug is also indicated for influenza prophylaxis in patients age 5 years and older.

  Adverse events. Headache, GI disturbances, dizziness, and upper respiratory symptoms are sometimes reported. Bronchospasms or declines in lung function, or both, may occur in patients with underlying respiratory disorders and may require a rapid-acting bronchodilator for control.

- **Oseltamivir** (75 mg PO q12h for 5 days) is an orally administered neuraminidase inhibitor that is active against influenza A and B. It is indicated for treatment of uncomplicated

  acute influenza in adults and children 1 year of age or older who have been symptomatic for up to 2 days. This agent is also indicated for prophylaxis of influenza A and B in adults and children 1 year of age or older.

  Adverse events include nausea, vomiting, and diarrhea. Dizziness and headache may also occur.

- **Peramivir** (600 mg IV single-dose therapy) is an IV neuraminidase inhibitor that is active against influenza A and B. It is FDA approved for single-dose treatment of acute, uncomplicated influenza in adults who have been symptomatic for up to 2 days. The agent has not been proven to be effective for serious influenza requiring hospitalization.

  Adverse events include diarrhea and rare cases of skin reactions, behavioral disturbances, neutrophils <1000/μL, hyperglycemia, creatine phosphokinase elevation, and elevation of hepatic transaminases.

Antiherpetic Agents

GENERAL PRINCIPLES

Antiherpetic agents are nucleotide analogs that inhibit viral DNA synthesis.

- **Acyclovir** is active against herpes simplex virus (HSV) and varicella-zoster virus (VZV) (400 mg PO q8h for HSV, 800 mg PO five times a day for localized VZV infections, 5-10 mg/kg IV q8h for severe HSV infections, and 10 mg/kg IV q8h for severe VZV infections and HSV encephalitis).
  - It is indicated for treatment of primary and recurrent genital herpes, severe herpetic stomatitis, and herpes simplex encephalitis. It can be used as prophylaxis in patients who have frequent HSV recurrences (400 mg PO q12h). It is also used for herpes zoster ophthalmicus, disseminated primary VZV in adults (significant morbidity compared to the childhood illness), and severe disseminated primary VZV in children.
  - **Adverse events.** Reversible crystalline nephropathy may occur; preexisting renal failure, dehydration, and IV bolus dosing increase the risk of this effect. Rare cases of CNS disturbances, including delirium, tremors, and seizures, may also occur, particularly with high doses, in patients with renal failure and in the elderly.
- **Valacyclovir** (1000 mg PO q8h for herpes zoster, 1000 mg PO q12h for initial episode of genital HSV infection, and 500 mg PO q12h or 1000 mg PO q24h for recurrent episodes of HSV) is an orally administered prodrug of acyclovir used for the treatment of acute herpes zoster infections and for treatment or suppression of genital HSV infection. It is converted to acyclovir in the body. An advantage over oral acyclovir is less frequent dosing.

  The most common **adverse effect** is nausea. Valacyclovir can rarely cause CNS disturbances, and high

doses (8 g/d) have been associated with development of hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura in immunocompromised patients, including those with HIV and bone marrow and solid organ transplants.

- **Famciclovir** (500 mg PO q8h for herpes zoster, 250 mg PO q8h for the initial episode of genital HSV infection, and 125 mg PO q12h for recurrent episodes of genital HSV infection) is an orally administered antiviral agent used for the treatment of acute herpes zoster reactivation and for treatment or suppression of genital HSV infections.

Adverse events include headache, nausea, and diarrhea.

Anticytomegalovirus Agents

- **Ganciclovir** (5 mg/kg IV q12h for 14-21 days for induction therapy of cytomegalovirus [CMV] retinitis, followed by 6 mg/kg IV for 5 days every week or 5 mg/kg IV q24h; the oral dose is 1000 mg PO q8h with food) is used to treat CMV.

  - It has activity against HSV and VZV, but safer drugs are available to treat those infections. The drug is widely distributed in the body, including the CSF.
  - It is indicated for treatment of CMV retinitis and other serious CMV infections in immunocompromised patients (e.g., transplant and AIDS patients). Chronic maintenance therapy is generally required to suppress CMV disease in patients with AIDS.
  - **Adverse events.** Neutropenia, which may require treatment with granulocyte colony-stimulating factor for management (300 µg SC daily to weekly), is the main therapy-limiting adverse effect. Thrombocytopenia, rash, confusion, headache, nephrotoxicity, and GI disturbances may also occur. Blood counts and electrolytes should be monitored weekly while the patient is receiving therapy. Other agents with nephrotoxic or bone marrow suppressive effects may enhance the adverse effects of ganciclovir.
- **Valganciclovir** (900 mg PO q12-24h) is the oral prodrug of ganciclovir. This agent has excellent bioavailability and can be used for treatment of CMV retinitis and, thus, has supplanted the use of oral ganciclovir, which has poor oral bioavailability. Adverse events are the same as those for ganciclovir.
- **Foscarnet** (60 mg/kg IV q8h or 90 mg/kg IV q12h for 14-21 days as induction therapy, followed by 90-120 mg/kg IV q24h as maintenance therapy for CMV; 40 mg/kg IV q8h for acyclovir-resistant HSV and VZV) is used to treat CMV retinitis in patients with AIDS. It is typically considered for use in patients who are not tolerating or not responding to ganciclovir.
  - Foscarnet is used for CMV disease in bone marrow transplant patients to avoid the bone marrow-suppressive effects of ganciclovir. It is also used for treatment of acyclovir-resistant HSV/VZV infections and ganciclovir-resistant CMV infections.
  - **Adverse events.** Risk for nephrotoxicity is a major concern. CrCl should be determined at baseline, and electrolytes (PO_4, Ca^{2+}, Mg^{2+}, and K^+) and serum creatinine should be checked at least twice a week. Normal saline (500-1000 mL) should be given before and during infusions to minimize nephrotoxicity. Foscarnet should be avoided in patients with a serum creatinine of >2.8 mg/dL or baseline CrCl of <50 mL/min. Concomitant use of other nephrotoxins (e.g., amphotericin, aminoglycosides, pentamidine, NSAIDs, cisplatin, or cidofovir) should also be avoided. Foscarnet chelates divalent cations and can cause tetany even with normal serum calcium levels. Use of foscarnet with pentamidine can cause severe hypocalcemia. Other side effects include seizures, phlebitis, rash, and genital ulcers. **Prolonged therapy with foscarnet**

should be monitored by physicians who are experienced with administration of home IV therapy and can systematically monitor patients' laboratory results.

- **Cidofovir** (5 mg/kg IV qwk for 2 weeks as induction therapy, followed by 5 mg/kg IV q14d chronically as maintenance therapy) is used primarily to treat CMV retinitis in patients with AIDS. It can be administered through a peripheral IV line.
  - **Adverse events.** The most common adverse event is nephrotoxicity. It should be avoided in patients with a CrCl of <55 mL/min, a serum creatinine >1.5 mg/dL, significant proteinuria, or a recent history of receipt of other nephrotoxic medications.
  - **Each cidofovir dose should be administered with probenecid** (2 g PO 3 hours before the infusion and then 1 g at 2 and 8 hours after the infusion) along with 1 L normal saline IV 1-2 hours before the infusion to minimize nephrotoxicity. Patients should have a serum creatinine and urine protein check before each dose of cidofovir is given. These patients should be followed by a physician regularly, because administration of this drug requires systematic monitoring of laboratory studies.

ANTIFUNGAL AGENTS

Amphotericin B

GENERAL PRINCIPLES

- **Amphotericin B** is fungicidal by interacting with ergosterol and disrupting the fungal cell membrane. Reformulation of this agent in various lipid vehicles has decreased some of its adverse side effects. Amphotericin B formulations are not effective for *Pseudallescheria boydii*, *Candida lusitaniae*, or *Aspergillus terreus* infections.
- **Amphotericin B deoxycholate** (0.3-1.5 mg/kg q24h as a single infusion over 2-6 hours) was once the mainstay of antifungal therapy but has now been supplanted by lipid-based formulations of the drug as a result of their improved tolerability.
- **Lipid complexed preparations** of amphotericin B, including liposomal amphotericin B (3-6 mg/kg IV q24h), amphotericin B lipid complex (5 mg/kg IV q24h), and amphotericin B colloidal dispersion (3-4 mg/kg IV q24h), have decreased nephrotoxicity and are generally associated with fewer infusion-related reactions than amphotericin B deoxycholate. Liposomal amphotericin B has the most FDA-approved uses and also appears to be the best tolerated lipid amphotericin B formulation.

SPECIAL CONSIDERATIONS

- The major **adverse event** of all amphotericin B formulations, including the lipid formulations, is **nephrotoxicity**. Patients should receive 500 mL of normal saline before and after each infusion to minimize nephrotoxicity. Irreversible renal failure appears to be related to cumulative doses. Therefore, concomitant administration of other known nephrotoxins should be avoided if possible.
- Common **infusion-related effects** include fever/chills, nausea, headache, and myalgias. Premedication with 500-1000 mg of acetaminophen and 50 mg of diphenhydramine may control many of these symptoms. More severe reactions may be prevented by premedication with hydrocortisone 25-50 mg IV. Intolerable infusion-related chills can be managed with meperidine 25-50 mg IV.
- Amphotericin B therapy is associated with **potassium and magnesium wasting** that generally requires supplementation. Serum creatinine and electrolytes (including Mg^{2+} and K^{+}) should be monitored at least

two to three times a week.

Azoles

GENERAL PRINCIPLES

Azoles are fungistatic agents that inhibit ergosterol synthesis.

- **Fluconazole** (100-800 mg PO/IV q24h) is the drug of choice for many localized candidal infections, such as UTIs, thrush, vaginal candidiasis (150-mg single dose), esophagitis, peritonitis, and hepatosplenic infection. It is also a viable agent for severe disseminated candidal infections (e.g., candidemia) and the treatment of choice for consolidation therapy of cryptococcal meningitis following an initial 14-day course of an amphotericin B product, or as a second-line agent for primary treatment of cryptococcal meningitis (400-800 mg PO q24h for 8 weeks, followed by 200 mg PO q24h thereafter for chronic maintenance treatment).
  - Fluconazole does not have activity against *Aspergillus* spp. or *Candida krusei* and, therefore, should not be used for treatment of those infections. *Candida glabrata* may also be resistant to fluconazole. Its absorption is not dependent on gastric acid.

- **Itraconazole** (200-400 mg PO q24h) is a triazole with broad-spectrum antifungal activity.
  - It is commonly used to treat the endemic mycoses like coccidioidomycosis, histoplasmosis, blastomycosis, and sporotrichosis.
  - It is an alternative therapy for *Aspergillus* and can also be used to treat infections caused by dermatophytes, including onychomycosis of the toenails (200 mg PO q24h for 12 weeks) and fingernails (200 mg PO q12h for 1 week, with a 3-week interruption, and then a second course of 200 mg PO q12h for 1 week).
  - The capsules require adequate gastric acidity for absorption and, therefore, should be taken with food or carbonated beverage, whereas the liquid formulation is not significantly affected by gastric acidity and is better absorbed on an empty stomach. As a result, the liquid formulation is preferred for most patients.
- **Posaconazole** (delayed-release tablet and IV doses are 300 mg PO/IV q12h on day 1, followed by 300 mg PO/IV q24h; oral suspension dose is 200 mg PO q8h for prophylaxis and 100-400 mg PO q12-24h for oropharyngeal candidiasis treatment) is an oral azole agent that is FDA approved for prophylaxis of invasive aspergillosis and candidiasis in hematopoietic stem cell transplant patients with graft-versus-host disease or in patients with hematologic malignancies experiencing prolonged neutropenia from chemotherapy as well as treatment of oropharyngeal candidiasis. This drug has also shown some benefit for treatment of mucormycosis, although it is not approved by the FDA for this use.
  - Each suspension dose should be administered with a full meal, liquid supplement, or acidic carbonated beverage (e.g., ginger ale). Acid-suppressive therapy may significantly reduce absorption of the oral suspension, but not the delayed-release tablets.
  - Rifabutin, phenytoin, and cimetidine significantly reduce posaconazole concentrations and should not routinely be used concomitantly.
  - Posaconazole significantly increases bioavailability of cyclosporine, tacrolimus, and midazolam, necessitating dosage reductions of these agents when used with posaconazole. Dosage reduction of vinca alkaloids, statins, and calcium channel blockers should also be considered.

- Terfenadine, astemizole, pimozide, cisapride, quinidine, and ergot alkaloids are contraindicated with posaconazole.

- **Voriconazole** (loading dose of 6 mg/kg IV [two doses 12 hours apart], followed by a maintenance dose of 4 mg/kg IV q12h or 200 mg PO q12h [100 mg PO q12h if <40 kg]) is a triazole antifungal with a spectrum of activity against a wide range of pathogenic fungi. It has enhanced in vitro activity against all clinically important species of *Aspergillus*, as well as *Candida* (including most nonalbicans), *Scedosporium apiospermum*, and *Fusarium* spp.
  - It is the treatment of choice for most forms of invasive aspergillosis, for which it demonstrates typical response rates of 40-50% and superiority over conventional amphotericin B. It is also effective in treating candidemia, esophageal candidiasis, and *Scedosporium* and *Fusarium* infections.
  - An advantage of voriconazole is the easy transition from IV to PO therapy because of excellent bioavailability. For refractory fungal infections, a dose increase of 50% may be useful. The maintenance dose is reduced by 50% for patients with moderate hepatic failure.
  - Because of its metabolism through the **cytochrome P450 system** (enzymes 2C19, 2C9, and 3A4), there are several **clinically significant drug interactions** that must be considered. Rifampin, rifabutin, carbamazepine (markedly reduced voriconazole levels), sirolimus (increased drug concentrations), and astemizole (prolonged QT_c) are contraindicated with voriconazole. Concomitantly administered cyclosporine, tacrolimus, and warfarin require more careful monitoring.

- **Isavuconazonium sulfate, the prodrug of isavuconazole** (372 mg isavuconazonium sulfate [equivalent to 200 mg isavuconazole] PO/IV q8h for 48 hours, then 372 mg

isavuconazonium sulfate [equivalent to 200 mg isavuconazole] PO/IV q24h), is an azole with broad-spectrum antifungal activity that is FDA approved for treatment of invasive aspergillosis and invasive mucormycosis.
  - The oral formulation has a 98% oral bioavailability that is unaffected by food.
  - The IV formulation does not contain a cyclodextrin-based solubilizing vehicle and can be safely used in patients with CrCl ≤50 mL/min.
  - It is not associated with QT_c prolongation, but rather a minor QT_c shortening.
  - Rifampin, carbamazepine, long-acting barbiturates, and St. John's wort significantly reduce isavuconazole concentrations and are contraindicated with isavuconazole.
  - High-dose ritonavir and ketoconazole can significantly increase isavuconazole concentrations and are contraindicated with isavuconazole.

SPECIAL CONSIDERATIONS

Nausea, diarrhea, and rash are mild side effects of the azoles. Hepatitis is a rare but serious complication. Therapy must be monitored closely in the setting of compromised liver function, and LFTs should be monitored regularly with chronic use. These agents may also cause prolongation of the QT_c interval.

Itraconazole levels should be checked after 1 week of therapy to confirm absorption. Serum level monitoring is also advisable with use of oral formulations of posaconazole and voriconazole. The IV formulations of voriconazole and posaconazole should not be used routinely in patients with a CrCl of <50 mL/min because of the potential for accumulation and toxicity from the cyclodextrin vehicle. Transient visual disturbance is a common adverse effect (30%) of voriconazole. **This class of antibiotics has major drug interactions.**

Echinocandins

This class of antifungals inhibits the enzyme (1,3)-β-d-glucan synthase that is essential in fungal cell wall synthesis.

- **Caspofungin acetate** (70 mg IV loading dose, followed by 50 mg IV q24h) has fungicidal activity against most *Aspergillus* and *Candida* spp., including azole-resistant *Candida* strains. However, *Candida guilliermondii* and *Candida parapsilosis* may be less susceptible. Caspofungin does not have appreciable activity against *Cryptococcus*, *Histoplasma*, *Blastomyces*, *Coccidioides*, or *Mucor* spp. It is FDA approved for treatment of candidemia and refractory invasive aspergillosis and as empiric therapy in febrile neutropenia.
  - Metabolism is primarily hepatic, although the cytochrome P450 system is not significantly involved. An increased maintenance dosage is necessary with the use of drugs that induce hepatic metabolism (e.g., efavirenz, nelfinavir, phenytoin, rifampin, carbamazepine, dexamethasone). The maintenance dose should be reduced to 35 mg for patients with moderate hepatic impairment; however, no dose adjustment is necessary for renal failure.
  - In vitro and limited clinical data suggest a synergistic effect when caspofungin is given in conjunction with itraconazole, voriconazole, or amphotericin B for *Aspergillus* infections.
  - **Adverse events:** Fever, rash, nausea, and phlebitis at the injection site are infrequent.
- **Micafungin sodium** is used for candidemia (100 mg IV q24h), esophageal candidiasis (150 mg IV q24h), and as fungal prophylaxis for patients undergoing hematopoietic stem cell transplantation (50 mg IV q24h). The spectrum of activity is similar to that of anidulafungin and caspofungin. Although micafungin increases serum concentrations of sirolimus and nifedipine, these increases may not be clinically significant. Micafungin may increase cyclosporine concentrations in about 20% of patients. No change in dosing is necessary in renal or hepatic dysfunction.

  Adverse events include elevated LFTs and rare cases of rash and delirium.

- **Anidulafungin** (200 mg IV loading dose, followed by 100 mg IV q24h) is useful for treatment of candidemia and other systemic *Candida* infections (intra-abdominal abscess and peritonitis) as well as esophageal candidiasis (100-mg loading dose, followed by 50 mg daily). The spectrum of activity is similar to that of caspofungin and micafungin. Anidulafungin is not a substrate inhibitor or inducer of cytochrome P450 isoenzymes and does not have clinically relevant drug interactions. No dosage change is necessary in renal or hepatic insufficiency.

  Adverse events include possible histamine-mediated reactions, elevations in LFTs, and, rarely, hypokalemia.

Miscellaneous

- **Flucytosine** (25 mg/kg PO q6h) exerts its fungicidal effects on susceptible *Candida* and *Cryptococcus* spp. by interfering with DNA synthesis.
  - Main clinical uses are in the treatment of cryptococcal meningitis and severe *Candida* infections in combination with amphotericin B. This agent should not be used alone due to risk for rapid emergence of resistance.
  - **Adverse events** include dose-related bone marrow suppression and bloody diarrhea due to intestinal flora conversion of flucytosine to 5-fluorouracil.

- Peak drug concentrations should be kept between 50-100 µg/mL. Close monitoring of serum concentrations and dose adjustments are critical in the setting of renal insufficiency. LFTs should be obtained at least once a week.

- **Terbinafine** (250 mg PO q24h for 6-12 weeks) is an allylamine antifungal agent that kills fungi by inhibiting ergosterol synthesis. It is FDA approved for the treatment of onychomycosis of the fingernails (6 weeks of treatment) or toenails (12 weeks of treatment). It is not generally used for systemic infections.

  Adverse events include headache, GI disturbances, rash, LFT abnormalities, and taste disturbances. This drug should not be used in patients with hepatic cirrhosis or a CrCl of <50 mL/min because of inadequate data. It has only moderate affinity for cytochrome P450 hepatic enzymes and does not significantly inhibit the metabolism of cyclosporine (15% decrease) or warfarin.

16
Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome

Caline Mattar

Rachel Presti

Hilary E. L. Reno

SEXUALLY TRANSMITTED INFECTIONS, ULCERATIVE DISEASES

- Current sexually transmitted infection (STI) treatment guidelines are found at *www.cdc.gov/std/*.
- Treatment options for each infection can be found in Table 16-1.

Genital Herpes

GENERAL PRINCIPLES

Genital herpes is caused by **herpes simplex virus (HSV)**, types 1 and 2, usually type 2. The proportion of herpes caused by HSV-1 continues to increase.

DIAGNOSIS

- Infection is characterized by painful grouped vesicles in the genital and perianal regions that rapidly ulcerate and form shallow tender lesions.
- The initial episode may be associated with inguinal adenopathy, fever, headache, myalgias, and aseptic meningitis; recurrences are usually less severe. Asymptomatic shedding of virus is frequent and leads to transmission.
- Confirmation of HSV infection requires culture or polymerase chain reaction (PCR); however, clinical presentation is often adequate for diagnosis.

Syphilis

GENERAL PRINCIPLES

- Syphilis is caused by the spirochete *Treponema pallidum*.
- There is a high degree of HIV co-infection in patients with syphilis, from 40-70%, and HIV infection should be excluded with appropriate testing (*JAMA 2003;290(11):1510*).
- Syphilis can have an atypical course in HIV-infected patients; treatment failures and progression to neurosyphilis are more frequent in this population.

TABLE 16-1 Treatment of Sexually Transmitted Infections

Infection	Recommended Regimen(s)	Alternative Regimens and

		Notes
Genital ulcer disease		
Herpes simplex		
First episode	• Acyclovir 400 mg PO three times a day × 7-10 d or 200 mg PO five times daily × 7-10 d • Valacyclovir 1 g PO two times a day × 7-10 d • Famciclovir 250 mg PO three times a day × 7-10 d	
Recurrent episodes	• Acyclovir 400 mg PO three times a day × 5 d or 800 mg two times a day × 5 d or 800 mg PO three times a day × 2 d • Valacyclovir 1 g PO once a day × 5 d or 500 mg PO two times a day × 3 d • Famciclovir 1 g PO two times a day × 1 d or 125 mg PO two times a day × 5 d or 500 mg once, then 250 mg two times a day × 2 d	In patients with HIV: • Acyclovir 400 mg PO three times a day × 5-10 d • Valacyclovir 1 g PO twice a day × 5-10 d • Famciclovir 500 mg PO twice a day × 5-10 d
Suppressive therapy	• Acyclovir 400 mg PO twice a day • Valacyclovir 500 mg or 1 g PO once daily • Famciclovir 250 mg PO twice daily	In patients with HIV: • Acyclovir 400-800 mg PO twice to three times a day • Valacyclovir 500 mg PO twice a day • Famciclovir 500 mg PO twice a day
Syphilis		
Primary, secondary, or early latent <1 yr	• Benzathine penicillin G 2.4 million units IM single dose	Penicillin-allergic: • Doxycycline 100 mg PO twice daily × 14 d • Tetracycline 500 mg PO four times daily × 14 d
Latent >1 yr, latent unknown duration	• Benzathine penicillin G 2.4 million units IM once weekly × 3 doses	• Doxycycline 100 mg PO twice daily × 28 d • Tetracycline 500 mg PO four times daily × 28 d
Neurosyphilis		

	• Aqueous crystalline penicillin G 18-24 million U/d × 10-14 d	• Procaine penicillin 2.4 million units IM once daily + probenecid 500 mg PO four times daily × 10-14 d
Pregnancy	• Penicillin is the recommended treatment—desensitize if necessary	
Chancroid	• Azithromycin 1 g PO single dose • Ceftriaxone 250 mg IM single dose	• Ciprofloxacin 500 mg PO twice daily × 3 d • Erythromycin base 500 mg PO twice daily × 7 d • Some resistance has been reported for these regimens.
Lymphogranuloma venereum	• Doxycycline 100 mg PO twice daily × 21 d	• Erythromycin 500 mg PO four times a day × 21 d
Urethritis/cervicitis		
Gonorrhea	• Ceftriaxone 250 mg IM once + azithromycin 1 g PO once even if testing for *Chlamydia trachomatis* is negative • Given concern for antibiotic resistance, dual treatment is recommended.	• Cefotaxime 500 mg IM × 1 or cefoxitin 2 g IM + probenecid 1 g PO × 1 • Oral cephalosporin treatment is not recommended as long as ceftriaxone is available.
Disseminated gonococcal infection	• Ceftriaxone 1 g IV daily or cefotaxime 1 g IV every 8 h × 7 d	
Chlamydia	• Azithromycin 1 g PO single dose • Doxycycline 100 mg PO twice daily × 7 d	• Erythromycin base 500 mg PO four times a day × 7 d • Retesting is recommended in 3 months.
Pelvic inflammatory disease		
Outpatient	• Ceftriaxone 250 mg IM once + doxycycline 100 mg PO twice daily × 14 d + consider metronidazole 500 mg orally twice daily × 14 d	• Cefoxitin 2 g IM + probenecid 1 g PO once can be substituted for ceftriaxone
Inpatient	• (Cefoxitin 2 g IV every 6 h or cefotetan 2 g IV every 12 h) + doxycycline 100 mg PO twice daily ×	• Clindamycin 900 mg IV every 8 h + gentamicin 2 mg/kg loading dose, then 1.5 mg/kg every 8 h

	14 d + consider metronidazole 500 mg PO twice daily × 14 d	+ doxycycline 100 mg PO twice daily × 14 d • Ampicillin-sulbactam 3 g IV every 6 h + doxycycline 100 mg PO twice daily × 14 d
Vaginitis/vaginosis		
Trichomonas	• Metronidazole 2 g PO single dose • Tinidazole 2 g PO single dose	Metronidazole 500 mg PO twice daily × 7 d
Pregnancy	• Metronidazole 2 g PO × 1 (not teratogenic)	
Bacterial vaginosis	• Metronidazole 500 mg PO twice daily × 7 d • Clindamycin cream 2% intravaginal at bedtime × 7 d • Metronidazole gel 0.75% intravaginal once a day for 5 d	• Tinidazole 2 g PO once daily × 2 d or 1 g PO once daily × 5 d • Clindamycin 300 mg PO twice daily × 7 d • Clindamycin ovules 100 mg intravaginal × 3 d
Candidiasis	• Intravaginal azoles in variety of strengths for 1-7 d • Fluconazole 150 mg PO × 1	
Severe candidiasis	• Fluconazole 150 mg PO every 72 h × 2-3 doses	• Intravaginal azoles for 7-14 d • Culture and sensitivities maybe helpful
Recurrent candidiasis	• Fluconazole 100, 150, or 200 mg PO once weekly × 6 mo	

See *cdc.gov/std/* for the current sexually transmitted infection treatment guidelines.

DIAGNOSIS

Clinical Presentation

- **Primary syphilis** develops within several weeks of exposure and manifests as one or more painless, indurated, superficial ulcerations (chancre).
- **Secondary syphilis** develops 2-10 weeks after the chancre resolves and may produce a rash, mucocutaneous lesions, adenopathy, and constitutional symptoms.

- **Tertiary syphilis** follows between 1-20 years after infection and includes cardiovascular, gummatous,

and neurologic disease (general paresis, tabes dorsalis, or meningovascular syphilis).

Diagnostic Testing

- In **primary syphilis**, dark-field microscopy of lesion exudates, when available, may reveal spirochetes. A nontreponemal serologic test (e.g., rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) should be confirmed with a treponemalspecific test (e.g., fluorescent treponemal antibody absorption or *T. pallidum* particle agglutination).
- Diagnosis of **secondary syphilis** is made on the basis of positive serologic studies and the presence of a compatible clinical illness.
- **Latent syphilis** is a serologic diagnosis in the absence of symptoms—early latent syphilis is serologically positive for <1 year, and late latent syphilis is serologically positive for >1 year.
- To exclude **neurosyphilis**, a lumbar puncture should be performed in all patients with neurologic, ophthalmic, or auditory signs or symptoms. Additionally, some experts recommend lumbar puncture in HIV-infected patients with evidence of tertiary disease, treatment failure, or late latent syphilis (*Clin Infect Dis 2007;44:1222*). VDRL should be performed on cerebrospinal fluid (CSF).
- Response to treatment should be monitored with nontreponemal serologic tests at 3, 6, and 12 months after treatment. In patients with HIV, tests should be checked every 3 months after treatment for 1 year.

Chancroid

GENERAL PRINCIPLES

Chancroid is caused by *Haemophilus ducreyi*.

DIAGNOSIS

- Chancroid produces a painful genital ulcer and tender suppurative inguinal lymphadenopathy.
- Identification of the organism is difficult and requires special culture media.

Lymphogranuloma Venereum

GENERAL PRINCIPLES

Lymphogranuloma venereum (LGV) is caused by *Chlamydia trachomatis* (serovars L_1, L_2, or L_3).

DIAGNOSIS

- Manifests as a painless genital ulcer, followed by heaped up, matted inguinal lymphadenopathy. Proctocolitis with pain and discharge can occur with anal infection (*Clin Infect Dis 2007;44:26*).
- Diagnosis is based on clinical suspicion and *C. trachomatis* nucleic acid and antibody testing, if available.

SEXUALLY TRANSMITTED INFECTIONS, VAGINITIS, AND VAGINOSIS

Trichomoniasis

DIAGNOSIS

Clinical Presentation

- Clinical symptoms of infection by *Trichomonas vaginalis* include malodorous purulent vaginal discharge, dysuria, and genital inflammation.
- Examination reveals profuse frothy discharge and cervical petechiae.
- *T. vaginalis* is often asymptomatic, especially in males.

Diagnostic Testing

- Nucleic acid amplification tests (NAATs) and antigen detection tests are available to detect *T. vaginalis* and offer improved sensitivity over the traditional visualization of motile trichomonads on a saline wet mount of vaginal discharge.
- Elevated vaginal pH (≥4.5) may be seen.

Bacterial Vaginosis

GENERAL PRINCIPLES

The replacement of normal lactobacilli with anaerobic bacteria in the vagina leads to bacterial vaginosis.

DIAGNOSIS

Three of the following criteria are needed to make the diagnosis:

- Homogenous, thin, white discharge
- Presence of clue cells on microscopic examination
- Elevated vaginal pH (≥4.5)
- Fishy odor associated with vaginal discharge before or after addition of 10% potassium hydroxide (KOH) (whiff test)

Vulvovaginal Candidiasis

GENERAL PRINCIPLES

Vulvovaginal candidiasis is not generally considered an STI but commonly develops in the setting of oral contraceptive use or antibiotic therapy. Recurrent infections may be a presenting manifestation of unrecognized HIV infection.

DIAGNOSIS

- Thick, cottage cheese-like vaginal discharge in conjunction with intense vulvar inflammation, pruritus, and dysuria is often present.
- Definitive diagnosis requires visualization of fungal elements on a KOH preparation of the vaginal discharge.

TREATMENT

- Therapy is often initiated on the basis of the clinical presentation.
- Fluconazole failure may indicate the presence of a **non-*Candida albicans* species**.

Cervicitis/Urethritis

GENERAL PRINCIPLES

Cervicitis and urethritis are frequent presentations of infection with ***Neisseria gonorrhoeae* or *C. trachomatis***, and occasionally *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *T. vaginalis*. These infections often coexist, and clinical presentations can be identical.

DIAGNOSIS

Clinical Presentation

- Women with urethritis, cervicitis, or both complain of mucopurulent vaginal discharge, dyspareunia, and dysuria.
- Men with urethritis may have dysuria and purulent penile discharge.
- Most infections with these STIs are asymptomatic.
- Disseminated gonococcal infection (DGI) can present with fever, tenosynovitis, vesicopustular skin lesions, and polyarthralgias. DGI may also manifest solely as septic arthritis of the knee, wrist, or ankle (see Chapter 25, Arthritis and Rheumatologic Diseases).

Diagnostic Testing

- A positive NAAT performed on endocervical, vaginal, urethral (men), urine, or extragenital samples is recommended to make the diagnosis of *C. trachomatis* or *N. gonorrhoeae* infection. In the case of *N. gonorrhoeae*, a Gram stain of endocervical or urethral discharge with gram-negative intracellular diplococci can rapidly establish the diagnosis. Culture can be performed on urethral or endocervical swab specimens.
- Recommendations for testing include NAAT testing at extragenital sites of sexual contact (pharynx, rectum), especially in men who have sex with men (MSM).
- In addition to NAAT studies, patients with suspected DGI should have blood cultures drawn. In the setting of septic arthritis, synovial fluid analysis and culture is indicated.

TREATMENT

Because of increasing resistance concerns, treatment options for *N. gonorrhoeae* infection are reduced (see Table 16-1).

Pelvic Inflammatory Disease

GENERAL PRINCIPLES

Pelvic inflammatory disease (PID) is an upper genital tract infection in women, usually preceded by cervicitis. Long-term consequences of untreated PID include chronic pain, increased risk of ectopic pregnancy, and infertility.

DIAGNOSIS

Clinical Presentation

Symptoms can range from mild pelvic discomfort and dyspareunia to severe abdominal pain with fever, which may signal complicating perihepatitis (Fitz-Hugh-Curtis syndrome) or tubo-ovarian abscess.

Diagnostic Testing

- Cervical motion tenderness or uterine or adnexal tenderness, vaginal discharge or friability, and the presence of many white blood cells per low-power field on a saline preparation of vaginal or endocervical fluid are consistent with a diagnosis of PID.
- NAATs or culture of endocervical specimens should be obtained to identify *C. trachomatis* or *N. gonorrhoeae* infection.
- All women diagnosed with PID should be screened for HIV infection.

TREATMENT

Severely ill, pregnant, and HIV-infected women with PID should be hospitalized. Patients unable to tolerate oral antibiotics also warrant admission.

HIV TYPE 1

GENERAL PRINCIPLES

Definition

HIV type 1 is a retrovirus that predominantly infects lymphocytes that bear the CD4 surface protein, as well as coreceptors belonging to the chemokine receptor family (CCR5 or CXCR4), and causes AIDS.

Classification

Diagnosis of AIDS by the Centers for Disease Control and Prevention (CDC) classification is made on the basis of CD4 cell count <200 cells/μL, CD4 percentage <14%, or development of one of the 25 AIDS-defining conditions (*MMWR Recomm Rep 1992;41 (RR-17):1*).

Epidemiology

- HIV type 1 is common throughout the world. By the most recent estimates, over 34 million people worldwide are living with HIV or AIDS, with a significant burden of disease in sub-Saharan Africa (*http://www.who.int/hiv/data/en/index.html*).
- In the United States, 1.3 million people are estimated to be infected with HIV with one-fifth of these people unaware of their infection. The CDC estimates that as many as 70% of the 50,000 new annual infections in the United States are transmitted by persons who are unaware of their HIV status.
- Despite comprising only 14% of the population in the United States, African Americans account for nearly 44% of all new cases of HIV in this country. Hispanics are also disproportionately affected by HIV. Women comprise approximately 24% of the US epidemic (*http://www.cdc.gov/hiv/topics/women*).
- MSM remain the population most heavily affected by HIV in the United States. Of all new HIV infections in 2009, 61% were MSM (*http://www.cdc.gov/nchhstp/newsroom/docs/HIV-Infections-2006-2009.pdf*).

- **HIV type 2** is endemic to regions in West Africa. It is characterized by much slower progression to AIDS and resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Pathophysiology

- After entering the host cell, viral RNA is reverse transcribed into DNA using the HIV **reverse transcriptase**. This viral DNA is inserted into the host genome through the activity of the viral **integrase**. The host cell machinery is then used to produce the relevant viral proteins, which are appropriately truncated by a viral **protease**. Infectious viral particles bud away to infect other CD4 lymphocytes.
- Most infected cells are killed by the host CD8 T-cell response.
- Long-lived latently infected cells persist, especially memory T cells.
- Infection usually leads to CD4 T-cell depletion and **impaired cell-mediated immunity** over a period of 8-10 years.
- Without treatment, >90% of infected patients will progress to AIDS, which is characterized by the development of opportunistic infections (OIs), wasting, and viral-associated malignancies.

Risk Factors

- The virus is primarily transmitted sexually but also via parenteral and perinatal exposure.
- The highest risk of transmission is through blood transfusions (9250 per 10,000 exposures). Sharing needles or needlestick injuries result in transmission in 50 per 10,000 exposures.
- Among sexual practices, unprotected anal receptive intercourse carries the highest risk of transmission (138 per 10,000 exposures), followed by insertive anal intercourse, vaginal receptive intercourse, and vaginal insertive intercourse. Oral intercourse carries a lower risk of transmission.

Prevention

- HIV transmission can be prevented by safe sex practices, which include condom use (male or female) for vaginal, oral, and anal intercourse, decreasing the number of sexual partners, and avoiding needle sharing.
- Postexposure prophylaxis (PEP), or the provision of antiretroviral therapy (ART) after needlestick injury or high-risk sexual exposure, can prevent infection.
- Preexposure prophylaxis (PrEP), or continuous ART in HIV-negative patients, has proven to decrease the rate of HIV transmission. The current guidelines recommend the use of PrEP for the following high-risk groups (*http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf*):
  - MSM
  - Heterosexual HIV-discordant couples
  - Those with multiple sexual partners with inconsistent condom use
  - Commercial sex workers
  - IV drug users
- A combination of emtricitabine-tenofovir is the approved regimen for PrEP. Prior to starting PrEP, it is essential to document a negative HIV test, no signs or symptoms of acute HIV infection, hepatitis B status, and normal renal function. These patients should be followed every 3 months for repeat HIV

testing as well as STI screening, risk reduction counseling, and monitoring of renal and hepatic function.

DIAGNOSIS

Clinical Presentation

- Acute retroviral syndrome is experienced by up to 75% of patients and is similar to other acute viral illnesses such as infectious mononucleosis due to Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infection. Common presenting symptoms of acute retroviral syndrome are fever, sore throat, nonspecific rash, myalgias, headache, and fatigue.

- As the acute illness resolves spontaneously, many people present to care only after OIs (see later section for clinical presentations) occur late in infection once significant immune compromise has occurred (CD4 count <200 cells/μL). Late presentation can be avoided by routine screening.

History

Initial evaluation of persons with a confirmed HIV infection should include the following measures:

- Complete history with emphasis on previous OIs, viral co-infections, and other complications.
- Psychological and psychiatric history. Depression and substance use are common and should be identified and treated as necessary.
- Family and social support assessment.
- Assessment of knowledge and perceptions regarding HIV is also crucial to initiate ongoing education regarding the nature and ramifications of HIV infection.

Physical Examination

A complete physical exam is important to evaluate for manifestations of immune compromise. Initial findings may include the following:

- Oral findings: thrush (oral candidiasis), hairy leukoplakia, aphthous ulcers
- Lymphatic system: generalized lymphadenopathy
- Skin: psoriasis, eosinophilic folliculitis, Kaposi sarcoma, molluscum contagiosum, *Cryptococcus*
- Abdominal exam: evidence of hepatosplenomegaly
- Genital exam: presence of ulcers, genital warts, vaginal discharge, and rectal discharge
- Neurologic exam: note presence of sensory deficits and cognitive testing

Diagnostic Criteria

- The updated CDC guidelines for screening published in June of 2014 recommend the use of the fourth-generation assay, an antigen/antibody test that involves the detection of the p24 antigen as well as antibodies to HIV-1 and HIV-2. The p24 antigen is a viral capsid protein that can be detected as early as 4-10 days from acute infection, up to 2 weeks earlier than the antibody tests alone. An eclipse phase of infection, during which no testing is positive, still exists for up to 7 days after exposure.
- If the fourth-generation assay is positive, then a differentiation test for HIV-1 and HIV-2 antibodies is performed.
- If the HIV-1 and HIV-2 antibody differentiation test is negative for both HIV-1 and HIV-2, then nucleic acid testing (NAT) of HIV-1 RNA via PCR should be performed (Figure 16-1). If the NAT is positive, this indicates acute infection. Viral loads during acute infection are typically in the range of several million copies per milliliter, so a viral load <1000 should be repeated to confirm infection.

Diagnostic Testing

The CDC recommends that **all persons age 13-64 years be offered HIV testing in all health care settings using an opt-out format** (*MMWR Recomm Rep 2006;55:1-17*).

- These recommendations are based on the following considerations: significant individual health benefits if highly active ART (HAART) is initiated earlier in the course of illness, significant public health benefits with knowledge of HIV status leading to changes in risk behaviors, and the availability of inexpensive, reliable, and rapid testing technology.
- **Persons at high risk should be screened for HIV infection at least annually. High-risk groups include** IV drug users, MSM, sexual partners of a known HIV patient, persons involved in sex trading and their sexual partners, persons with STIs, persons who have multiple sexual partners or who engage in unprotected intercourse,

persons who consider themselves at risk, and persons with findings that are suggestive of HIV infection.

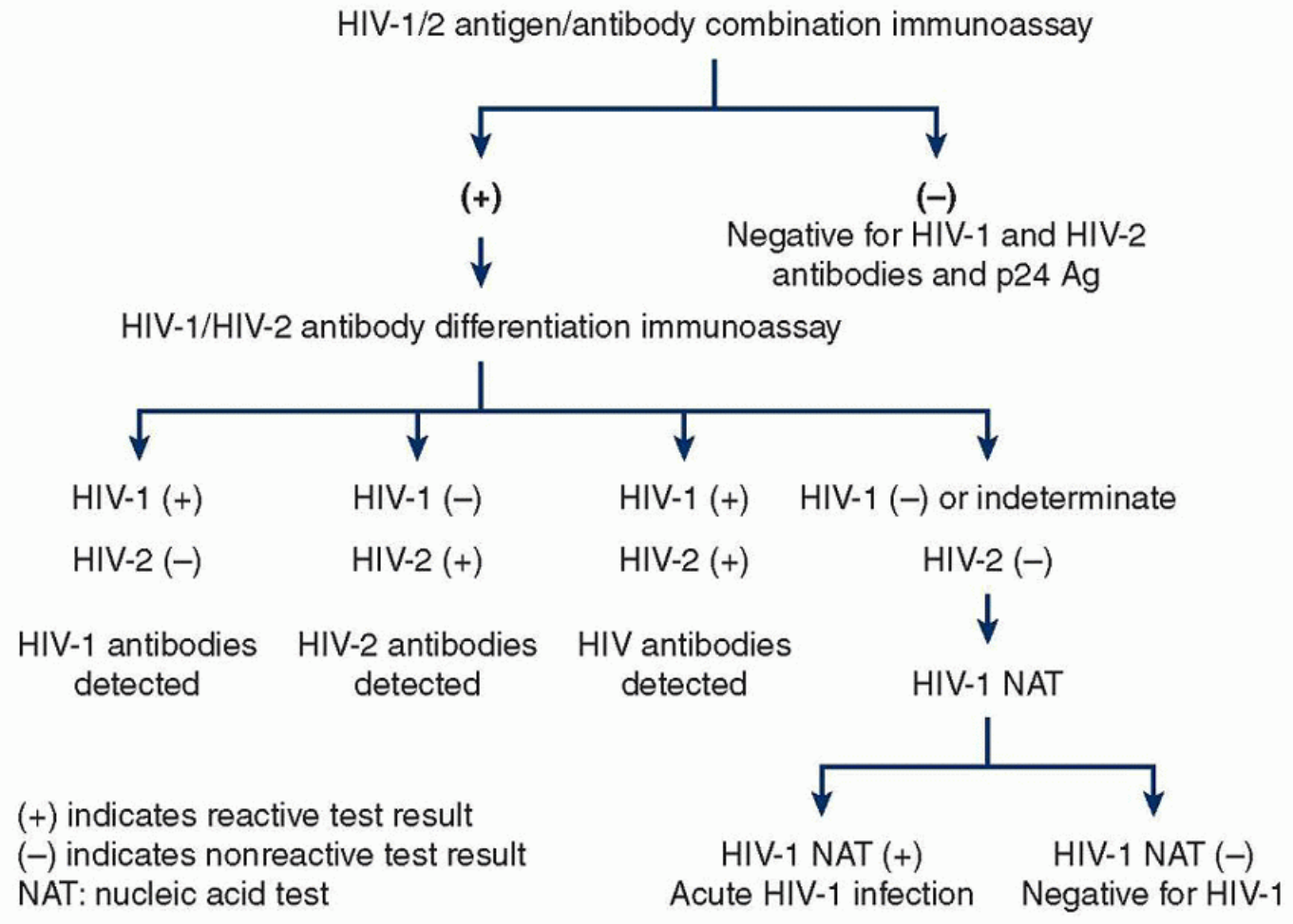


Figure 16-1. Recommended laboratory HIV testing algorithm for serum or plasma specimens. (From Centers for Disease Control and Prevention. National HIV Testing Day and new testing recommendations. *MMWR Morb Mortal Wkly Rep* 2014;63(25):537. Available at: http://www.cdc.gov/hiv/pdf/testingHIValgorithmQuickRef.pdf.)

- Other groups for whom HIV testing is indicated
  - Pregnant women (opt-out screening)
  - Patients with active TB
  - Donors of blood, semen, and organs

- Persons with occupational exposures (e.g., needlesticks) and source patients of the exposures

Laboratories

- **Complete blood cell** (CBC) count and **comprehensive metabolic panel** (CMP) with assessment of liver and kidney parameters, as well as **urinalysis** to evaluate for proteinuria and glycosuria.
- **CD4 cell count** (normal range, 600-1500 cells/μL) and CD4 percentage. Significant immune deficiency requiring prophylactic antibiotics occurs with CD4 <200 cells/μL.
- **Virologic markers:** Plasma HIV RNA predicts the rate of disease progression.
- **Fasting lipid panel.** HIV is associated with an increased risk of metabolic syndrome and cardiovascular disease. Lipids can be affected by several antiretrovirals.
- **TB testing by interferon-γ release assay.**
- **RPR test for syphilis screening, confirmed by fluorescent treponemal antibody assay.**
- ***Toxoplasma* and hepatitis A, B (HBsAg, HBsAb, HBcAb), and C serologies.**
- **Chlamydia/gonococcal urine/cervical probe** for all patients. If patients report receptive anal sex, **rectal probes for gonorrhea and *Chlamydia*** are recommended. For those reporting receptive oral sex, **pharyngeal sample for gonorrhea** should be obtained (*Clin Infect Dis 2009;49:651*). NAAT is preferred.

- **Cervical Papanicolaou smear** (most commonly using the thin prep method).
- **HIV drug resistance testing** for reverse transcriptase, protease, and integrase genes at baseline and with treatment failure.
- **HLA B5701** for patients in whom one is considering the use of abacavir.
- **CCR5** tropism testing for patients in whom one is considering the use of maraviroc.
- **Glucose-6-phosphate dehydrogenase (G6PD) level** on initiation of care or prior to starting therapy with an oxidant drug in those with a predisposing ethnic background.

TREATMENT

Immunizations

- From "Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America" (*http://www.idsociety.org/Organism/#HIV/AIDS*).
- **Pneumococcal vaccine:** HIV infection is an indication for both the pneumococcal conjugate (Prevnar) and polysaccharide (Pneumovax) vaccines. If naïve, the conjugate vaccine should be given initially, then the polysaccharide vaccine after 6 months. Some experts recommend deferring the vaccine until the CD4 cell counts are >200 cells/μL because responses are poor when vaccination occurs with low CD4 cell counts. A single booster Pneumovax after 5 years is recommended.
- **Hepatitis A and B virus (HAV and HBV):** Vaccination for HAV and HBV is recommended if seronegative. Antibody response to these vaccines is improved with undetectable HIV viral load and higher CD4 count.
- **Influenza:** Annual inactivated influenza vaccination is recommended for all HIV-infected patients regardless of CD4 cell count. Use of the intranasally administered, live, attenuated vaccine is not currently recommended for HIV-infected persons.

- **Varicella:** The live, attenuated varicella vaccine (chickenpox, Varivax) can be safely given to persons with CD4 cell counts >200 cells/mL but is contraindicated for persons with CD4 counts <200 cells/mL. There is currently no recommendation to give the zoster vaccine (Zostavax), although recently presented data demonstrated that it was safe and induces effective immune responses in HIV-infected adults with CD4 counts >200 cells/mL. The Advisory Committee on Immunization Practices (ACIP) is expected to revise recommendations based on these study findings.
- **Measles/mumps/rubella (MMR):** MMR is a vaccine that can be safely given to persons with CD4 cell counts >200 cells/μL but is contraindicated for persons with CD4 counts <200 cells/μL.
- **Tetanus/diphtheria/pertussis:** All adults should receive tetanus/diphtheria (Td) booster every 10 years with a one-time substitution with tetanus/diphtheria/acellular pertussis vaccine (Tdap).
- **Human papillomavirus (HPV) vaccine:** HPV-associated malignancies are common in HIV-infected patients. The three-dose vaccine series is safe and effective in HIV-positive subjects and is currently recommended for females age 11-26 years and males age 12-26 years.

Medications

ART

- **Current recommendations from the International AIDS Society-USA (IAS-USA)** (*http://www.iasusa.org/guidelines/*) for the initiation of ART are to treat everyone infected with HIV, although the strength of that recommendation varies with CD4 count and the presence of co-infections or symptoms.
- Treatment decisions should be individualized by patient readiness, drug interactions, adherence issues, drug toxicities, comorbidities, and the level of risk indicated by CD4 T-cell counts.

- Women, especially if pregnant, should receive optimal ART to reduce the risk of vertical transmission.
- Maximal and durable suppression of HIV replication is the goal of therapy once it is initiated. **HAART** should be individualized and closely monitored by measuring plasma HIV viral load. Reductions in plasma viremia correlate with increased CD4 cell counts and prolonged AIDS-free survival. Isolated viral “blips” are not indicative of virologic failure, but confirmed virologic rebound should trigger an evaluation of adherence, drug interactions, and viral resistance.
- Any change in ART increases future therapeutic constraints and potential drug resistance.
- **Antiretroviral drugs:** Approved antiretroviral drugs are grouped into five categories. Experts currently recommend using three active drugs from two different classes to maximally and durably suppress HIV viremia.
  - **Nucleotide and nucleoside reverse transcriptase inhibitors (NRTIs)** constrain HIV replication by incorporating into the elongating strand of DNA, causing chain termination. All nucleoside analogs have been associated with **lactic acidosis**, presumably related to mitochondrial toxicity, although current recommended NRTIs have low incidence.
  - **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** inhibit HIV by binding noncompetitively to the reverse transcriptase. A single dosage of nevirapine at the time of labor has been shown to decrease perinatal transmission of the virus. Side effects of NNRTIs include rash, hepatotoxicity, and Stevens-Johnson syndrome (more likely with nevirapine). Central nervous system (CNS) side effects are commonly experienced with the use of efavirenz.
  - **Integrase strand transfer inhibitors (INSTIs)** target DNA strand transfer and integration into a human genome. They tend to have better safety and tolerability profiles than other classes and are

associated with a rapid decrease in viral load after initiation. Elvitegravir requires coadministration of the pharmacologic booster, cobicistat, which leads to increased incidence of gastrointestinal (GI) intolerance. Due to its interaction with the cytochrome P450 system, **cobicistat has important drug interactions** that should be evaluated. Few drug interactions exist with the other INSTIs, raltegravir and dolutegravir.

- **Protease inhibitors (PIs)** block the action of the viral protease required for protein processing late in the viral cycle. GI intolerance is one of the most commonly encountered adverse effects. All PIs can produce increased bleeding in hemophiliacs. These agents have also been associated with metabolic abnormalities such as glucose intolerance, increased cholesterol and triglycerides, and body fat redistribution. Boosting with ritonavir is a common practice to achieve better therapeutic concentrations. Due to its metabolism via cytochrome P450, **boosted PIs have important drug interactions**, and concomitant medications should be reviewed carefully.
- **HIV entry inhibitors** target different stages of the HIV entry process. Two drugs are available in this class. **Enfuvirtide (T-20)** is a fusion inhibitor that prevents the fusion of the virus into the host cell. T-20 is only available for use as an SC injection, 90 mg bid. The most frequent side effect for T-20 is a significant local site reaction after the injection. **Maraviroc** is a CCR5 receptor blocker. Initiation of CCR5 inhibitor requires baseline determination of HIV coreceptor tropism (CCR5 or CXCR4).

- **Initial therapy:** ART should be started in an outpatient setting by a physician with expertise in the management of HIV infection. Adherence is the key factor for success. Treatment should be individualized and adapted to the patient's lifestyle and comorbidities. Any treatment decision influences future therapeutic options because of the possibility of drug cross-resistance. **Potent initial ART generally consists of a combination of two NRTIs, usually plus an NNRTI, an INSTI, or a boosted PI. It should be noted that many of the first-line regimens are co-formulated as single-tablet daily regimens. Current first-line regimens are listed below:**
  - **Atripla: co-formulated tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC) and efavirenz (NNRTI-based regimen)**

  - **Complera: co-formulated TDF/FTC and rilpivirine (NNRTI-based regimen, recommended for those with initial viral loads <100,000 copies/mL)**
  - **Stribild: co-formulated TDF/FTC, elvitegravir, and cobicistat (INSTI based)**
  - **Triumeq: co-formulated abacavir, epivir, and dolutegravir (INSTI based)**
  - **TDF/FTC with ritonavir-boosted atazanavir (PI based)**
  - **TDF/FTC with ritonavir-boosted darunavir (PI based)**
- **Treatment monitoring:** After starting or changing ART, the viral load should be checked at 4-6 weeks with an expected 10-fold reduction (1.0 $\log_{10}$) and suppression to <50 copies/mL by 24 weeks of therapy. The regimen should then be reassessed if response to treatment is inadequate. When the HIV RNA becomes undetectable and the patient is on a stable regimen, monitoring can be done every 3-6 months.
- **Treatment failure** is defined as less than a log (10-fold) reduction of the viral load 4-6 weeks after starting a new antiretroviral regimen; failure to reach an undetectable viral load after 6 months of treatment; detection of the virus after initial complete suppression of viral load, which suggests development of resistance; or persistent decline of CD4 cell count or clinical deterioration. Confirmed treatment failure should prompt changes in HAART based on results of genotype testing. In this situation, at least two of the drugs should be substituted with other drugs that have no expected cross-resistance. **HIV resistance testing** at this stage may help determine a salvage regimen in patients with prior ART.

The importance of adherence should be stressed. Referral to an HIV specialist is highly recommended in this situation.

- **Drug interactions:** Antiretroviral medications, especially PIs, have multiple drug interactions. **PIs and cobicistat both inhibit and induce the P450 system**, and thus interactions are frequent with other inhibitors of the P450 system, including macrolides (erythromycin, clarithromycin) and antifungals (ketoconazole, itraconazole), as well as other inducers such as rifamycins (rifampin, rifabutin) and anticonvulsants (phenobarbital, phenytoin, carbamazepine). **Drugs with narrow therapeutic indices that should be avoided or used with extreme caution** include antihistamines (although loratadine is safe), antiarrhythmics (flecainide, encainide, quinidine), long-acting opiates (fentanyl, meperidine), long-acting benzodiazepines (midazolam, triazolam), warfarin, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (pravastatin is the safest), and oral contraceptives. Sildenafil concentrations are increased, whereas methadone and theophylline concentrations are decreased with concomitant administration of certain PIs and NNRTIs.

COMPLICATIONS

Complications of ART: The long-term use of antiretrovirals has been associated with toxicity, the pathogenesis of which is only partially understood at this time.

- **Hyperlipidemia**, especially hypertriglyceridemia, is associated mainly with PIs (especially ritonavir). Improvement has been seen after treatment with atorvastatin, pravastatin, and/or gemfibrozil.
- **Peripheral insulin resistance, impaired glucose tolerance, and hyperglycemia** have been associated with the use of PI-based regimens, mainly indinavir and ritonavir. Lifestyle changes or changing ART can be considered in these cases.
- **Osteopenia and osteoporosis** are well described in HIV-infected individuals. The pathogenic mechanism of this problem is likely related to the inflammatory milieu of HIV itself, although the use of TDF may contribute.
- **Osteonecrosis**, particularly of the hip, has been increasingly associated with HIV disease.
- **Lipodystrophy syndrome** is an alteration in body fat distribution and can be stigmatizing to individuals. Changes consist of the accumulation of visceral fat in the abdomen, neck (buffalo hump), and pelvic areas, and/or the depletion of SC fat, causing facial or

peripheral wasting. Lipodystrophy has been associated in particular with older PIs and NRTIs and is uncommon with currently recommended regimens

- **Lactic acidosis** with liver steatosis is a rare but sometimes fatal complication associated with NRTIs. The mechanism appears to be part of mitochondrial toxicity. Higher rates of lactic acidosis have been reported with the use of the older drugs stavudine and didanosine.

SPECIAL POPULATIONS

Pregnancy

- Maximally suppressive ART during pregnancy is critical in preventing mother-to-child transmission.
- Current guidelines (*http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0*) recommend that all HIV-infected partners in a couple planning pregnancy should attain virologic suppression before attempting conception.

Periconception PrEP for the HIV-uninfected partner may provide additional protection to reduce the risk of sexual transmission and should be discussed with the couple.

- If a pregnant woman is already suppressed on ART and is tolerating that regimen, she should be maintained on her current ART regardless of the agents (including efavirenz).
- ART-naïve pregnant women should be started on a combination regimen of TDF/FTC with boosted atazanavir, boosted lopinavir, or raltegravir. Nevirapine has been associated with hepatotoxicity and should be avoided in those with preexisting liver disease or high CD4 count.
- Intrapartum IV zidovudine should be given to women during labor, although it is not required for women with consistent undetectable viral loads in late pregnancy.
- Cesarean delivery should be scheduled for women with HIV viral loads >1000 in late pregnancy.
- ART should be continued after delivery, consistent with current guidelines to treat everyone to prevent disease progression and HIV transmission.
- Neonatal zidovudine prophylaxis should be given for 4 weeks if the mother has maintained virologic suppression. Neonatal prophylaxis using zidovudine and nevirapine should be offered if the mother did not receive antepartum suppressive ART.

Acute HIV Infection

ART given immediately after diagnosing acute infection may provide additional benefits.

- The initiation of early ART in acute infection will suppress the extraordinarily high viral loads seen at this time and reduce further transmission of HIV.
- Early ART may reduce the reservoir of latent virus.
- Early ART maintains immune function and may allow for immunologic control of HIV off ART in some settings.

Hepatitis

- High rates of coinfection with HBV and hepatitis C virus (HCV) occur in HIV-infected patients.
- Several HIV ART medications (tenofovir, emtricitabine, and lamivudine) also have activity against HBV. Any plan to treat HBV in co-infected patients should ensure that the regimen is fully active against both HIV and HBV. Discontinuation of ART that has been suppressing unrecognized HBV disease can result in reactivation of HBV with resultant acute, and sometimes fatal, HBV infection.
- HCV therapy is rapidly evolving, and a complete delineation of treatment is available in Chapter 19, Liver Diseases.
- Older interferon-based therapy had a minor effect on HIV viral load, with approximately one or two log-reductions in HIV while on therapy. It was not well tolerated and worked

poorly in HIV-infected patients, with most studies showing only 15% of patients with sustained virologic response.

- Newer directly acting HCV agents appear to be as effective in HIV-infected patients as in monoinfected HCV patients; however, there are significant drug-drug interactions that should be considered, particularly with PI-based therapy, efavirenz, and therapy using the boosting agent cobicistat.

Aging

- With the success of ART, HIV-related mortality is decreasing and HIV-infected persons are experiencing prolonged survival.
- The CDC estimates that, in 2015, one-half of all HIV-infected persons will be over the age of 50 years.
- HIV infection is associated with premature end-organ disease, and thus many of the comorbidities associated with aging may be exacerbated in this growing population, including cardiovascular disease, insulin resistance and diabetes, osteoporosis, neurocognitive impairment, and physical frailty.
- Certain non-AIDS-defining cancers are more common in HIV-infected patients, including anal cancer, lung cancer, and hepatocellular carcinoma. The extent to which this is due to HIV infection versus other risk factors like smoking and hepatitis co-infection is unclear.
- The role of long-term HIV infection and ART use in these comorbidities is poorly understood, although the use of NNRTI and PI drug classes is associated with lipid profiles that may exacerbate cardiovascular disease (*AIDS 2003;17:1179*). Higher rates of smoking and alcohol use also exacerbate these comorbidities.

REFERRAL

- All HIV positive patients should be referred to a HIV specialist, if possible.
- Counseling regarding contraception, safer sex practices, medication adherence, and proper health maintenance is essential.
- Social work referral is important to ensure adequate social support system including housing, mental health assistance, and substance abuse treatment

OUTCOME/PROGNOSIS

With the advent of potent HAART, which causes durable virologic suppression and reconstitution of the immune system, the mortality among HIV-infected persons continues to decline. In the modern era of HAART, noninfectious conditions start to play a much more important role in the mortality among persons with HIV (*AIDS 2007;21(15):2093*).

Opportunistic Infections

GENERAL PRINCIPLES

- Potent ART has decreased the incidence, changed the manifestations, and improved the outcome of OIs.
- A clinical syndrome associated with the immune enhancement induced by potent ART, **immune reconstitution syndrome (IRIS)**, generally presents as local inflammatory reactions. Examples include recurrent symptoms of cryptococcal meningitis, paradoxical reactions with TB reactivation, localized *Mycobacterium avium* complex (MAC) adenitis, aggravation of hepatitis viral infection, and CMV vitreitis immediately after the initiation of potent ART.
- In the case of IRIS, ART is usually continued, and the addition of low-dose steroids might decrease the degree of inflammation. TB and cryptococcal meningitis are the only OIs for which delay of ART is recommended to prevent IRIS.

- Additional details with updates may be found in the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (*http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf*).

TREATMENT

- **Prophylaxis for OIs** can be divided into primary and secondary prophylaxis.
- **Primary prophylaxis** is established before an episode of OI occurs. Institution of primary prophylaxis depends on the level of immunosuppression as judged by the patient's CD4 cell count and percentage (Table 16-2).
- **Secondary prophylaxis** is instituted after an episode of infection has been adequately treated. Most OIs will require extended therapy.
- **Withdrawal of prophylaxis:** Recommendations suggest withdrawing primary and secondary prophylaxis for most OIs if sustained immunologic recovery has occurred (CD4 cell counts consistently >150-200 cells/μL) (*MMWR Recomm Rep 2009;58(RR-4):1*).

PULMONARY SYNDROMES

Pneumocystis jirovecii Pneumonia

General Principles

Pneumocystis jirovecii pneumonia (PCP) is the most common infection in patients with AIDS and is the leading cause of death in this population.

Diagnosis

Positive direct immunofluorescent stain from induced sputum samples or bronchoalveolar lavage fluid. Alternatively, histopathologic demonstration of organisms in tissue is also adequate for diagnosis.

TABLE 16-2 Opportunistic Infection Prophylaxis

Opportunistic Infection	Indications for Prophylaxis	Medications
PCP	CD4 <200 cells/μL	TMP-SMX DS PO daily or three times per week one tablet daily, is the preferred regimen Alternatives: dapsone[a], atovaquone, aerosolized pentamidine
Toxoplasmosis[b]	CD4 <100 cells/μL,	TMP-SMX DS PO daily Alternatives: combination of dapsone + pyrimethamine and leucovorin; atovaquone
Mycobacterium avium complex prophylaxis	CD4 cell count <50 cells/μL	Azithromycin 1200 mg PO weekly Alternatives: clarithromycin or rifabutin

DS, double strength; PCP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Glucose-6-phosphate dehydrogenase (G6PD) testing should be done for dapsone.

[b] If toxoplasmosis IgG is positive.

Treatment

- **Trimethoprim-sulfamethoxazole (TMP-SMX)** is the treatment of choice. The dosage is 15-20 mg/kg of the TMP component IV daily, divided q6-8h for severe cases, with a switch to oral therapy when the patient's condition improves. Total duration of therapy is 21 days. Prednisone should be added with severe disease as defined below. For patients who cannot receive TMP-SMX, the following alternatives are available:
  - For mild to moderately severe disease (arterial oxygen tension [PaO_2] >70 mm Hg or alveolar arterial oxygen gradient [$P(A\text{-}a)O_2$] <35 mm Hg):
    - TMP, 5 mg/kg PO q8h, and dapsone, 100 mg PO daily. G6PD deficiency should be ruled out before dapsone is used.
    - Clindamycin, 600 mg IV or PO q8h, plus primaquine, 30 mg PO daily. G6PD deficiency should be ruled out before primaquine is used.
    - Atovaquone, 750 mg PO q8h. This drug should be administered with meals to increase absorption.
  - For severe disease (PaO_2 <70 mm Hg or $P[A\text{-}a]O_2$ >35 mm Hg):
    - Prednisone taper should be added. The most frequently prescribed prednisone regimen is 40 mg PO bid on days 1-5 and 40 mg daily on days 6-10, followed by 20 mg on days 11-21.
    - IV pentamidine is used in cases when all other options are exhausted and requires close monitoring for side effects.
- Primary prophylaxis is indicated (see Table 16-2). Secondary PCP prophylaxis can be discontinued if the CD4 count is >200 cells/μL for more than 3 months as a result of ART.

Mycobacterium tuberculosis

General Principles

M. tuberculosis is more frequent among HIV-infected patients, particularly IV drug abusers. Primary or reactivated disease is common (*MMWR Recomm Rep 2009;58(RR-4):1*).

Diagnosis

- Clinical manifestations depend on the level of immunosuppression. Patients with higher CD4 cell counts tend to exhibit classic presentations with **apical cavitary disease**.
- Profoundly immunosuppressed patients may demonstrate atypical presentations that can resemble disseminated primary infection, with diffuse or localized pulmonary infiltrates and hilar lymphadenopathy.
- Extrapulmonary dissemination is more common in patients with HIV.

Treatment

- For treatment recommendations, see Chapter 14, Treatment of Infectious Diseases.
- Current recommendations suggest the **substitution of rifabutin for rifampin** in patients who are receiving concomitant ART, especially PIs. The dosage for rifabutin needs readjustment due to many significant interactions (*http://www.hivmedicationguide.com/*). In subjects who are ART naïve, ART can be delayed for a few weeks after TB-specific therapy is started.

FEBRILE SYNDROMES

M. avium Complex Infection

General Principles

MAC infection is the most commonly occurring mycobacterial infection in AIDS patients and is responsible for significant morbidity in patients with advanced disease (CD4 cell count <100 cells/μL).

Diagnosis

Clinical Presentation

- Disseminated infection with fever, weight loss, and night sweats is the most frequent presentation.
- MAC infection can result in bacteremia in AIDS patients.

Diagnostic Testing

- Anemia and an elevated alkaline phosphatase level are the usual laboratory abnormalities.
- Mycobacterial blood cultures should be sent in suspected cases.

Treatment

- Initial therapy should include a **macrolide** (i.e., clarithromycin, 500 mg PO bid) and **ethambutol**, 15 mg/kg PO daily.
- Rifabutin, 300 mg PO daily, or a fluoroquinolone can be added in severe cases and based on sensitivities.
- Secondary prophylaxis for disseminated MAC can be discontinued if the CD4 count has a sustained increase >100 cells/μL for 6 months or longer in response to ART, and if 12 months of therapy for MAC is completed and there are no symptoms or signs attributable to MAC.

Histoplasma capsulatum Infections

General Principles

- The severity of infection depends on the degree of the patient's immunosuppression.
- Histoplasmosis often occurs in AIDS patients who live in endemic areas such as the Mississippi and Ohio River Valleys.
- Such infections are usually disseminated at the time of diagnosis.

Diagnosis

- Suspect histoplasmosis in patients with fever, hepatosplenomegaly, and weight loss.
- Pancytopenia develops due to bone marrow involvement.
- Diagnosis is made by a positive culture or biopsy demonstrating 2-4 µm budding yeast, but the urine and serum *Histoplasma* antigens can also be used for diagnosis and to monitor treatment.

Treatment

- Disseminated disease is treated with **liposomal amphotericin B**, 3 mg/kg IV daily for 2 weeks or until the patient clinically improves, followed by **itraconazole**, 200 mg PO bid indefinitely.
- CNS disease is initially treated with **liposomal amphotericin B**, 5 mg/kg IV daily for 4-6 weeks, before starting itraconazole.
- Itraconazole absorption should be documented by a serum drug level.
- Discontinuation of itraconazole is possible if sustained increase in CD4 count is observed >100-200 cells/µL for more than 6 months.

Other Causes of Febrile Illness

- Bacterial infection and sepsis are more common in HIV-infected patients.
- Bacterial pneumonia, especially due to pneumococcus.
- Other disseminated fungal infections, depending on local incidence, including *Cryptococcus*, *Penicillium*, and *Coccidioides.*
- CMV and other disseminated herpes viral infections.

CENTRAL NERVOUS SYSTEM AND RETINAL DISEASE

Cryptococcus neoformans

General Principles

- The severity of infection depends on the degree of the patient's immunosuppression.
- **Cryptococcal meningitis** is the most frequent CNS fungal infection in AIDS patients.

Diagnosis

- Patients with CNS infection usually present with headaches, fever, and possibly mental status changes, but presentation can be more subtle.
- Cryptococcal infection can also present as pulmonary or cutaneous disease.
- Diagnosis is based on **lumbar puncture** results and on the determination of latex cryptococcal antigen, which is usually positive in the serum and in the CSF.
- **CSF opening pressure** should always be measured to assess the possibility of elevated intracranial pressure.

Treatment

- Initial treatment is with a lipid preparation of **amphotericin** dosed at 3-4 mg/kg/d IV, and **5-flucytosine**, 25 mg/kg PO q6h for at least 2 weeks, followed by **fluconazole**, 400 mg PO daily for at least 8 weeks and then 200 mg PO daily, either lifelong or until immune reconstitution occurs. Fluconazole can be discontinued in those who are asymptomatic with regard to signs and symptoms of cryptococcosis and have a sustained increase (>6 months) in their CD4+ counts to ≥200 cells/μL.
- The 5-flucytosine level should be monitored during therapy to avoid toxicity.
- Alternative initial therapy is with amphotericin B, 0.7 mg/kg/d IV, and flucytosine, 25 mg/kg PO q6h. Repeat lumbar punctures (removing up to 30 mL CSF until the pressure is <20-25 cm H_2O) may be required to relieve elevated intracranial pressure.
- In persons who have persistent elevation of intracranial pressure, a temporary lumbar drain is indicated.

Toxoplasma gondii

Diagnosis

Toxoplasmosis typically causes multiple CNS lesions and presents with encephalopathy and focal neurologic findings.

Diagnostic Testing

Laboratories

Disease represents reactivation of a previous infection, and the serologic workup is usually positive.

Imaging

- MRI of the brain is the best radiographic technique for diagnosis.
- Often the diagnosis relies on response to empiric treatment, as seen by a reduction in the size of the mass lesions.

Treatment

- **Sulfadiazine**, 25 mg/kg PO q6h, plus **pyrimethamine**, 200 mg PO on day 1, followed by 75 mg PO daily, is the therapy of choice.
- **Leucovorin**, 5-10 mg PO daily, should be added to prevent hematologic toxicity.
- For patients who are allergic to sulfonamides, clindamycin, 600 mg IV or PO q8h, can be used instead of sulfadiazine.
- Doses are reduced after 6 weeks of therapy.
- Secondary prophylaxis can be discontinued among patients with a sustained increase in CD4 count >200 cells/μL for more than 6 months as a result of response to ART and if the initial therapy is complete and there are no symptoms or signs attributable to toxoplasmosis.

Varicella-Zoster Virus

Diagnosis

- Varicella-zoster virus may cause typical dermatomal lesions or disseminated infection including retinal necrosis.
- May cause encephalitis, which is more common with ophthalmic distribution of facial nerve.

Treatment

Acyclovir, 10 mg/kg IV q8h for 7-14 days, is the recommended therapy. For milder cases, administration of acyclovir (800 mg PO five times a day), famciclovir (500 mg PO tid), or valacyclovir (1 g PO tid) for 1 week is usually effective.

JC Virus

Diagnosis

- Associated with progressive multifocal leukoencephalopathy. Symptoms include mental status changes, weakness, and disorders of gait.
- Characteristic periventricular and subcortical white matter lesions are seen on MRI.

Treatment

Potent ART has improved the survival of patients with progressive multifocal leukoencephalopathy.

CMV Retinitis

CMV retinitis accounts for 85% of CMV disease in patients with AIDS. It commonly develops in a setting of profound CD4 depletions (CD4 cell count <50 cells/μL).

Diagnosis

- CMV viremia can be detected by PCR and is usually present in end-organ disease but can also be seen in the absence of end-organ disease.
- The diagnosis of CMV retinitis is made based on characteristic findings during ophthalmoscopic exam.

Treatment

- Treatment of CMV retinitis can be local or systemic and is administered in two phases, induction and maintenance.
- **Ganciclovir** is given at an induction dosage of 5 mg/kg IV bid for 14-21 days and a maintenance dosage of 5 mg/kg IV daily indefinitely (unless immune reconstitution occurs). The most common side effect of ganciclovir is **myelotoxicity**, resulting in neutropenia. The neutropenia may respond to granulocyte colony-stimulating factor therapy. An intraocular ganciclovir implant is effective but does not provide systemic CMV therapy.

- **Valganciclovir**, a ganciclovir prodrug, has drug levels equivalent to those of IV ganciclovir. For induction, 900 mg PO bid for 14-21 days is given, followed by 900 mg once a day. **Treatment is indefinite unless immunologic recovery occurs.** Adverse effects are similar to those of ganciclovir.
- Alternatives include **IV foscarnet, IV cidofovir, and intraocular fomivirsen** (which does not provide systemic therapy). Both IV foscarnet and cidofovir administrations carry a significant risk of **nephrotoxicity**; therefore, adequate hydration and electrolyte monitoring (including calcium) are required.
- For other **invasive CMV disease**, the optimal therapy is with IV ganciclovir, PO valganciclovir, IV foscarnet, or a combination of two drugs (in persons with prior anti-CMV therapy), for at least 3-6 weeks. Foscarnet has the best CSF penetration and is the drug of choice for CMV encephalitis and myelopathy. Long-term maintenance therapy is indicated.

ESOPHAGITIS

Candida

General Principles

- The severity of infection depends on the degree of the patient's immunosuppression.
- Candidiasis is common in the HIV-infected host.
- Other causes of esophagitis include HSV, CMV, and *Histoplasma*.

Diagnosis

Location of infection can be oral, esophageal, or vaginal.

Treatment

- Oral and vaginal candidiasis usually responds to local therapy with troches or creams **(nystatin** or **clotrimazole)**.
- For patients who do not respond or who have esophageal candidiasis, **fluconazole**, 100-200 mg PO daily, is the treatment of choice.

Special Considerations

Fluconazole-resistant candidiasis is increasing, especially in patients with advanced disease who have been receiving antifungal agents for prolonged periods.

- **Caspofungin or micafungin**, echinocandins, can be considered for refractory cases.
- **Itraconazole** oral suspension (200 mg bid) is occasionally effective, as is **posaconazole** oral solution, and posaconazole is generally better tolerated than itraconazole. **Voriconazole** may also be useful.

DIARRHEA

Cryptosporidium

Diagnosis

- *Cryptosporidium* causes chronic watery diarrhea with malabsorption in HIV-infected patients.
- Diagnosis is based on the visualization of the parasite in an acid-fast stain of stool.

Treatment

- No effective specific therapy has been developed as ART is essential.
- **Nitazoxanide**, 500 mg PO bid, may be effective.

Cyclospora, Isospora, Microsporidia, and Campylobacter jejuni

Diagnosis

These organisms cause chronic diarrhea. Microsporidia can also cause biliary tree disease in patients with advanced infection.

Treatment

- *Cyclospora* is treated with **TMP-SMX**, one double-strength (DS) tablet PO bid for 7-10 days. *Isospora* is treated with **TMP-SMX**, one DS tablet PO qid for 10 days, followed by chronic suppression with TMP-SMX, one DS tablet PO daily.
- Microsporidia are treated with **albendazole**, 400 mg PO bid, but this regimen has only modest success for *Enterocytozoon bieneusi* infections. Relapses are common when therapy is stopped.
- *C. jejuni* is treated with either azithromycin, 500 mg PO daily, or ciprofloxacin, 500-750 mg PO bid.

ASSOCIATED NEOPLASMS

Kaposi Sarcoma

GENERAL PRINCIPLES

Kaposi sarcoma is caused by co-infection with human herpesvirus-8 (HHV-8), also called Kaposi sarcoma-associated herpesvirus (KSHV).

DIAGNOSIS

In AIDS patients, it commonly presents as cutaneous lesions, but can be disseminated. The GI tract and lungs are the usual visceral organs involved.

TREATMENT

- Local therapy with **liquid nitrogen** or intralesional injection with alitretinoin or vinblastine has been used. Cryotherapy or radiation may be useful as well.

- Systemic therapy involves chemotherapy (e.g., liposomal doxorubicin, paclitaxel, liposomal daunorubicin, thalidomide, retinoids), radiation, and interferon-α.

Lymphoma

GENERAL PRINCIPLES

- Lymphomas commonly associated with AIDS are non-Hodgkin lymphoma, CNS and systemic lymphoma, and lymphomas of B-cell origin.
- **EBV** appears to be the associated pathogen.

DIAGNOSIS

- Primary CNS lymphomas are common and can be multicentric.
- Diagnosis is based on clinical symptoms, the presence of enhancing brain lesions, brain biopsy, and a positive EBV-PCR of the CSF.
- Other OIs need to be ruled out.
- Other potential extranodal sites of involvement including bone marrow, GI tract, and liver require tissue biopsy to confirm the diagnosis.

TREATMENT

Treatment involves **chemotherapy** and **radiation**.

Cervical and Perianal Neoplasias

GENERAL PRINCIPLES

- Both HIV-infected men and women are at high risk for HPV-related disease.
- Certain HPV subtypes such as 16 and 18 are oncogenic.
- Cancer can also arise from perianal condyloma acuminata.

DIAGNOSIS

- Screening for vaginal dysplasia with a Papanicolaou smear is indicated every 6 months during the first year and, if results are normal, annually thereafter.
- Screening for anal intraepithelial neoplasms is currently under evaluation and is recommended by some experts in populations such as MSM, any patient with a history of anogenital condylomas, and women with abnormal vulvar or cervical histology (*http://hivguidelines.org/Content.aspx*).

TREATMENT

Refer to Chapter 22, Cancer, for specific treatments of these neoplasms.

SEXUALLY TRANSMITTED INFECTIONS IN PATIENTS WITH HIV

For treatment, see Table 16-1.

Genital Herpes

HIV-infected individuals are more likely to have prolonged and severe disease as well as treatment failures due to the development of resistance. Treatment guidelines are slightly different for HIV-infected patients. See Table 16-1.

Genital Warts

GENERAL PRINCIPLES

Genital warts are caused by HPV. Different serotypes have been associated with the lesions, notably types 6 and 11. Other common HPV types (16, 18, 31, and 33) are associated with malignant transformation in different anatomic sites. Genital warts in HIV-infected persons are typically more resistant to treatment and have a higher chance of recurrence (*http://www.cdc.gov/STD/treatment/2006/genital-warts.htm*).

DIAGNOSIS

Diagnosis is made on the basis of physical exam and history. In some situations, biopsy of the lesions may be necessary.

TREATMENT

Local therapy is aimed at the removal of the warts. HPV vaccination is recommended in women and men under the age of 27 (see previous section on immunizations).

Syphilis

See the section on STIs for more complete information.

Additional Resources

- *www.aifsinfo.org*
- *www.aidsmeds.com*
- *www.thebody.com*
- *www.hivmedicine.com*
- *www.hivinsite.ucsf.edu*

17
Solid Organ Transplant Medicine

Rupinder Sodhi

Rowena Delos Santos

Solid Organ Transplant Basics

GENERAL PRINCIPLES

- Solid organ transplantation is a **treatment, not a cure**, for end-stage organ failure of the kidney, liver, pancreas, heart, and lung. Small intestine and vascularized composite allografts are performed in smaller numbers at specialized centers throughout the country. The benefits of organ replacement coexist with the risks of chronic immunosuppression. Thus, not all patients with organ failure are transplant candidates.
- Organs remain in short supply with increasing waiting times for potential recipients. **Living-donor transplants** are increasingly common in kidney transplantation and are being evaluated in liver and lung transplantation as a partial solution to this shortage. Xenotransplantation is **not** currently a viable option.
- **Immunologic considerations** prior to the transplant must be fully evaluated, including ABO compatibility with the donor, HLA typing, and some degree of immune response testing to the proposed donor. Newer protocols using desensitization techniques have had some success in overcoming these immunologic barriers.

DIAGNOSIS

- For indications and contraindications of heart, lung, kidney, and liver transplantations, see sections devoted to cardiology, pulmonology, nephrology, and hepatology.
- **Evaluation of the transplant patient.** The evaluation of the transplant recipient with general medical or surgical problems should encompass the details of the patient's organ transplant and treatment. Thus, the following should always be reviewed when taking a history from an organ transplant recipient:
  - Cause of organ failure
  - Treatment for organ failure prior to transplantation
  - Type and date of transplant
  - Cytomegalovirus (CMV) serology of donor and recipient
  - Induction immunosuppression, particularly use of antibody-based induction therapy
  - Initial allograft function (e.g., nadir creatinine, forced expiratory volume in 1 second [FEV_1], ejection fraction, synthetic function, and transaminases)
  - Current allograft function
  - Complications of transplantation (e.g., surgical problems, acute rejection, delayed graft function, infections, chronic organ dysfunction)
  - Current immunosuppression regimen and recent drug levels

TREATMENT

- **Immunosuppression.** Immunosuppressive medications are used to promote acceptance of a graft

(induction therapy), to prevent rejection (maintenance therapy), and to reverse episodes of acute rejection (rejection therapy). These agents are associated with

immunosuppressive effects, immunodeficiency toxicities (e.g., infection and malignancy), and nonimmune toxicities (e.g., nephrotoxicity, diabetes mellitus, bone disease, gout, hyperlipidemia, cardiovascular disease, or neurotoxicity) (*N Engl J Med 2004;351:2715*). Immunosuppressive medications should only be prescribed and administered by physicians and nurses who have appropriate knowledge and expertise. Many variables factor into the choice and dose of drug, and the guidelines for each specific organ are different.

- **Glucocorticoids.** Glucocorticoids are immunosuppressive and anti-inflammatory. Their mechanisms of action include inhibition of cytokine transcription, induction of lymphocyte apoptosis, downregulation of adhesion molecule and major histocompatibility complex expression, and modification of leukocyte trafficking (*N Engl J Med 2005;353:1711*).
  - Side effects of chronic glucocorticoid therapy are well known.
  - As a result of the associated morbidity, steroids are tapered rapidly in the immediate posttransplant period to achieve maintenance doses of 0.1 mg/kg or less.
  - Further strategies are being developed to minimize side effects: steroid-free immunosuppression, rapid steroid tapering, and steroid withdrawal.
  - Although most long-term transplant recipients have abnormalities in the adrenal axis, increases in glucocorticoid therapy are not indicated for routine surgery or illness (*Arch Surg 2008;143:1222*).
- **Antiproliferative agents**
  - **Azathioprine** is a purine analog that is metabolized by the liver to 6-mercaptopurine (active drug), which in turn is catabolized by xanthine oxidase. Azathioprine inhibits DNA synthesis and thereby suppresses lymphocyte proliferation. The major dose-limiting toxicity of this agent is myelosuppression, which is usually reversible after dose reduction or discontinuation of the drug. The usual maintenance dose is 1.5-2.5 mg/kg/d in a single dose. Drug levels are generally not obtained. Azathioprine is generally considered safe in pregnancy.
  - **Mycophenolic acid (MPA)** is available in two forms: MPA or its precursor, mycophenolate mofetil (which is converted to the active metabolite, MPA). MPA inhibits the rate-limiting step in de novo purine synthesis. Because lymphocytes are dependent on the de novo pathway for purine synthesis, lymphocyte proliferation is selectively inhibited by MPA.
  - **Major adverse effects** of MPA are gastrointestinal disturbances (nausea, diarrhea, and abdominal pain) and hematologic disturbances (leukopenia and thrombocytopenia).
  - Antacids that contain magnesium and aluminum interfere with the absorption of MPA and should not be given concurrently.
  - Proton pump inhibitors can also interfere with the bioavailability of mycophenolate mofetil, but not enteric-coated MPA, which is absorbed in the small intestine.
  - MPA is not used in pregnancy due to its teratogenicity in animal models.
  - The usual dose is 1-2 g daily in divided doses, although lesser doses may be used with concomitant tacrolimus than cyclosporine (CsA), because of enterohepatic circulation affecting MPA levels. Additionally, the dosage of MPA should be reduced in chronic renal impairment. Drug levels can be obtained to verify absorption or compliance, but the clinical utility of MPA levels has not been determined.

- **Mammalian target of rapamycin (mTOR) inhibitors.** Sirolimus and everolimus inhibit the activation of a regulatory kinase, mTOR, and thus prohibit T-cell progression from the G_1 to the S phase of the cell cycle. Unlike the calcineurin inhibitors, mTOR inhibitors do not affect cytokine transcription but inhibit cytokine- and growth factorinduced cell proliferation.
  - The major adverse effects include hyperlipidemia (hypertriglyceridemia), anemia, proteinuria, difficulty with wound healing, cytopenias, peripheral edema, oral ulcers, and gastrointestinal symptoms, although other less common side effects are present.

  - Although not directly nephrotoxic, mTOR inhibitors may compound the vasoconstriction of calcineurin inhibitors and potentiate their nephrotoxicity. Thus, mTOR inhibitors are best used alone or with steroids and/or other antiproliferative agents.
  - Sirolimus interacts with CsA metabolism, making monitoring of both drugs difficult.
  - The typical dose of sirolimus is 2-5 mg daily in a single dose. Everolimus is administered at 0.75-1.50 mg twice daily. Therapeutic drug monitoring is being perfected, with current trough levels between 5-15 ng/mL for sirolimus and 3-8 ng/mL for everolimus most commonly being used.
  - Sirolimus should be avoided in moderate to advanced chronic kidney disease and immediately postoperatively because it is associated with poorer wound healing, delayed graft function (kidney transplant), anastomotic bronchial dehiscence (lung transplant), and hepatic artery thrombosis (liver transplant); limited data are available regarding use of everolimus in the immediate postoperative period.
  - Sirolimus is not used in pregnant women due to teratogenicity in animal models.
- **Calcineurin inhibitors.** Calcineurin inhibitors inhibit T-lymphocyte activation and proliferation. **They remain the most commonly used immunosuppressant, despite their side effect of nephrotoxicity.** IV calcineurin inhibitors should be avoided because of their extreme toxicity and must never be given as a bolus under any circumstance.
  - **Cyclosporine (CsA)** is a cyclic 11-amino acid peptide derived from a fungus. Its major nonimmune side effect is nephrotoxicity due to glomerular afferent arteriolar vasoconstriction. This action leads to an immediate decline in glomerular filtration rate of up to 30% and a long-term vaso-occlusive fibrotic renal disease that often results in chronic kidney disease in recipients of all organ transplants. Angiotensin-converting enzyme inhibitors, mTOR inhibitors, volume depletion, and nephrotoxins may potentiate this effect. Acute nephrotoxicity is reversible with dose reduction; chronic nephrotoxicity is generally irreversible and nearly universally present in all patients after 8-10 years of therapy.
  - Other **adverse effects** include gingival hyperplasia, hirsutism, tremor, hypertension, glucose intolerance, hyperlipidemia, hyperkalemia, and rarely, thrombotic microangiopathy. CsA has a narrow therapeutic window, and doses are adjusted based on blood levels (recommended maintenance 12-hour trough levels of 100-300 ng/mL and 2-hour peak levels of 800-1200 ng/mL). Usual doses are 6-8 mg/kg/d in divided doses, with careful attention to levels and toxicities.
  - **Tacrolimus** is a macrolide and, like CsA, is nephrotoxic. Tacrolimus is more neurotoxic and diabetogenic than CsA, but it is associated with less hirsutism, hypertension, and gingival hyperplasia. Tacrolimus dosing is based on trough blood levels (recommended maintenance levels of 5-10 ng/mL). Usual starting dose is 0.15 mg/kg/d in divided doses.
- **Biologic agents**
  - **Polyclonal antibodies**

- Antithymocyte globulin is produced by injecting human thymocytes into animals and collecting sera. This process generates antibodies against a wide variety of human immune system antigens. When subsequently infused into human patients, T lymphocytes are depleted as a result of complement-mediated lysis and clearance of antibody-coated cells by the reticuloendothelial system. Lymphocyte function is also disrupted by blocking and modulating the expression of cell surface molecules by the antibodies. Infusion is through a central vein over 4-6 hours. The most common side effects are fever, chills, and arthralgias.
- Other important **adverse effects** include myelosuppression, serum sickness, and rarely, anaphylaxis. Two preparations are available: horse antithymocyte globulin (ATGAM) and rabbit antithymocyte globulin (Thymoglobulin). Current literature suggests that rabbit antithymocyte globulin is more efficacious. These drugs can be

used at the time of transplantation to promote engraftment ("induction") or as a subsequent treatment for acute rejection. The long-term risk of increased malignancy, particularly lymphoma, remains a concern with these agents.

- **Monoclonal antibodies**
  - **Anti-interleukin-2 receptor monoclonal antibody.** Basiliximab (chimeric) is a monoclonal antibody that competitively inhibits the interleukin-2 receptor (CD25) and thereby inhibits activation of T cells. Chimerization results in antibodies with an extended half-life and minimizes the chance of developing antimurine antibodies. This drug is administered by a peripheral vein perioperatively at the time of transplantation and is associated with few side effects.
  - Belatacept, used in kidney transplants, is a fusion protein that blocks T-cell costimulation (CD80/86) and subsequent activation. It is contraindicated for use in nonrenal transplantation and additionally in patients seronegative for Epstein-Barr virus (EBV) due to increased posttransplant lymphoproliferative disease (PTLD) in EBV-seronegative recipients.
  - Other biologic agents used off-label in transplantation include **alemtuzumab**, a monoclonal antibody against CD52, a molecule present on B and T cells; **eculizumab**, a humanized monoclonal antibody blocking activation of complement protein C5; and **rituximab**, a chimeric monoclonal antibody against the B-cell protein CD20.
  - IV immunoglobulin **(IVIG)** has immunomodulatory effects. Due to these effects, IVIG is sometimes used in the treatment of antibody-mediated rejection. Side effects include flushing, myalgias, chills, headache, and rarely, anaphylaxis.

- **Infection prophylaxis**
  - **Immunization.** Pneumococcal and hepatitis B vaccination should be given at the time of pretransplant evaluation. Influenza A vaccination should be administered yearly. Live vaccines should be avoided after transplantation and if transplant is imminent (e.g., planned living donor kidney transplant) (*Am J Transplant 2004;4(suppl 10):160*). Varicella vaccination in seronegative patients and hepatitis A vaccination (particularly in liver transplant candidates) should be considered before transplant (*Clin Infect Dis 2009;49:1550*).
  - **Trimethoprim-sulfamethoxazole** prevents urinary tract infections, *Pneumocystis jirovecii* pneumonia, and *Nocardia* infections. The optimal dose and duration of prophylaxis have not been determined, although a minimum of 1 year is generally recommended. In sulfaallergic patients, dapsone, aerosolized pentamidine, and atovaquone are alternatives.
  - **Acyclovir** prevents reactivation of herpes simplex virus (HSV) and varicella-zoster virus but is

ineffective in CMV prophylaxis. HSV can be a serious infection in immunosuppressed individuals, and some form of prophylaxis should be used during the first year. Patients with recurrent HSV infections (oral or genital) should be considered candidates for long-term prophylaxis. Lifetime acyclovir should also be used in EBV-seronegative patients who receive an EBV-positive organ.

- **Ganciclovir** or **valganciclovir** prevents reactivation of CMV infection when administered to patients who were previously CMV seropositive, received a CMV-positive organ, or both. Typically, they are administered for 3-12 months following transplantation. CMV hyperimmune globulin or IV ganciclovir can also be used for this purpose. Alternatively, patients can be monitored for the presence of CMV replication in the bloodstream by polymerase chain reaction before symptoms develop and can be treated preemptively.
- **Fluconazole** or **ketoconazole** can be given to patients with a high risk of systemic fungal infections or recurrent localized fungal infections. Both medications increase CsA and tacrolimus levels (see Treatment under the Solid Organ Transplant Basics section).
- **Nystatin suspension**, **clotrimazole** troches, or weekly **fluconazole** is used to prevent oropharyngeal candidiasis (thrush).

GRAFT REJECTION

Acute Rejection, Kidney

GENERAL PRINCIPLES

Most episodes of acute rejection occur in the first year after transplantation. The low incidence of acute rejection today usually entails a careful search for inadequate drug levels, noncompliance, or less common forms of rejection (such as antibody-mediated rejection or plasma cell rejection). Late acute rejection (>1 year after transplantation) usually results from inadequate immunosuppression or patient nonadherence.

Definition

An immunologically mediated, acute deterioration in renal function associated with specific pathologic changes on renal biopsy including lymphocytic interstitial infiltrates, tubulitis, and arteritis (cellular rejection) and/or glomerulitis, capillaritis, and positive staining of the peritubular capillaries for the complement component C4d (antibody-mediated rejection).

Epidemiology

Kidney allograft rejection currently occurs in only 10% of patients. Patients who do not receive induction therapy have a 20-30% incidence of acute rejection.

Associated Conditions

Diagnosis of acute renal allograft rejection is made by percutaneous renal biopsy after excluding prerenal azotemia via hydration and repeating laboratory tests. Further workup includes evaluation for calcineurin inhibitor nephrotoxicity (trough and/or peak levels and associated signs), infection (urinalysis and culture), obstruction (renal ultrasound), and surgical complications such as urine leak (renal scan). Newer techniques evaluating early markers of acute rejection in the blood and urine are being developed.

DIAGNOSIS

Clinical Presentation

Manifestations include an elevated serum creatinine, decreased urine output, increased edema, or worsening hypertension. Initial symptoms are often absent except for the rise in creatinine. Constitutional symptoms (fever, malaise, arthralgia, painful or swollen allograft) are uncommon in current practice.

Differential Diagnosis

Differential diagnosis varies with duration after transplantation (Table 17-1).

Acute Rejection, Lung

GENERAL PRINCIPLES

- Of the solid organ transplants, the lung is the most immunogenic organ. The majority of patients have at least one episode of acute rejection. Multiple episodes of acute rejection predispose to the development of chronic rejection (bronchiolitis obliterans syndrome).
- **Lung transplant rejection** occurs frequently and most commonly in the first few months after transplantation.

TABLE 17-1 Differential Diagnosis of Renal Allograft Dysfunction

>1 Wk After Transplant	<3 Mo After Transplant	>3 Mo After Transplant
Acute tubular necrosis	Acute rejection	Prerenal azotemia
Hyperacute rejection	Calcineurin inhibitor toxicity	Calcineurin inhibitor toxicity
Accelerated rejection	Prerenal azotemia	Acute rejection (nonadherence, low levels)
Obstruction	Obstruction	Obstruction
Urine leak (ureteral necrosis)	Infection	Recurrent renal disease
Arterial or venous thrombosis	Interstitial nephritis	De novo renal disease
Atheroemboli	Recurrent renal disease BK virus nephropathy	Renal artery stenosis (anastomotic or atherosclerotic) BK virus nephropathy

DIAGNOSIS

Diagnosis is generally made by fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsies.

Clinical Presentation

Manifestations are nonspecific and include fever, dyspnea, and a nonproductive cough. The chest radiograph is usually unchanged and is generally nondiagnostic even when abnormal (perihilar infiltrates, interstitial edema, pleural effusions). Change in pulmonary function testing is not specific for rejection, but a 10% or greater decline in forced vital capacity or FEV_1, or both, is usually clinically significant.

Differential Diagnosis

It is important to attempt to distinguish rejection from infection, because although the symptoms are similar, the treatments are markedly different.

Acute Rejection, Heart

GENERAL PRINCIPLES

Heart transplant recipients typically have two to three episodes of acute rejection in the first year after transplantation with a 50-80% chance of having at least one rejection episode, most commonly in the first 6 months.

DIAGNOSIS

- Diagnosis is established by endomyocardial biopsy performed during routine surveillance or as prompted by symptoms. None of the noninvasive techniques has demonstrated sufficient sensitivity and specificity to replace the endomyocardial biopsy. Repeated endomyocardial biopsies predispose to severe tricuspid regurgitation.

- **Manifestations** may include symptoms and signs of left ventricular dysfunction, such as dyspnea, paroxysmal nocturnal dyspnea, orthopnea, syncope, palpitations, new gallops, and elevated jugular venous pressure. Many patients are asymptomatic. Acute rejection may also be associated with a variety of tachyarrhythmias (atrial more often than ventricular).

Acute Rejection, Liver

GENERAL PRINCIPLES

- Many liver transplant recipients may be maintained on minimal immunosuppression. Acute rejection typically occurs within the first 3 months after transplant and often in the first 2 weeks after the operation. Acute rejection in the liver is generally reversible and does not portend a potentially serious adverse outcome as in other organs. Recurrent viral hepatitis is a much more frequent and morbid problem.
- **Liver transplant recipients** commonly experience acute allograft rejection, with at least 60% having one episode.

DIAGNOSIS

Diagnosis is made by liver biopsy after technical complications are excluded.

Clinical Presentation

Manifestations may be absent with only a slight elevation in transaminases, or patients may have signs and symptoms of liver failure including fever, malaise, anorexia, abdominal pain, ascites, decreased bile output, elevated bilirubin, and elevated transaminases.

Differential Diagnosis

Differential diagnosis of early liver allograft dysfunction includes primary graft nonfunction, preservation injury, vascular thrombosis, biliary anastomotic leak, or stenosis. These disorders should be excluded clinically or by Doppler ultrasonography. Late allograft dysfunction may be due to rejection, recurrent hepatitis B or C, CMV infection, EBV infection, cholestasis, or drug toxicity.

Acute Rejection, Pancreas

GENERAL PRINCIPLES

- The majority of rejection episodes occur within the first 6 months after transplant. Unlike other organs, clinical findings and biochemical markers correlate poorly with rejection; in particular, if hyperglycemia occurs due to rejection, it is often late, severe, and irreversible. Because 80% of pancreas transplants are performed with a simultaneous kidney transplant with the same immunologic status, renal allograft function and histopathology can be a valuable surrogate for diagnosis of pancreas allograft rejection.
- Most pancreas transplants are done with quadruple immunosuppression, consisting of an induction agent and triple maintenance immunosuppression, including corticosteroids. One-year posttransplant acute rejection rates range between 20-30%; this contributes significantly to early and late graft loss.

DIAGNOSIS

At time of surgery, the exocrine (digestive enzymes) secretions of the pancreas can be drained into the recipient's intestine (enteric drainage) or into the bladder (bladder drainage).

Serum amylase and lipase are used in both the enteric- and bladder-drained recipient to monitor for rejection but lack specificity. For the bladder-drained allograft, a fall in urinary amylase correlates with rejection. However, allograft biopsy remains the gold standard, demonstrating septal, ductal, and acinar inflammation and endotheliitis. If a recipient received a simultaneous kidney transplant from the same donor, the creatinine and renal biopsy may also be used to diagnose rejection, although isolated pancreas or kidney rejection may rarely occur.

Clinical Presentation

Manifestations may be absent with only a slight elevation in serum amylase and lipase or fall in urinary amylase (bladder drained). **Hyperglycemia is a late manifestation of rejection.**

Differential Diagnosis

Differential diagnosis of hyperglycemia includes thrombosis (affecting 7% of recipients), islet cell drug toxicity, steroid effect, infection, development of insulin resistance, or recurrent autoimmune disease.

Differential diagnosis of elevated serum lipase includes graft pancreatitis, peripancreatic fluid/infection, obstruction, dehydration, and PTLD.

Chronic Allograft Dysfunction

GENERAL PRINCIPLES

- Chronic allograft dysfunction accounts for the vast majority of late graft losses and is the major obstacle to long-term graft survival.
- Chronic allograft dysfunction (formerly chronic rejection) is a slowly progressive, insidious decline in function of the allograft characterized by gradual vascular and ductal obliteration, parenchymal atrophy, and interstitial fibrosis.

DIAGNOSIS

- Diagnosis is often difficult and generally requires a biopsy. The process is mediated by immune and nonimmune factors.
- The manifestations of chronic rejection are unique to each organ system.

TREATMENT

To date, no effective therapy is available for established immune-mediated chronic allograft dysfunction. Some patients, particularly those with renal transplants, will require a second solid organ transplant. Current investigational strategies are aimed at prevention.

Complications

GENERAL PRINCIPLES

- **Infections**
  - **Posttransplant infections are a significant cause of morbidity and, in some cases, mortality for transplant recipients. Types of infections vary depending on the time since transplantation** (*N Engl J Med 1998;338:1741*) (Table 17-2).
  - **CMV infection** from reactivation of CMV in a seropositive recipient or new infection from a CMV-positive organ can lead to a wide range of presentations from a mild viral syndrome to allograft dysfunction, invasive disease in multiple organ systems, and

even death. CMV-seronegative patients who receive a CMV-seropositive organ are at substantial risk, particularly in the first year.

TABLE 17-2 Timing and Etiology of Posttransplant Infections

Time Period	Infectious Complication	Etiology

<1 mo after transplant	Nosocomial pneumonia, wound infection, urinary tract infection, catheter-related sepsis, biliary, chest, or other drainage catheter infection	Bacterial or fungal infections
1-6 mo after transplant	Opportunistic infections	Cytomegalovirus *Pneumocystis jirovecii* *Aspergillus* spp. *Toxoplasma gondii* *Listeria monocytogenes* *Strongyloides stercoralis* West Nile virus Varicella-zoster virus (VZV)
	Reactivation of preexisting infections	*Mycobacteria* spp. Endemic mycoses Viral hepatitis
>6 mo after transplant	Community-acquired infections	Bacterial Tick-borne disease Influenza Metapneumovirus Norovirus
	Chronic progressive infection	Reactivated VZV (zoster) Hepatitis B Hepatitis C HIV Cytomegalovirus Epstein-Barr virus Papillomavirus Polyomavirus (BK)
	Opportunistic infections	*P. jirovecii* *L. monocytogenes* *Nocardia asteroides*

		Cryptococcus neoformans *Aspergillus* spp. West Nile virus

- Because of the potential progression and severity of untreated disease, treatment is usually indicated in viremic transplant patients without tissue diagnosis of invasive disease. Seroconversion with a positive IgM titer or a fourfold increase in IgM or IgG titer suggests acute infection; however, many centers now use polymerase chain reaction-based diagnostic techniques from blood samples, and treatment is usually administered in the patient with evidence of viremia (*J Am Soc Nephrol 2001;12:848*).
- Treatment is with oral valganciclovir, 450-900 mg PO bid, or IV ganciclovir, 2.5-5.0 mg/kg bid for 3-4 weeks or until clearance of the virus. Both drugs are adjusted

for renal function. Hyperimmune globulin is often used with ganciclovir for patients with organ involvement.
- Foscarnet and cidofovir are more toxic alternatives and should be reserved for ganciclovir-resistant cases.

- **Hepatitis B and C.** Patients with active hepatitis or cirrhosis are not considered for nonhepatic transplantation. Immunosuppression increases viral replication in organ transplant recipients with either hepatitis B or C.
  - **Hepatitis B** can recur as fulminant hepatic failure even in patients with no evidence of viral DNA replication before transplantation. In liver transplantation, the risk of recurrent hepatitis B virus infection can be reduced by the administration of hepatitis B immunoglobulin during and after transplantation. Lamivudine therapy initiated before transplantation to lower viral load has shown decreased likelihood of recurrent hepatitis B virus.
  - **Hepatitis C** typically progresses slowly in nonhepatic transplants, and the effect of immunosuppression on mortality due to liver disease remains to be determined. Treatment protocols for hepatitis C in the nonhepatic transplant population are not yet established. Hepatitis C nearly always recurs in liver transplant recipients whose original disease was due to hepatitis C. Therapy for recurrent hepatitis C virus with ribavirin and interferon has been available, but treatment is evolving, with newer and effective therapies including protease inhibitors and polymerase inhibitors that achieve a sustained virologic response.
- **EBV** plays a role in the development of PTLD. This life-threatening lymphoma is treated by withdrawal or reduction in immunosuppression and often aggressive chemotherapy. The role of newly discovered viral agents such as human herpesvirus (HHV)-6, HHV-7, HHV-8, and polyomavirus (BK and JC) after transplantation remains to be established. BK virus is known to cause interstitial nephritis, resulting in renal allograft loss, and occasionally ureteral stricture, resulting in obstruction. Because BK virus nephropathy results primarily from reactivation of latent BK in the transplanted organ, this is rarely seen in nonrenal transplant recipients.
- **Fungal and parasitic infections**, such as *Cryptococcus*, *Mucor*, aspergillosis, and *Candida* spp., result in increased mortality after transplantation and should be aggressively diagnosed and treated. The role of prophylaxis with oral fluconazole has not been established.

- **Renal disease.** Chronic allograft dysfunction is the leading cause of allograft loss in renal transplant

recipients. Chronic calcineurin inhibitor (CsA or tacrolimus) nephrotoxicity may also lead to chronic renal insufficiency and end-stage renal disease (ESRD), requiring dialysis or transplantation in recipients of lung, heart, liver, or pancreas transplants. The incidence of ESRD secondary to calcineurin inhibitor toxicity in recipients of solid organ transplants is at least 10%, and the incidence of significant chronic kidney disease approaches 50% (*N Engl J Med 2003;349:931*).

- **Malignancy** occurs in transplant patients with an overall incidence that is three- to fourfold higher than that seen in the general population (age matched). Cancers with an increased risk of fivefold or greater compared to the general population are Kaposi sarcoma, non-Hodgkin lymphoma, and skin, lip, vulvar, anal, and liver cancer, illustrating the oncogenic potential of associated viral infections (*JAMA 2011;306:1891*).
  - **Skin and lip cancers** are the most common de novo malignancies (40-50%) seen in transplant recipients, with an incidence 10-250 times that of the general population. Risk factors include immunosuppression, UV radiation, and human papillomavirus infection. These cancers develop at a younger age, and they are more aggressive in transplant patients. Protective clothing, sunscreens, and avoiding sun exposure are recommended. Examination of the skin is the principal screening test, and early diagnosis offers the best prognosis. The mTOR inhibitors may be better immunosuppressive choices in patients with recurrent skin cancer as long as no contraindications exist.

  - **PTLD** accounts for one-fifth of all malignancies after transplantation, with an incidence of approximately 1%. This is 30- to 50-fold higher than in the general population, and the risk increases with the use of antilymphocyte therapy for induction or rejection. The majority of these neoplasms are large-cell non-Hodgkin lymphomas of the B-cell type. PTLD results from EBV-induced B-cell proliferation in the setting of chronic immunosuppression. The EBV-seronegative recipient of a seropositive organ is at greatest risk. The presentation is often atypical and should always be considered in the patient with new symptoms. Diagnosis requires a high index of suspicion followed by a tissue biopsy. Treatment includes reduction or withdrawal of immunosuppression and chemotherapy.

SPECIAL CONSIDERATIONS

- **Important drug interactions** are always a concern given the polypharmacy associated with transplant patients. Before prescribing a new medication to a transplant recipient, always investigate drug interactions.
- The combination of **allopurinol and azathioprine** should be avoided due to the risk of profound myelosuppression.
- CsA and tacrolimus are metabolized by cytochrome P450 (3A4). Therefore, CsA and tacrolimus levels are decreased by drugs that induce cytochrome P450 activity, such as rifampin, isoniazid, barbiturates, phenytoin, and carbamazepine. Conversely, CsA and tacrolimus levels are increased by drugs that compete for cytochrome P450, such as verapamil, diltiazem, nicardipine, azole antifungals, erythromycin, and clarithromycin. Similar effects are seen with sirolimus and everolimus.
- **Tacrolimus and CsA** should not be taken together because of the increased risk of severe nephrotoxicity.
- Lower doses of MPA should be used when either tacrolimus or sirolimus is taken concurrently.
- Concomitant administration of CsA and sirolimus may result in a twofold increase in sirolimus levels; to avoid this drug interaction, CsA and sirolimus should be dosed 4 hours apart.

18
Gastrointestinal Diseases

C. Prakash Gyawali

Amit Patel

Gastrointestinal Bleeding

GENERAL PRINCIPLES

Acute gastrointestinal (GI) bleeding is a common clinical problem that results in substantial morbidity and health care costs, especially when it develops in hospitalized patients (*Gut 2011;60:1327*).

- **Overt GI bleeding** is the passage of fresh or altered blood in emesis or stool.
- **Occult GI bleeding** refers to a positive fecal occult blood test (stool guaiac or fecal immunochemical test) or iron deficiency anemia without visible blood in the stool.
- **Obscure GI bleeding** consists of GI blood loss of unknown origin that persists or recurs after negative initial endoscopic evaluation (*Gastroenterology 2007;133:1697*).

DIAGNOSIS

Clinical Presentation

History

- Hematemesis, coffee-ground emesis, and/or aspiration of blood or coffee-ground material from a nasogastric (NG) tube indicate an upper GI source of blood loss.
- **Melena**, black sticky stool with a characteristic odor, usually suggests an upper GI source, although small bowel and right-sided colonic bleeds can also result in melena.
- Various shades of **bloody stool (hematochezia)** are seen with distal small bowel or colonic bleeding, depending on the rate of blood loss and colonic transit. Rapid upper GI bleeding can present with hematochezia, typically associated with hemodynamic compromise or circulatory shock.
- **Anorectal bleeding** usually results in bright red blood coating the exterior of formed stool associated with distal colonic symptoms (e.g., rectal urgency, straining, or pain with defecation).
- **Anemia** from blood loss can cause fatigue, weakness, abdominal pain, pallor, or dyspnea.
- Estimation of the amount of blood loss is often inaccurate. If the baseline hematocrit is known, the drop in hematocrit provides a rough estimate of blood loss. In general, lower GI bleeding causes less hemodynamic compromise than upper GI bleeding.
- **Coagulation abnormalities** can propagate bleeding from a preexisting lesion in the GI tract. Disorders of coagulation (e.g., liver disease, von Willebrand disease, vitamin K deficiency, and disseminated intravascular coagulation) can influence the course of GI bleeding (see Chapter 20, Disorders of Hemostasis and Thrombosis).
- **Medications** known to affect the coagulation process or platelet function include warfarin, heparin, low-molecular-weight heparin, aspirin, NSAIDs, thienopyridines (clopidogrel [Plavix], prasugrel [Effient], ticlopidine [Ticlid]), thrombolytic agents, glycoprotein IIb/IIIa receptor antagonists (abciximab [ReoPro], eptifibatide [Integrilin], tirofiban [Aggrastat]), direct thrombin inhibitors (argatroban, bivalirudin, dabigatran etexilate), and direct factor Xa inhibitors (rivaroxaban [Xarelto], apixaban).

- **NSAIDs and aspirin** can result in mucosal damage anywhere in the GI tract. Therefore, dual antiplatelet therapy (e.g., clopidogrel plus aspirin) or concomitant aspirin and anticoagulation with warfarin can escalate the risk for GI bleeding by both initiating and propagating bleeding.

Physical Examination

- **Color of stool.** Direct examination of spontaneously passed stool or on **digital rectal examination (DRE)** can help localize the level of bleeding. Moreover, DRE may identify anorectal abnormalities including anal fissures, which induce extreme discomfort during the DRE.
- Fresh blood on an **NG aspirate** may indicate ongoing upper GI bleeding requiring urgent endoscopic attention (*Gastrointest Endosc 2004;59:172*). The aspirate should be considered positive only if blood or dark particulate matter ("coffee grounds") is seen; **hemoccult testing of NG aspirate has no clinical utility**. A bleeding source in the duodenum can result in a negative NG aspirate. Gastric lavage with water or saline may be useful in assessing the activity and severity of upper GI bleeding and in clearing the stomach of blood and clots before endoscopy. After a diagnosis of upper GI bleeding is made, the NG tube can be removed in a stable patient.
- Constant monitoring or frequent assessment of vital signs is necessary early in the evaluation, as a sudden increase in pulse rate or decrease in blood pressure (BP) may suggest recurrent or ongoing blood loss.
- If the baseline BP and pulse are within normal limits, sitting the patient up and/or having the patient stand may result in **orthostatic hemodynamic changes** (drop in systolic BP of >20 mm Hg, rise in pulse rate of >10 bpm). Orthostatic changes are seen with loss of 10-20% of the circulatory volume; supine hypotension suggests a >20% loss. Hypotension with a systolic BP of <100 mm Hg or baseline tachycardia >100 bpm suggests significant hemodynamic compromise that requires urgent volume resuscitation (*N Engl J Med 2008;359:928*).

Diagnostic Testing

Laboratories

- Complete blood cell (CBC) count
- Coagulation parameters (international normalized ratio [INR], partial thromboplastin time [PTT])
- Blood group, cross-matching of two to four units of blood
- Comprehensive metabolic profile (creatinine, blood urea nitrogen, liver function tests)

Diagnostic Procedures

- **Endoscopy**
  - **Esophagogastroduodenoscopy (EGD)**, with high diagnostic accuracy and therapeutic capability, is the preferred investigative test in upper GI bleeding. Volume resuscitation or blood transfusion should precede endoscopy in hemodynamically unstable patients. Patients with ongoing bleeding or at risk for an adverse outcome (Table 18-1) benefit most from urgent EGD, while stable patients can be endoscoped electively during the hospitalization. IV erythromycin (infusion of 125-250 mg completed 30 minutes before EGD) empties the stomach of blood and clots and improves visibility for EGD (*Gastrointest Endosc 2011;73:245*). Second-look EGD after hemostasis has no proven benefit in reducing surgical intervention or overall mortality (*J Gastroenterol Hepatol 2010;25:8*).
  - **Colonoscopy** can be performed after a rapid bowel purge in clinically stable patients; the purge

solution can be infused through an NG tube when not tolerated orally. While diagnostic yield is highest with colonoscopy performed within 24 hours of presentation, (*Am J Gastroenterol 2005;100:2395*), patient outcome does not necessarily improve (*Am J Gastroenterol 2010;105:2636*). Therapeutic colonoscopy, however, may reduce transfusion requirements, need for surgery, and length of hospital stay. All patients with acute lower GI bleeding from an unknown source should eventually undergo colonoscopy during the initial hospitalization, regardless of the initial mode of investigation.

- **Anoscopy** may be useful in the detection of internal hemorrhoids and anal fissures but does not replace the need for colonoscopy.

TABLE 18-1 Rockall Score for Risk Stratification of Acute Upper Gastrointestinal (GI) Bleeding

	Variable	Points
Complete Rockall Score / Clinical Rockall Score	Age	
	<60 yr	0
	60–79 yr	1
	≥80 yr	2
	Shock	
	Heart rate >100 bpm	1
	Systolic blood pressure <100 mm Hg	2
	Coexisting illness	
	Coronary artery disease, congestive heart failure, other major illness	2
	Renal failure, hepatic failure, metastatic cancer	3
	Endoscopic diagnosis	
	No finding, Mallory-Weiss tear	0
	Peptic ulcer, erosive disease, esophagitis	1
	Cancer of the upper GI tract	2
	Endoscopic stigmata of recent bleeding	
	Clean based ulcer, flat pigmented spot	0
	Blood in upper GI tract, active bleeding, visible vessel, clot	2

A clinical score of 0 or a complete score of 2 or less indicate low risk for rebleeding or death. Adapted from Gralnek et al. *N Engl J Med* 2008;359:928, with permission.

- **Push enteroscopy** allows evaluation of the proximal small bowel beyond reach of a standard

EGD, especially if no source is found on careful colonoscopy.

- **Capsule endoscopy** is most useful after the upper gut and the colon have been thoroughly examined and the bleeding source is suspected in the small bowel (*Gastroenterology 2007;133:1697*). In overt obscure GI bleeding, capsule endoscopy has higher diagnostic yield with similar long-term outcomes when compared with angiography (*Am J Gastroenterol 2012;107:1370*). However, images cannot be viewed in real time, exact localization within the small bowel cannot be pinpointed, and therapy cannot be administered; consequently, improvements in diagnostic yield may not translate into better outcomes (*Gastroenterology 2010;138:1673*).
- **Single- and double-balloon enteroscopy** allows visualization of most of the small bowel through either an oral or anal approach. Balloons at the endoscope tip and overtube can be consecutively inflated and deflated to facilitate deep insertion into the small bowel.
- **Intraoperative enteroscopy** may assist endoscopic therapy or surgical resection of an actively bleeding source in the small bowel.

- **CT enteroclysis** has value when both conventional endoscopy and capsule endoscopy are nondiagnostic in obscure-overt bleeding with prominent anemia (*Gastrointest Endosc 2011;73:1002*).
- **Tagged red blood cell (RBC) scanning** involves labeling RBCs with technetium-99m that may extravasate into the bowel lumen with active bleeding, detected as pooling of the radioactive tracer on gamma camera scanning, to identify the potential bleeding site. **CT angiography** may have similar benefit in localizing bleeding prior to catheter angiography (*J Vasc Interv Radiol 2010;21:848*). These tests are particularly useful in unstable active bleeding precluding urgent colonoscopy.
- **Arteriography** demonstrates extravasation of the dye into the intestine when bleeding rates exceed 0.5 mL/min, thereby localizing bleeding. Arteriography is often performed after bleeding is initially localized by other means. Selective cannulation and infusion of vasopressin vasoconstrict the bleeding vessel; moreover, the vessel can be embolized.

TREATMENT

- **Restoration of intravascular volume.** Two large-bore (16- to 18-gauge) IV lines or a central venous line should be urgently placed to provide IV fluid resuscitation. Circulatory shock may require volume administration using pressure infusion devices, guided by the patient's condition and degree of volume loss (*N Engl J Med 2008;359:928*). **Packed RBC transfusion** should be used for volume replacement whenever possible; O-negative blood or simultaneous multiple-unit transfusions may be indicated if bleeding is massive. Transfusion should be continued until hemodynamic stability is achieved and the hematocrit reaches ≥25-30%. Overcorrection of volume and blood counts does not necessarily improve outcome and may even be detrimental in variceal bleeding (*Aliment Pharmacol Ther 2010;32:215*).
- **Oxygen administration.** Supplemental oxygen enhances the oxygen-carrying capacity of blood and should be universally administered in acute GI bleeding.
- **Correction of coagulopathy.** Coagulopathy (INR ≥1.5) increases morbidity and mortality in acute GI bleeding (*Aliment Pharmacol Ther 2011;33:1010*) and should be corrected if possible. Platelet infusion

may be indicated when the platelet count is <50,000/μL.

- **Endotracheal intubation** protects the airway and prevents aspiration in obtunded patients with massive hematemesis and in active variceal bleeding.
- **Risk stratification.** Validated risk stratification tools, such as the Rockall and Glasgow-Blatchford scores, are available to identify patients at highest risk for an adverse outcome (*Aliment Pharmacol Ther 2011;34:470*). The Rockall score (see Table 18-1) has a *clinical* component that is rapidly calculated at presentation and a *complete* final score that takes endoscopic findings into account (*Gut 1996;38:316*).

Medications

- **Nonvariceal upper GI bleeding.** Pre-endoscopic IV **proton pump inhibitors** (PPIs) (40 mg IV bolus bid or 80 mg IV bolus followed by 8 mg/h continuous infusion) impact the proportion of patients who have high-risk stigmata of hemorrhage and reduce need for endoscopic therapy in bleeding peptic ulcer disease (PUD) (*Am J Gastroenterol 2012;10:345*). However, meta-analysis does not show benefits in rebleeding, surgical intervention, or mortality between IV infusions and IV bolus therapy in unselected cases (*Arch Intern Med 2010;170:751*). PPI therapy, IV or oral (e.g., omeprazole 40 mg PO bid or equivalent), is more effective than IV histamine-2 receptor antagonist (H_2RA) therapy (*Am J Gastroenterol 2014;109:1005*).
- **Variceal bleeding. Octreotide** (an octapeptide that mimics endogenous somatostatin) infusion acutely reduces portal pressures and controls variceal bleeding, improving the

diagnostic yield and therapeutic success of subsequent endoscopy. Octreotide should be initiated immediately (50- to 100-μg bolus, followed by infusion at 25-50 μg/h) and continued for 3-5 days after EGD if variceal hemorrhage is confirmed (*Gastrointest Endosc 2014;80:221*). Both **terlipressin** and **octreotide** achieve similar hemostatic effects with comparable safety to octreotide as adjuvants to endoscopic therapy in variceal bleeding (*Hepatology 2014;60:954*; *Aliment Pharmacol Ther 2012;35:1267*). A 7-day course of antibiotic prophylaxis with an IV third-generation cephalosporin (ceftriaxone) is recommended (see Chapter 19, Liver Diseases) in any patient with cirrhosis and variceal bleeding; a fluoroquinolone is an alternative (*Hepatology 2009;49:2087*).
- **Thalidomide** may be an effective approach for refractory chronic bleeding from GI vascular malformations (*Gastroenterology 2011;141:1629*).

Other Nonpharmacologic Therapies

- **Endoscopic therapy**
  - **Therapeutic endoscopy** offers the advantage of endoscopic hemostasis. Therefore, EGD should be performed early in acute upper GI bleeding (within 12-24 hours).
  - **Variceal ligation** or **banding** is the endoscopic therapy of choice for esophageal varices, with endotracheal intubation for airway protection if bleeding is massive or the patient is obtunded (*Gastrointest Endosc 2014;80:221*). Variceal banding has value in both primary and secondary prophylaxis of variceal bleeding, with benefits similar to that from β-blocker therapy alone (*Gastroenterology 2010;139:1238*). Complications include superficial ulceration, dysphagia, and transient chest discomfort.
  - **Sclerotherapy** is also effective but is used mostly when variceal banding is not technically feasible.
  - Endoscopic injection of **cyanoacrylate (glue)** is more effective than β-blocker therapy in primary and secondary prophylaxis of gastric variceal bleeding, but not esophageal variceal bleeding (*Gut 2010;59:729*).

- **Transjugular intrahepatic portosystemic shunt (TIPS)** is a radiologic procedure wherein an expandable metal stent is deployed between the hepatic veins and the portal vein to reduce portal venous pressure in refractory esophageal and/or gastric variceal bleeding from portal hypertension (*Hepatology 2007;46:922*). Early TIPS may be of value in reducing treatment failure and mortality in acute variceal bleeding (*N Engl J Med 2010;362:2370*). Encephalopathy may occur in up to 25% of patients and is treated medically (see Chapter 19, Liver Diseases). Assessment with duplex Doppler ultrasound for TIPS stenosis is recommended if variceal bleeding recurs or if esophageal or gastric varices redevelop.
- **Balloon-occluded retrograde transvenous obliteration (BRTO)** is a newer treatment option for gastric variceal bleeding, where gastric varices are obliterated through a gastrorenal shunt (*J Gastroenterol Hepatol 2009;24:372*). BRTO appears to be equivalent to TIPS for short-term management of bleeding gastric varices (*J Vasc Interv Radiol 2014;25:355*).

Surgical Management

- **Emergent total colectomy** may rarely be required for massive, unlocalized, colonic bleeding; this should be preceded by EGD to rule out a rapidly bleeding upper source whenever possible. Certain lesions (e.g., neoplasia, Meckel diverticulum) require surgical resection for a cure.
- **Total or partial colectomy** may be required for ongoing or recurrent diverticular bleeding.
- **Splenectomy** is curative in bleeding gastric varices from splenic vein thrombosis.
- **Shunt surgery** (portacaval or distal splenorenal shunt) is now rarely performed; this can be considered in patients with good hepatic reserve.

SPECIAL CONSIDERATIONS

Cardiac Patients and Gastrointestinal Bleeding

- In acute coronary syndromes (ACS), GI bleeding increases 30-day all-cause mortality rates by a factor of almost 5 (*J Am Coll Cardiol 2009;29:1293*). Antiplatelet and anticoagulant therapy, especially dual antiplatelet therapy (e.g., aspirin plus clopidogrel), are significant risk factors. Among patients on low-dose aspirin with history of PUD bleeding, continuous aspirin therapy increases the risk for recurrent PUD bleeding (*Ann Intern Med 2010;152:1*).
- **PPI prophylaxis** decreases the risk of GI bleeding, without significant effects on the incidence of hospital-acquired pneumonia or 30-day mortality (*Aliment Pharmacol Ther 2011;34:519*).
- Despite concerns that PPIs competitively inhibit the cytochrome P450 enzyme that activates clopidogrel, randomized controlled trials have not substantiated higher vascular events with concurrent use of clopidogrel and PPI (*N Engl J Med 2010;11:363*; *Heart 2013;99:520*). Among PPIs, pantoprazole may have the least pharmacodynamic interaction with clopidogrel (*Eur J Gastroenterol Hepatol 2011;23:396*).
- **Left ventricular assist devices (LVADs)**, used in end-stage heart failure, are associated with GI bleeding rates significantly higher than those seen with dual antiplatelet therapy or anticoagulation (*Clin Gastroenterol Hepatol 2014;12:1461*). Bleeding is predominantly overt and from upper GI sources, especially angiodysplastic lesions, making EGD or push enteroscopy the initial investigation of choice (*Gastrointest Endosc 2012;75:973*).

Dysphagia and Odynophagia

GENERAL PRINCIPLES

Definition

- **Oropharyngeal dysphagia** consists of difficulty in transferring food from the mouth to the esophagus, often associated with nasopharyngeal regurgitation and aspiration. Typical causes include neuromuscular or structural disorders involving the pharynx and proximal esophagus (*Gastroenterology 1999;116:452*).
- **Esophageal dysphagia** is the sensation of impairment in passage of food down the tubular esophagus. Potential etiologies include obstructive processes (such as webs, rings, neoplasia) or esophageal motor disorders (*Gastroenterology 1999;117:233*).
- **Odynophagia** is pain on swallowing food and fluids and may indicate the presence of esophagitis, particularly infectious esophagitis or pill esophagitis.

DIAGNOSIS

Oropharyngeal Dysphagia

- Assessment is initiated with a detailed neurologic exam. **Barium videofluoroscopy (modified barium swallow)** evaluates the oropharyngeal swallow mechanism and may identify laryngeal penetration.
- Ear, nose, and throat exam; flexible nasal endoscopy; and imaging studies may identify structural etiologies.
- Laboratory tests for polymyositis, myasthenia gravis, and other neuromuscular disorders should be considered in the absence of clear neurologic or structural etiologies.

Esophageal Dysphagia

- **EGD** is the initial test of choice, as it provides information on mucosal abnormalities, allows tissue sampling (to evaluate for esophageal eosinophilia, for instance), and offers

the option of dilation, which should be performed for most esophageal strictures (*Gastrointest Endosc 2014;79:191*).
- **Barium swallow** has value in defining anatomy, especially subtle rings and strictures, which may only be seen with a barium pill or a solid barium bolus.
- Acute esophageal obstruction is best investigated with endoscopy. Barium studies should not be performed when esophageal obstruction is expected, as it may take several days for barium to clear, thereby delaying endoscopy. If a contrast study is needed, water-soluble contrast should be used in this setting.
- **Esophageal manometry,** preferably **high-resolution manometry (HRM)**, should be performed when other studies are normal or suggest an esophageal motility disorder. The image-based paradigm of Clouse plots on HRM provide several advantages over conventional manometry, including simplified testing procedures, easier analysis, and improved diagnostic utility (*Gastrointest Endosc Clin N Am 2014;24:527*).

TREATMENT

- Modification of diet and swallowing maneuvers may benefit patients with dysphagia, especially

oropharyngeal dysphagia. Patients with dysphagia are typically advised to chew their food well and eat foods of soft consistencies.

- Enteral feeding through a gastrostomy tube is indicated in patients with frank tracheal aspiration on attempted swallowing.
- Endoscopic retrieval of an obstructing food bolus relieves acute dysphagia.
- Nutrition needs to be addressed in patients with prolonged dysphagia causing weight loss.

Medications

- Mucosal inflammation from reflux disease can be treated with acid suppression.
- Odynophagia generally responds to specific therapy when the cause is identified (e.g., PPIs for reflux disease, antimicrobial agents for infectious esophagitis). Viscous lidocaine swish-and-swallow solutions may afford symptomatic relief.
- Anticholinergic medication (e.g., transdermal scopolamine) helps drooling of saliva.
- **Glucagon** (2-4 mg IV bolus) or sublingual **nitroglycerin** can be attempted in acute food impaction, but meat tenderizer should not be administered.

Other Nonpharmacologic Therapies

- Esophageal dilation is performed for anatomic narrowings. Empiric bougie dilation performed when a defined narrowing is not identified may also provide symptomatic benefit.
- Pneumatic dilation of the lower esophageal sphincter (LES) is sometimes performed for achalasia (see Esophageal Motor Disorders section). Botulinum toxin injections into the LES provide temporary symptom relief in achalasia and in errors of LES relaxation (*Gastrointest Endosc 2014;79:191*).
- Esophageal stent placement can alleviate dysphagia in inoperable neoplasia.

Nausea and Vomiting

GENERAL PRINCIPLES

- Nausea and vomiting may result from side effects of medications, systemic illnesses, central nervous system (CNS) disorders, and primary GI disorders.
- Vomiting that occurs during or immediately after a meal can result from acute pyloric stenosis (e.g., pyloric channel ulcer) or from functional disorders, while vomiting within

30-60 minutes after a meal may suggest gastric or duodenal pathology. Delayed vomiting after a meal with undigested food from a previous meal can suggest gastric outlet obstruction or gastroparesis.

- Symptoms of gastroparesis may be indistinguishable from chronic functional nausea and vomiting with normal gastric emptying (*Clin Gastroenterol Hepatol 2011;9:567*).

DIAGNOSIS

- **Bowel obstruction and pregnancy should be ruled out.**
- **Medications** should be carefully scrutinized for potential offenders, and systemic illnesses (acute and chronic) should be evaluated as etiologies or contributing factors.
- Endoscopy and/or imaging should be considered in the setting of nonresolving or “red flag” symptoms, such as hematemesis or weight loss.

TREATMENT

- Correction of fluid and electrolyte imbalances is an important supportive measure.
- Oral intake should be limited to clear liquids, if tolerated. Many patients with self-limited illnesses require no further therapy.
- NG decompression may be required for patients with bowel obstruction or protracted nausea and vomiting of any etiology.
- Patients with protracted nausea and vomiting may require enteral feeding through jejunal tubes or, rarely, even total parenteral nutrition (TPN).

Medications

Empiric pharmacotherapy is often initiated while investigation is in progress or when the etiology is thought to be self-limited.

- **Phenothiazines and related agents.** Prochlorperazine (Compazine), 5-10 mg PO tid-qid, 10 mg IM or IV q6h, or 25 mg PR bid, and promethazine (Phenergan), 12.5-25.0 mg PO, IM, or PR q4-6h, may be effective. Drowsiness is a common side effect, and acute dystonic reactions or other extrapyramidal effects may occur.
- **Dopamine antagonists** include metoclopramide (10 mg PO 30 minutes before meals and at bedtime, or 10 mg IV PRN), a prokinetic agent that also has central antiemetic effects. Drowsiness and extrapyramidal reactions may occur, and a warning has been issued by the U.S. Food and Drug Administration (FDA) regarding the risk of permanent **tardive dyskinesia** with high-dose and/or long-term use (*Aliment Pharmacol Ther 2010;31:11*). Tachyphylaxis may limit long-term efficacy. Domperidone is an alternate agent that does not cross the blood-brain barrier and therefore has no CNS side effects; however, it is not uniformly available.
- **Antihistaminic agents** are most useful for nausea and vomiting related to motion sickness but may also be useful for other causes. Agents include diphenhydramine (Benadryl, 25-50 mg PO q6-8h or 10-50 mg IV q2-4h), dimenhydrinate (Dramamine, 50-100 mg PO or IV q4-6h), and meclizine (Antivert, 12.5-25.0 mg 1 hour before travel).
- **Serotonin 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists. Ondansetron** (Zofran, 0.15 mg/kg IV q4h for three doses or 32 mg IV infused over 15 minutes beginning 30 minutes before chemotherapy) is effective in chemotherapy-associated emesis. It can also be used in emesis that is refractory to other medications (4-8 mg PO or IV up to q8h), especially the sublingual formulation.
- **Neurokinin-1 (NK-1) receptor antagonist. Aprepitant** (Emend, 125 mg PO day 1, 80 mg PO days 2 and 3) is an alternative agent intended for chemotherapy-induced nausea and vomiting.

Diarrhea

GENERAL PRINCIPLES

- **Acute diarrhea** consists of the abrupt onset of increased frequency and/or fluidity of bowel movements. Infectious agents, toxins, and drugs are the major causes of acute diarrhea. In hospitalized patients, pseudomembranous colitis, antibiotic- or drugassociated diarrhea, and fecal impaction should be considered (*Gastroenterology 2004; 127:287*).

- **Chronic diarrhea** consists of passage of loose stools with or without increased stool frequency for more than 4 weeks.

DIAGNOSIS

- Most acute infectious diarrheal illnesses last less than 24 hours and could be viral in etiology; therefore, stool studies are unnecessary in short episodes without fever, dehydration, or presence of blood or pus in the stool (*N Engl J Med 2004;350:38*).
- Stool cultures, *Clostridium difficile* toxin assay, ova and parasite examinations, and sigmoidoscopy may be warranted in patients with severe, prolonged, or atypical symptoms.
- The **fecal osmotic gap** can be calculated in patients with chronic diarrhea and voluminous watery stools as follows: 290 − 2(stool [Na^+] + stool [K^+]). The osmotic gap is **<50 mOsm/kg in secretory diarrhea** but **>125 mOsm/kg in osmotic diarrhea**.
- A positive fecal occult blood test or fecal leukocyte test suggests inflammatory diarrhea.
- **Steatorrhea** is traditionally diagnosed by demonstration of fat excretion in stool of >7 g/d in a 72-hour stool collection while the patient is on a 100-g/d fat diet. Sudan staining of a stool specimen is an alternate test; >100 fat globules per high-power field (HPF) is abnormal.
- Laxative screening should be considered when chronic diarrhea remains undiagnosed.

Clinical Presentation

- **Acute diarrhea**
  - **Viral enteritis** and **bacterial infections** with *Escherichia coli* and *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia* spp. constitute the most common causes.
  - **Pseudomembranous colitis** is usually seen in the setting of antimicrobial therapy and is caused by toxins produced by *C. difficile* (*Am J Gastroenterol 2013;108:478*).
  - **Giardiasis** is confirmed by identification of *Giardia lamblia* trophozoites in the stool, in duodenal aspirate, or in small bowel biopsy specimens. A stool immunofluorescence assay is also available for rapid diagnosis.
  - **Amebiasis** may cause acute diarrhea, especially in travelers to areas with poor sanitation and in homosexual men. Stool examination for trophozoites or cysts of *Entamoeba histolytica* or a serum antibody test confirms the diagnosis.
  - **Medications** that can cause acute diarrhea include laxatives, antacids, cardiac medications (e.g., digitalis, quinidine), colchicine, and antimicrobial agents; symptoms typically respond to discontinuation.
  - **Graft-versus-host disease** should be considered when diarrhea develops after organ transplantation, especially bone marrow transplantation; **sigmoidoscopy with biopsies** should be pursued to confirm this diagnosis (*Aliment Pharmacol Ther 2013;38:955*).
- **Chronic diarrhea.** After a careful history, a thorough physical examination, and routine laboratory tests, chronic diarrhea can typically be classified into one of the following categories: watery diarrhea (secretory or osmotic), inflammatory diarrhea, or fatty diarrhea (steatorrhea) (*J Gastroenterol Hepatol 2014;29:6*).

TREATMENT

- Adequate hydration, including IV hydration in severe cases, represents an essential initial step in the therapy of diarrheal disease.
- Antibiotic-associated diarrhea and *C. difficile* infections can be prevented by restricting high-risk antibiotics and using antibiotics based on sensitivity analysis.
- Symptomatic therapy is useful in simple self-limiting GI infections where diarrhea is frequent or troublesome, while diagnostic workup is in progress, when specific management fails to improve symptoms, and/or when a specific etiology is not identified.
  - **Loperamide**, **opiates** (tincture of opium, belladonna, and opium capsules), and **anticholinergic agents** (diphenoxylate and atropine [Lomotil]) are the most effective nonspecific antidiarrheal agents.
  - **Pectin** and **kaolin** preparations (bind toxins) and **bismuth subsalicylate** (antibacterial properties) are also useful in symptomatic therapy of acute diarrhea.
  - **Bile acid-binding resins** (e.g., cholestyramine) are beneficial in bile acid-induced diarrhea.
  - **Octreotide** is useful in hormone-mediated secretory diarrhea but can also be of benefit in refractory diarrhea.

Medications

- **Empiric antibiotic therapy** is only recommended in patients with moderate-to-severe disease and associated systemic symptoms while awaiting stool cultures. Antibiotics can increase the possibility of hemolytic-uremic syndrome associated with Shiga toxin-producing *E. coli* infections (*E. coli* O157:H7), especially in children and the elderly (*N Engl J Med 2000;342:1930*).
- Oral **metronidazole** is the treatment of choice for mild to moderate pseudomembranous colitis, whereas oral **vancomycin** can be used for resistant cases or intolerance to metronidazole (*Am J Gastroenterol 2013;108:478*). **Fidaxomicin** and **fecal microbiota transplant** represent newer treatment options (*Am J Gastroenterol 2014;109:1065*; see Chapter 14, Treatment of Infectious Diseases).
- Symptomatic amebiasis is treated with **metronidazole**, followed by **paromomycin** or **iodoquinol** to eliminate cysts.
- Therapy for giardiasis consists of metronidazole or tinidazole, with quinacrine representing an alternative agent.

SPECIAL CONSIDERATIONS

- **Opportunistic agents**, including *Cryptosporidium*, *Microsporidium*, cytomegalovirus (CMV), *Mycobacterium avium* complex (MAC), and *Mycobacterium tuberculosis*, may cause **diarrhea in patients with advanced HIV** (CD4 counts <50 cells/μL). However, *C. difficile* may be the most commonly identified bacterial pathogen (*Gut 2008;57:861*).
- Other causes of diarrhea in this population include venereal infections (syphilis, gonorrhea, chlamydia, herpes simplex virus [HSV]) as well as other nonvenereal infections (amebiasis, giardiasis, salmonellosis, shigellosis). Intestinal lymphoma and Kaposi sarcoma can also cause diarrhea.
- Stool studies (ova and parasites, culture), endoscopic biopsies, and serologic testing may assist in diagnosis. Management consists of specific therapy if pathogens are identified; symptomatic measures may be of benefit in idiopathic cases (*Gastroenterol Clin North Am 2012;41:677*).

Constipation

GENERAL PRINCIPLES

Definition

Constipation consists of infrequent (and frequently incomplete) bowel movements, sometimes associated with straining and passage of pellet-like stools.

Etiology

- Recent changes in bowel habits may suggest an organic cause, whereas long-standing constipation is more likely to be functional.
- **Medications** (e.g., calcium channel blockers, opiates, anticholinergics, iron supplements, barium sulfate) and systemic diseases (e.g., diabetes mellitus, hypothyroidism, systemic sclerosis, myotonic dystrophy) may contribute.
- Female gender, older age, lack of exercise, low caloric intake, low-fiber diet, and disorders that cause pain on defecation (e.g., anal fissures, thrombosed external hemorrhoids) are other risk factors (*Am Fam Physician 2011;84:299*).

DIAGNOSIS

- Colonoscopy and barium studies help rule out structural disease and may be particularly important in individuals >50 years without prior colorectal cancer screening or with alarm features such as anemia, blood in the stool, or new-onset symptoms (*Gastroenterology 2013;144:211*).
- Colonic transit studies, anorectal manometry, and defecography are reserved for resistant cases without a structural explanation after initial workup.

TREATMENT

- Regular exercise and adequate fluid intake are nonspecific measures.
- Increase in **dietary fiber** intake to 20-30 g/d may have value. However, fecal impactions should be resolved before fiber supplementation is initiated.

Medications

- **Laxatives**
  - **Emollient laxatives** such as docusate sodium, 50-200 mg PO daily, and docusate calcium, 240 mg PO daily, allow water and fat to penetrate the fecal mass. Mineral oil (15-45 mL PO q6-8h) can be given orally or by enema.
  - **Stimulant cathartics** such as castor oil, 15 mL PO, stimulate intestinal secretion and increase intestinal motility. Anthraquinones (cascara, 5 mL PO daily; senna, one tablet PO daily to qid) stimulate the colon by increasing fluid and water accumulation in the proximal colon. Bisacodyl (10-15 mg PO at bedtime, 10-mg rectal suppositories) stimulates colonic peristalsis, resulting in effective and well-tolerated treatment for chronic constipation (*Clin Gastroenterol Hepatol 2011;9:577*).
  - **Osmotic cathartics** include nonabsorbable salts or carbohydrates that cause water retention in the

lumen of the colon. Magnesium salts include milk of magnesia (15-30 mL q8-12h) and magnesium citrate (200 mL PO), to be avoided in renal failure. Lactulose (15-30 mL PO bid-qid) can cause bloating as a side effect.

- **Lubiprostone** (8-24 µg PO bid) is a selective intestinal chloride channel activator, causing movement of fluid into the bowel lumen and stimulating peristalsis, thus facilitating spontaneous bowel movements in chronic idiopathic constipation (*Clin Gastroenterol Hepatol 2015;13(2):29*).

- **Linaclotide** (145-290 µg PO qday) is an agonist of the guanylate cyclase C receptor and also causes movement of fluid into the intestinal lumen, thereby improving symptoms of constipation (*N Engl J Med 2011;365:567*).

- **Enemas.** Sodium biphosphate (Fleet) enemas can be used for mild-to-moderate constipation and for bowel cleansing before sigmoidoscopy; these should be avoided in renal failure. Tap water enemas (1 L) are also useful. Oil-based enemas (cottonseed, Colace, hypaque) can be used in refractory constipation.
- **Polyethylene glycol** in powder form (MiraLax, 17 g PO daily to bid) can be used regularly or intermittently for the treatment of constipation.
- **Subcutaneous methylnaltrexone**, a selective peripherally acting µ-opioid receptor antagonist, is effective for rapid relief of opioid-induced constipation (*Am J Gastroenterol 2013;108:1566*; *N Engl J Med 2008;358:2332*). Prucalopride is approved in Europe for chronic constipation (*Aliment Pharmacol Ther 2010;32:1113*).
- **Bowel-cleansing agents.** Patients should be placed on a clear liquid diet the previous day and kept nothing by mouth (NPO) for 6 hours or overnight prior to colonoscopy. Patients may experience mild abdominal discomfort, nausea, and vomiting with the bowel preparation.
  - An iso-osmotic **polyethylene glycol solution** (PEG, GoLYTELY, or NuLYTELY, 1 gallon, administered at a rate of 8 oz every 10 minutes) is commonly used as a bowel-cleansing agent before colonoscopy. Lower volume preparations, such as PEG (2 L or 0.5 gallon) with ascorbic acid or other laxatives, are alternatives (*Aliment Pharmacol Ther 2010;32:637*).

    Nonabsorbable phosphate (Fleet phosphosoda, 20-45 mL with 10-24 oz liquid, taken the day before and morning of the procedure), a hyperosmotic solution, draws fluid into the gut lumen and produces bowel movements in 0.5-6.0 hours. It is also available in pill form (Visicol or OsmoPrep, 32-40 tablets, taken at the rate of 3-4 tablets every 15 min with 8 oz fluid). Phosphosoda can result in severe dehydration, hyperphosphatemia, hypocalcemia, hypokalemia, hypernatremia, and acidosis. A dreaded rare complication is **acute phosphate nephropathy**, where calcium phosphate deposits cause irreversible dysfunction of renal tubules resulting in renal failure. Consequently, phosphosoda is only used in limited instances.
  - **Split preparations.** Proximity of bowel preparation to procedure time improves effectiveness of cleansing and visualization during the procedure. Therefore, splitting bowel preparation into two doses may be useful, with one dose administered the evening prior and the second dose administered the morning of the procedure (*Am J Gastroenterol 2012;107:1036*; *Am J Gastroenterol 2010;105:1319*).
  - **Two-day bowel preparation** is sometimes indicated in elderly or debilitated individuals when conventional bowel preparation is contraindicated, not tolerated, or ineffective. This consists of magnesium citrate (120-300 mL PO) administered on two consecutive days while the patient remains on a clear liquid diet; bisacodyl (30 mg PO or 10-mg suppository) is administered on both days.
  - **Tap water enemas** (1-L volume) can cleanse the distal colon when colonoscopy is indicated in patients with proximal bowel obstruction.

- Other options: **Biofeedback therapy** and **sacral nerve stimulation** can be effective for idiopathic constipation resistant to medical treatment (*Gut 2010;59:333*).

LUMINAL GASTROINTESTINAL DISORDERS

Gastroesophageal Reflux Disease

GENERAL PRINCIPLES

Definition

Gastroesophageal reflux disease (GERD) is defined as symptoms and/or complications resulting from reflux of gastric contents into the esophagus and more proximal structures.

DIAGNOSIS

Clinical Presentation

- Typical esophageal symptoms of GERD include **heartburn** and **regurgitation**. GERD can also present as **chest pain**, where an important priority is to exclude a cardiac source before initiating a GI evaluation (*Am J Gastroenterol 2013;108:308*).
- **Extraesophageal manifestations** can include cough, laryngitis, asthma, and dental erosions.
- Symptom response to a therapeutic trial of PPIs can be diagnostic, but a negative response does not exclude GERD (*Gastroenterology 2008;135:1392*).

Differential Diagnosis

Other disorders that can result in esophagitis include:

- **Eosinophilic esophagitis (EoE)**, characterized by eosinophilic infiltration of esophageal mucosa, is increasingly recognized as an etiology for foregut symptoms.
  - Atopy (allergic rhinitis, eczema, asthma) is common, and food allergens may trigger the process. Transit symptoms (dysphagia) are prominent, but symptoms can also mimic GERD.
  - Common EGD findings include furrows, luminal narrowing, corrugations, and whitish plaques in the esophageal mucosa. The diagnosis of EoE is a clinicopathologic one, consisting of (a) symptoms related to esophageal dysfunction (such as dysphagia or food impaction), (b) ≥15 eosinophils per HPF on esophageal biopsies, and (c) exclusion of secondary causes of esophageal eosinophilia (such as GERD). Typically, a 2-month course of PPI bid should be given and followed by a repeat EGD with esophageal biopsies to rule out **PPI-responsive esophageal eosinophilia** and confirm the diagnosis of EoE (*Am J Gastroenterol 2013;108:679*).
  - First-line therapy for EoE includes **topical steroids** (swallowed fluticasone, 880-1760 µg/d in two to four divided doses, or swallowed budesonide, 2 mg/d in two to four divided doses); prednisone is an alternate option if topical steroids are ineffective (*Gastroenterology 2014;147:324*). Food allergen testing can be considered, but the yield is typically low. Regardless, elimination of dietary allergens is appropriate when identified. Concomitant GERD requires PPI therapy. Patients who do not respond to topical steroids may benefit from longer courses or higher doses of topical steroids, systemic steroids, elimination diet trials, or cautious esophageal dilation.

- **Infectious esophagitis** typically presents with dysphagia or odynophagia and is seen most often in immunocompromised states (AIDS, organ transplant recipients), esophageal stasis (abnormal motility [e.g., achalasia, scleroderma], mechanical obstruction [e.g., strictures]), malignancy, diabetes mellitus, and antibiotic use; however, it can rarely occur in the normal healthy host. The presence of typical oral lesions (thrush, herpetic vesicles) may suggest an etiologic agent. The usual presenting symptoms are dysphagia and odynophagia.
  - ***Candida* esophagitis** is the most common esophageal infection and typically occurs in the setting of esophageal stasis, impaired cell-mediated immunity from immunosuppressive therapy (e.g., with steroids or cytotoxic agents), malignancies, or AIDS. Endoscopic visualization of typical whitish plaques has near 100% sensitivity for diagnosis. Empiric antifungal agents are appropriate when concurrent oropharyngeal thrush is present, reserving endoscopy for nonresponse to therapy. **Fluconazole** 100-200 mg/d or **itraconazole** 200 mg/d for 14-21 days is recommended as initial therapy for *Candida* esophagitis; nystatin (100,000 units/mL, 5 mL tid for 3 weeks) and clotrimazole troches (10 mg four to five times a day for 2 weeks) are alternatives for oropharyngeal candidiasis. For infections refractory to azoles, a short course of parenteral **amphotericin B** (0.3-0.5 mg/kg/d) can be considered (*Best Pract Res Clin Gastroenterol 2008;22:639*).

  - **HSV esophagitis** is characterized by small vesicles and well-circumscribed ulcers on endoscopy and typical giant cells on histopathology. Viral antigen or DNA can be identified by immunofluorescent antibodies. Treatment consists of **acyclovir** 400-800 mg PO five times a day for 14-21 days or 5 mg/kg IV q8h for 7-14 days. **Famciclovir** and **valacyclovir** are alternate agents. The condition is usually self-limited in immunocompetent hosts (*Curr Opin Gastroenterol 2008;24:496*).
  - **CMV esophagitis**, which occurs almost exclusively in immunocompromised hosts, can cause erosions or frank ulcerations. **Ganciclovir** 5 mg/kg IV q12h or **foscarnet** 90 mg/kg IV q12h for 3-6 weeks can be used as initial therapy. Oral **valganciclovir** may also be effective.
  - Symptomatic relief can be achieved with 2% viscous **lidocaine** swish and swallow (15 mL PO q3-4h PRN) or **sucralfate** slurry (1 g PO qid).
- **Chemical esophagitis**
  - Ingestion of caustic agents (alkalis, acids) or medications such as oral potassium, doxycycline, quinidine, iron, NSAIDs, aspirin, and bisphosphonates can result in mucosal irritation and damage.
  - With caustic ingestions, cautious early EGD can evaluate the extent and degree of mucosal damage, and CT can rule out transmural esophageal necrosis in the setting of mucosal necrosis (*Best Pract Res Clin Gastroenterol 2013;27:679*).
  - The offending medication should be discontinued if possible. Mucosal coating agents (sucralfate) and acid suppressive agents may help. A second caustic agent to neutralize the first is contraindicated.

Diagnostic Testing

- **Endoscopy** with biopsies is primarily indicated for avoiding misdiagnosis of alternate causes of esophageal symptoms (e.g., EoE), identification of complications, and evaluation of treatment failures. **Alarm symptoms** of dysphagia, odynophagia, early satiety, weight loss, or bleeding should prompt

endoscopy (*N Engl J Med 2008;359:1700*).

- **Ambulatory pH or pH impedance monitoring** can be used to quantify esophageal acid exposure and reflux events and/or to assess symptom-reflux correlation in patients with ongoing symptoms despite acid suppression (especially if endoscopy is negative) or those with atypical symptoms. pH impedance testing detects all reflux events regardless of pH and is best performed off PPI therapy to increase yield; abnormal studies can predict symptomatic response to medical or surgical antireflux therapy (*Clin Gastroenterol Hepatol 2015;13(5):884*).
- **Esophageal manometry**, particularly HRM, may identify motor processes contributing to refractory symptoms.

TREATMENT

Medications

- Intermittent or prophylactic over-the-counter **antacids**, **H_2RAs**, and **PPIs** are effective with mild or intermittent symptoms.
- **PPIs** are more effective than standard-dose H_2RA and placebo in symptom relief and endoscopic healing of GERD. Modest gain is achieved by doubling the PPI dose in severe esophagitis or persistent symptoms. Continuous long-term PPI therapy is effective in maintaining remission of GERD symptoms, but the dose should be decreased after 8-12 weeks to the lowest dose that achieves symptom relief (*N Engl J Med 2008;359:1700*). Abdominal pain, headache, and diarrhea are common side effects. Long-term PPI use has been associated with bone demineralization, enteric infections, community-acquired pneumonia, and reduced circulating levels of vitamin B_{12} in observational studies, but benefits of PPI therapy continue to outweigh risks.

TABLE 18-2 Dosage of Acid-Suppressive Agents

Medication Therapy	Peptic Ulcer Disease	GERD	Parenteral
Cimetidine[a]	300 mg qid 400 mg bid 800 mg at bedtime	400 mg qid 800 mg bid	300 mg q6h
Ranitidine[a]	150 mg bid 300 mg at bedtime	150-300 mg bid-qid	50 mg q8h
Famotidine[a]	20 mg bid 40 mg at bedtime	20-40 mg bid	20 mg q12h
Nizatidine[a]	150 mg bid 300 mg at bedtime	150 mg bid	
Omeprazole	20 mg daily	20-40 mg daily-bid	

Esomeprazole	40 mg daily	20-40 mg daily-bid	20-40 mg q24h
Lansoprazole	15-30 mg daily	15-30 mg daily-bid	30 mg q12-24h
Dexlansoprazole		30-60 mg daily	
Pantoprazole	20 mg daily	20-40 mg daily-bid	40 mg q12-24h or 80 mg IV, then 8 mg/h infusion

GERD, gastroesophageal reflux disease.

[a]Dosage adjustment required in renal insufficiency.

- Standard doses of **H_2RAs** (Table 18-2) can result in symptomatic benefit and endoscopic healing in up to half of patients. Dosage adjustments are required in renal insufficiency.
- Reflux inhibitors consist of γ-aminobutyric acid (GABA) type B receptor agonists that block transient LES relaxations. **Baclofen**, the prototype agent, reduces reflux events, but central side effects can be limiting (*Aliment Pharmacol Ther 2012;35:1036*).

Surgical Management

- Indications for **fundoplication** include the need for continuous PPIs, noncompliance or intolerance to medical therapy in patients who are good surgical candidates, ongoing nonacid reflux despite adequate medical therapy, and patient preference for surgery. When symptoms are controlled on PPI therapy, medical therapy and fundoplication are equally effective. Although fundoplication could provide better symptom control and quality of life in the short term, new postoperative symptoms and surgical failure can also occur (*Surg Endosc 2011;25:2547*).
- Elevated esophageal acid exposure and correlation of symptoms to reflux events on ambulatory pH monitoring predict a higher likelihood of a successful surgical outcome.
- Patients with medical treatment failures need careful evaluation to determine whether symptoms are indeed related to acid reflux before surgical options are considered; these patients often have other diagnoses including EoE, esophageal motor disorders, visceral hypersensitivity, and functional heartburn.
- Potential complications of surgery include dysphagia, inability to belch, gas-bloat syndrome, and bowel symptoms including flatulence, diarrhea, and abdominal pain.

Lifestyle/Risk Modification

- Patients with nocturnal GERD symptoms may benefit from elevating the head of the bed and avoiding meals within 2-3 hours before bedtime.
- Weight loss may benefit certain overweight patients with GERD.
- Lifestyle modifications alone are unlikely to resolve symptoms in the majority of GERD patients and should be recommended in conjunction with medications.

COMPLICATIONS

- **Esophageal erosion and ulceration** (esophagitis) can rarely lead to overt bleeding and iron deficiency anemia.
- **Strictures** can form when esophagitis heals, leading to dysphagia. Endoscopic dilation and maintenance PPI therapy typically resolve dysphagia from strictures.
- **Barrett esophagus (BE)** is a reflux-triggered change from normal squamous esophageal epithelium to specialized intestinal metaplasia and carries a 0.5% per year risk of progression to esophageal adenocarcinoma. Endoscopic screening for BE should be considered for patients with GERD who are at high risk (long duration of GERD symptoms, ≥50 years of age, male gender, Caucasian); patients who are found with BE should undergo periodic surveillance every 3 to 5 years in the absence of dysplasia (*Am J Gastroenterol 2013;108:308*). If high-grade dysplasia is found in the setting of BE, endoscopic therapy (usually radiofrequency ablation) is preferred to surveillance or surgery (*Gastroenterology 2012;143:336*).

Esophageal Motor Disorders

GENERAL PRINCIPLES

Definition

- **Achalasia** is the most easily recognized motor disorder of the esophagus, characterized by failure of the LES to relax completely with swallowing and aperistalsis of the esophageal body (*Am J Gastroenterol 2013;108:1238*).
- **Diffuse esophageal spasm** is a spastic disorder characterized by premature, nonperistaltic contractions in the esophageal body (*Gastroenterology 2011;141:469*).
- **Esophageal hypomotility disorders** are characterized by fragmented, ineffective, or absent esophageal peristalsis, sometimes with LES hypomotility, leading to reflux symptoms.

DIAGNOSIS

Clinical Presentation

- Presenting symptoms in achalasia can include dysphagia, regurgitation, chest pain, weight loss, and aspiration pneumonia.
- Diffuse esophageal spasm and other spastic disorders may have obstructive symptoms (dysphagia, regurgitation) but also perceptive symptoms (chest pain) from heightened esophageal sensitivity.
- LES hypomotility diminishes barrier function, and esophageal body hypomotility affects esophageal clearance of refluxed material, which can lead to prolonged reflux exposure and reflux complications.

Diagnostic Testing

- **Esophageal HRM** represents the gold standard for the diagnosis of esophageal motor disorders (*Neurogastroenterol Motil 2013;25:99*). HRM features categorize achalasia into

three subtypes that have symptomatic and therapeutic implications (*Neurogastroenterol Motil 2014;27:160*).
- **Barium radiographs** may demonstrate a typical appearance of a dilated intrathoracic esophagus with impaired emptying, an air-fluid level, absence of gastric air bubble, and tapering of the distal esophagus

with a bird's beak appearance in achalasia. A beaded or corkscrew appearance may be seen with diffuse esophageal spasm. A dilated esophagus with an open LES and free gastroesophageal reflux may be seen with severe esophageal hypomotility.

- **Endoscopy** may help exclude a stricture or neoplasia of the distal esophagus in presumed achalasia and spastic disorders. Hypomotility disorders may also manifest a dilated esophagus but with a gaping gastroesophageal junction and evidence of reflux disease.

TREATMENT

Medications

- **Smooth muscle relaxants** such as nitrates or calcium channel blockers administered immediately before meals may afford short-lived symptom relief in spastic disorders and achalasia, but symptom response is suboptimal. Phosphodiesterase inhibitors may provide benefit in hypercontractile disorders but may be contraindicated in coronary disease.
- **Botulinum toxin** injection at endoscopy can improve dysphagia symptoms for several weeks to months in achalasia and spastic disorders with incomplete LES relaxation (*Am J Gastroenterol 2013;108:1238*). This approach may be useful in elderly and frail patients who are poor surgical risks or as a bridge to more definitive therapy.
- **Neuromodulators** (e.g., low-dose tricyclic antidepressants [TCAs]) may improve perceptive symptoms (such as chest pain) associated with spastic motor disorders and achalasia.
- **Antisecretory therapy** with a PPI is recommended for reflux associated with esophageal hypomotility disorders. No specific promotility therapy exists. Antireflux surgery should be approached with caution in advanced hypomotility disorders.

Surgical Management

Disruption of the circular muscle of the LES using **pneumatic dilation** or surgical incision **(Heller myotomy)** can result in durable symptom relief in achalasia, with comparable symptom outcomes (*N Engl J Med 2011;364:1807*). Gastroesophageal reflux can result, treated with lifelong acid suppression or concurrent partial fundoplication during myotomy. Esophageal perforation occurs in 3-5% of patients with pneumatic dilation, requiring prompt surgical repair. **Peroral endoscopic myotomy (POEM)** is a new technique with good short-term symptom improvement (*Gastroenterology 2013;145:309*; *Surgery 2013;154:885*).

COMPLICATIONS

- Complications of achalasia include aspiration pneumonia and weight loss.
- Achalasia is associated with a 0.15% risk of squamous cell cancer of the distal esophagus, a 33-fold higher risk relative to the nonachalasia population.

Peptic Ulcer Disease

GENERAL PRINCIPLES

Definition

PUD consists of mucosal breaks in the stomach and duodenum when corrosive effects of acid and pepsin overwhelm mucosal defense mechanisms. Other locations include esophagus, small bowel adjacent to gastroenteric anastomoses, and within a Meckel diverticulum.

Etiology

- ***Helicobacter pylori***, a spiral, gram-negative, urease-producing bacillus, is responsible for at least half of all PUD and the majority of ulcers that are not due to NSAIDs.
- PUD can develop in 15-25% of **chronic NSAID and aspirin** users. Past history of PUD, age >60 years, concomitant corticosteroid or anticoagulant therapy, high-dose or multiple NSAID therapy, and presence of serious comorbid medical illnesses increase risk for PUD (*J Clin Gastroenterol 1997;24:2*).
- A gastrin-secreting tumor or **gastrinoma** accounts for <1% of all peptic ulcers.
- Gastric cancer or lymphoma may manifest as a gastric ulcer.
- When none of these etiologies are evident, PUD is designated idiopathic. Most idiopathic PUD could be due to undiagnosed *H. pylori* or undetected NSAID use.
- Cigarette smoking doubles the risk for PUD; it delays healing and promotes recurrence.

DIAGNOSIS

Clinical Presentation

- Epigastric pain or dyspepsia may be presenting symptoms; however, symptoms are not always predictive of the presence of ulcers. Epigastric tenderness may be elicited on abdominal palpation. Ten percent may present with a complication (see Complications).
- In the presence of **alarm symptoms** (weight loss, early satiety, bleeding, anemia, persistent vomiting, epigastric mass, and lack of response to PPI), EGD should be performed to assess for complications or alternate diagnoses.

Diagnostic Testing

- **Endoscopy** is the gold standard for diagnosis of peptic ulcers. **Barium studies** also have good sensitivity for diagnosis of ulcers, but smaller ulcers and erosions may be missed, and tissue sampling for *H. pylori* or cancer cannot be performed.
- **Serum *H. pylori* antibody testing** is the cheapest noninvasive test with a sensitivity of 85% and a specificity of 79% for the diagnosis of *H. pylori* infection. The antibody remains detectable as long as 18 months after successful eradication and cannot be used to document successful eradication of the organism.
- **Stool *H. pylori* antigen testing** has 91% sensitivity and 93% specificity for the diagnosis of *H. pylori* infection and can confirm eradication of *H. pylori* after triple therapy.
- **Rapid urease assay** (e.g., *Campylobacter*-like organism [CLO] test) and histopathologic examination of endoscopic biopsy specimens are commonly used for diagnosis in patients undergoing endoscopy but may be falsely negative in patients on PPI therapy.
- **Carbon-labeled urea breath testing** is the most accurate noninvasive test for diagnosis, with sensitivity and specificity of 95%; it is often used to document successful eradication after therapy of *H. pylori* infection (*BMJ 2008;337:a1400*).

TREATMENT

Medications

- Regardless of etiology, **acid suppression** forms the mainstay of therapy of PUD. Gastric ulcers are typically treated for 12 weeks and duodenal ulcers for 8 weeks.
- Oral PPI or H_2RA therapy will suffice in most instances (see Table 18-2). Dosage adjustment of H_2RAs is necessary in renal insufficiency. Cimetidine can impair metabolism of many drugs, including warfarin anticoagulants, theophylline, and phenytoin.
- Two antibiotics and a PPI (triple therapy) is the standard regimen for ***H. pylori* eradication**, which promotes healing and markedly reduces PUD recurrence. Several antimicrobial and antisecretory agent regimens are available (Table 18-3). Levofloxacin-based

sequential or triple therapy may be superior to standard triple therapy (clarithromycin, amoxicillin, PPI) (*Hepatogastroenterology 2011;58:1148*). Other regimens may include LOAD (**l**evofloxacin, **o**meprazole, nit **a**zoxanide, and **d**oxycycline) for 7-10 days; ofloxacin, azithromycin, omeprazole, and bismuth for 14 days; and PPI, bismuth, tetracycline, and levofloxacin for 10 days (*Helicobacter 2014;19:74*; *Am J Gastroenterol 2011;106:1970*). Patients previously exposed to a macrolide antibiotic should be treated with a regimen that does not include clarithromycin.

TABLE 18-3 Regimens Used for Eradication of *Helicobacter pylori*

Medications and Doses	Comments
Clarithromycin (500 mg bid), amoxicillin (1 g bid), and PPI[a]	First-line therapy
Metronidazole (500 mg bid), amoxicillin (1 g bid), and PPI[a]	First-line therapy in setting of prior macrolide exposure
Clarithromycin (500 mg bid), metronidazole (500 mg bid), and PPI[a]	First-line therapy for penicillinallergic patients
Amoxicillin (1 g bid) and PPI[a] for 5 days, followed by clarithromycin (500 mg bid), metronidazole (500 mg bid), and PPI[a] for another 5 days	Sequential therapy
Tetracycline (500 mg qid), metronidazole (250 mg qid), bismuth (525 mg qid), and PPI[a]	Bismuth-containing quadruple therapy; salvage regimen
Levofloxacin (250 mg bid), amoxicillin (1 g bid), and PPI[a]	Levofloxacin-based triple therapy; salvage regimen

Two antibiotics selected by sensitivity testing on culture, bismuth (525 mg qid), and PPI[a]	Culture-guided therapy (if failed multiple regimens)

PPI, proton pump inhibitor.
Duration of therapy: 10-14 days. When using salvage regimens after initial treatment failure, choose drugs that have not been used before.

[a]Standard doses for PPI: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, all twice a day. Esomeprazole is used as a single 40-mg dose once a day.

- NSAIDs and aspirin should be avoided when possible; if continued, maintenance PPI therapy or a mucosal protective agent (misoprostol, 400-800 µg/d) is recommended (*Gut 2014;63:1061*).
- **Sucralfate** coats the eroded mucosal surface without blocking acid secretion and is often used in stress ulcer prophylaxis. Side effects include constipation and reduction of bioavailability of certain drugs (e.g., cimetidine, digoxin, fluoroquinolones, phenytoin, and tetracycline) when administered concomitantly.
- **Antacids** can be useful as supplemental therapy for pain relief in PUD.
- **Nonpharmacologic measures.** Cessation of cigarette smoking should be encouraged. Alcohol in high concentrations can damage the gastric mucosal barrier, but no evidence exists to link alcohol with ulcer recurrence.

Surgical Management

Surgery is still occasionally required for intractable symptoms, GI bleeding, Zollinger-Ellison syndrome, and complicated PUD. Surgical options vary depending on the location of the ulcer and the presence of complications.

SPECIAL CONSIDERATIONS

- **Zollinger-Ellison syndrome** is caused by a gastrin-secreting, non-β islet cell tumor of the pancreas or duodenum. Multiple endocrine neoplasia type I can be associated with this syndrome in one-quarter to one-third of patients (*Clin Gastroenterol Hepatol 2012;10:126*). The resultant hypersecretion of gastric acid can cause multiple PUD in unusual locations, ulcers that fail to respond to standard medical therapy, or recurrent PUD after surgical therapy. Diarrhea and GERD symptoms are common.
- Gastric acid output is typically >15 mEq/L, and gastric pH is <1.0. A fasting serum gastrin level while off acid suppression for at least 5 days serves as a screening test in patients who make gastric acid; a value >1000 pg/mL is seen in 90% of patients with Zollinger-Ellison syndrome. When serum gastrin is elevated but <1000 pg/mL, a secretin stimulation test may demonstrate a paradoxical 200-pg increment in serum gastrin level after IV secretin in patients with gastrinomas (*Aliment Pharmacol Ther 2009;29:1055*). High-dose PPIs are used for medical management. Specialized nuclear medicine scans (octreotide scans) can be useful in localizing the neoplastic lesion for curative resection. Long-term survival is principally related to underlying comorbidity rather than metastatic gastrinoma (*Dig Liver Dis 2011;43:439*).

COMPLICATIONS

- **GI bleeding** (see Gastrointestinal Bleeding section).

- **Gastric outlet obstruction** can occur with ulcers close to the pyloric channel and can manifest as nausea and vomiting, sometimes several hours after meals. Plain abdominal radiographs can show a dilated stomach with an air-fluid level. NG suction can decompress the stomach while fluids and electrolytes are repleted intravenously. Recurrence is common, and endoscopic balloon dilation or surgery is often necessary for definitive correction.
- **Perforation** occurs infrequently and usually necessitates emergent surgery. Perforation may occur in the absence of previous symptoms of PUD and may be asymptomatic in patients who are receiving glucocorticoids. A plain upright radiograph of the abdomen may demonstrate free air under the diaphragm.
- **Pancreatitis** can result from penetration into the pancreas from ulcers in the posterior wall of the stomach or duodenal bulb. The pain becomes severe and continuous, radiates to the back, and is no longer relieved by antisecretory therapy. Serum amylase may be elevated. CT scanning may be diagnostic. Surgery is often required for therapy.

MONITORING/FOLLOW-UP

- Repeat EGD or upper GI series should be performed 8-12 weeks after initial diagnosis of all gastric ulcers to document healing; repeat endoscopic biopsy should be considered for nonhealing ulcers to exclude the possibility of a malignant ulcer.
- Duodenal ulcers are almost never malignant; therefore, documentation of healing is unnecessary in the absence of symptoms.

Inflammatory Bowel Disease

GENERAL PRINCIPLES

- **Ulcerative colitis (UC)** is an idiopathic chronic inflammatory disease of the colon and rectum, characterized by mucosal inflammation and typically presenting with bloody diarrhea. Rectal involvement is almost universal.

- **Crohn disease (CD)** is characterized by transmural inflammation of the gut wall and can affect any part of the tubular GI tract.

DIAGNOSIS

Clinical Presentation

- Both disorders can present with diarrhea, weight loss, and abdominal pain. UC typically presents with bloody diarrhea. CD can also present with fistula formation, strictures, abscesses, or bowel obstruction.
- **Extracolonic manifestations** of inflammatory bowel disease (IBD) include arthritis, primary sclerosing cholangitis, and ocular and skin lesions.

Diagnostic Testing

- **Endoscopy** remains the preferred method for diagnosis, especially for UC, where contiguous inflammation is seen starting at the rectum and extending varying distances into the colon. Endoscopy may demonstrate colonic involvement in CD (erosions or ulcers with a patchy distribution and skip lesions); ileoscopy during colonoscopy may demonstrate terminal ileal involvement. **Histopathology** demonstrates chronic mucosal inflammation with crypt abscesses and cryptitis in UC and may demonstrate multinucleated giant cells and noncaseating granulomas in CD.

- Cross-sectional **imaging studies** (CT and MRI scans) have value in the evaluation of CD, especially when luminal narrowing (stricture) or extraluminal complications (abscess, fistula) are suspected. Although MRI and CT enterography both adequately assess disease activity and bowel involvement in CD, MRI may be superior to CT (*Gastroenterology 2014;146:374*; *Inflamm Bowel Dis 2011;17:1073*). Contrast radiography (small bowel follow-through series, barium enema) may also be useful, particularly in CD.
- **Serologic markers** play a limited role as adjuncts for diagnosis. Anti-*Saccharomyces cerevisiae* antibodies are typically seen in CD, and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are seen in UC. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) represent correlates for disease activity.
- ***C. difficile* colitis** is more frequent in IBD patients compared to non-IBD populations; therefore, **stool studies** are warranted to look for this organism with disease flares (*Clin Gastroenterol Hepatol 2007;5:339*). **CMV superinfection** can occur in patients on immunosuppressive agents and can be diagnosed by histopathology during endoscopy (*Am J Gastroenterol 2006;101:2857*).

TREATMENT

Medications

Treatment is based on the severity of disease, location, and associated complications (*Gastroenterology 2013;145:1459*). Management aims are to resolve the acute presentation and reduce future recurrences. Both UC and CD can be categorized into three categories of severity for management purposes:

- **Mild to moderate disease.** Patients have little to no weight loss and good functional capacity and are able to maintain adequate oral intake. UC patients have less than four bowel movements daily with no rectal bleeding or anemia, normal vital signs, and normal ESR, whereas CD patients have little or no abdominal pain. Treatment typically begins with aminosalicylates but can include antibiotics and glucocorticoids.
  - **5-Aminosalicylates (5-ASA).** Various formulations are available, each targeting different parts of the tubular gut, and are useful for both inducing and maintaining remission in mild to moderate disease. Infrequent hypersensitivity reactions include pneumonitis, pancreatitis, hepatitis, and nephritis.

    Sulfasalazine reaches the colon intact, where it is metabolized to 5-ASA and a sulfapyridine moiety. Benefit is seen in UC or CD limited to the colon, either as initial therapy (0.5 g PO bid, increased as tolerated to 0.5-1.5 g PO qid) or to maintain remission (1 g PO bid-qid). The sulfapyridine moiety is responsible for side effects of headache, nausea, vomiting, and abdominal pain, which are treated with dose reduction. Skin rash, fever, agranulocytosis, hepatotoxicity, and paradoxical exacerbation of colitis are rare hypersensitivity reactions. Reversible reduction in sperm counts can be seen in males. Folic acid supplementation is recommended because sulfasalazine can impair folate absorption.
  - **Mesalamine.** Newer 5-ASA preparations lack the sulfa moiety of sulfasalazine and are associated with fewer side effects but can be expensive.
    - **Asacol** is an oral formulation of 5-ASA released at a pH of 7 in the distal ileum. It is useful in UC and ileocecal/colonic CD at doses of 800-1600 mg PO tid.
    - **Pentasa** has a time- and pH-dependent release mechanism that allows drug availability throughout the small bowel and colon. It is useful in diffuse small bowel involvement with CD but can also be used in UC in doses of 0.5-1.0 g PO qid.

- **Apriso** also has a pH-dependent release mechanism and distributes mesalamine throughout the colon when administered in doses of 1.5 g PO once daily.
- **Balsalazide** (**Colazal**) is cleaved by colonic bacteria to mesalamine and an inert molecule. Therefore, it is only useful for colonic disease, at doses of 2.25 g PO tid for active disease and 1.5 g PO bid for maintenance.
- **Multimatrix delivery system mesalamine** (**Lialda**) uses a novel delivery system that allows sustained 5-ASA release throughout the colon while decreasing frequency of administration. It is useful in colonic disease at doses of 1.2-2.4 g PO qday-bid.

- **Olsalazine** (**Dipentum**) is a 5-ASA dimer cleaved by colonic bacteria and is useful in colonic disease. Significant diarrhea limits its use.

- **Antibiotics** are commonly used clinically in mild to moderate CD as well as perianal disease, but not in UC where the role of bacteria has not been established. Their role should be limited to colonic or ileocolonic CD, perianal disease, fistulas, and abscesses. Typical antibiotics used are **metronidazole** (250-500 mg PO tid) and **ciprofloxacin** (500 mg PO bid), usually concurrently, for 2-6 weeks.
  - **Budesonide** (Entocort; 6-9 mg PO qday) is a synthetic corticosteroid with first-pass liver metabolism that limits systemic toxicity while retaining local efficacy from high affinity to the glucocorticoid receptor, similar to oral corticosteroids. It is effective and safe for short-term use in mild to moderate ileocolonic CD and can replace mesalamine in inducing remission (*Gastroenterology 2013;145:1459*).
  - **Topical therapy** is useful in IBD limited to distal left colon. Topical mesalamine agents are superior to topical steroids or oral aminosalicylates for mild to moderate distal UC or ulcerative proctitis (*Am J Gastroenterol 2010;105:501*). Sitz baths, analgesics, hydrocortisone creams, and local heat may provide symptomatic benefit in perianal CD in conjunction with systemic therapy.
- **Moderate to severe disease** refers to CD patients who fail to respond to treatment for mild to moderate disease or those with significant weight loss, anemia, fever, abdominal pain or tenderness, and intermittent nausea and vomiting without bowel obstruction (*Am J Gastroenterol 2009;104:465*), or UC patients with more than six bloody bowel movements daily, fever, mild anemia, and elevated ESR. Predictive factors for moderate- to high-risk disease include age <30 years at initial diagnosis, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, and structuring or penetrating behavior (*Gastroenterology 2013;145:1459*). The goal of therapy is to induce remission rapidly with corticosteroids and to maintain remission with immunosuppressive agents and/or biologic agents as appropriate. Treatment is typically continued until the patient fails to respond to a particular agent or the agent is no longer tolerated.

  - **Glucocorticoids** are effective in inducing remission in moderate to severe disease, especially with flares of disease activity (*Gut 2011;60:571*).
    - **Prednisone** is started orally (typically 40-60 mg PO daily) and continued until symptom improvement. The dose can then be tapered on a weekly basis, because glucocorticoids are not recommended for maintenance therapy, and steroid-sparing alternatives should be sought for patients who appear dependent on these medications.
    - **Oral or parenteral glucocorticoids should not be prescribed before ruling out an infectious process and should not be initiated for the first time over the telephone.**
  - **Immunosuppressive agents**
    - **6-Mercaptopurine** (1.0-1.5 mg/kg/d PO), a purine analog, and **azathioprine** (1.5-2.5 mg/kg/d PO),

its S-imidazole precursor, cause preferential suppression of T-cell activation and antigen recognition, and are useful in maintaining a glucocorticoid-induced remission in both UC and CD. Both azathioprine and 6-mercaptopurine are effective for inducing remission in active CD (*Cochrane Database Syst Rev 2010;16:CD000545*). Response may be delayed for up to 1-2 months, with optimal response occurring about 4 months after treatment initiation. Side effects include reversible bone marrow suppression, pancreatitis, and allergic reactions.

Determination of **thiopurine methyltransferase (TPMT)** enzyme activity prior to initiation of therapy will identify genetic polymorphisms that may predispose to toxicity with the use of these agents (*Gastroenterology 2006;130:935*).

Routine blood cell counts should be performed, initially every 1-2 weeks, to monitor for acute or delayed bone marrow suppression. On stable doses, testing can be performed every 3 months.

6-Thioguanine (6-TG) metabolite levels assess adequacy of dosing, whereas high 6-methyl mercaptopurine (6-MMP) levels may predict hepatotoxicity. Addition of allopurinol to the regimen preferentially pushes metabolism toward the active metabolite (6-TG) rather than the toxic metabolite (6-MMP) (*Aliment Pharmacol Ther 2010;31:640*).

- **Methotrexate** (15-25 mg IM or PO weekly) is effective as a steroid-sparing agent in CD but not UC. Side effects include hepatic fibrosis, bone marrow suppression, alopecia, pneumonitis, allergic reactions, and teratogenicity. In CD patients in remission, methotrexate is not as effective as azathioprine or infliximab for mucosal healing (*Aliment Pharmacol Ther 2011;33:714*), and methotrexate added to infliximab is no more effective than infliximab monotherapy (*Gastroenterology 2014;146:681*).

  Baseline CXR and monitoring of CBC and liver function tests should be performed routinely.

  Patients with abnormal transaminases may require a liver biopsy to assess for hepatic fibrosis prior to treatment, and subsequent biopsies are performed for significant elevations thereafter.

- **Anti-tumor necrosis factor-α (anti-TNF-α) monoclonal antibodies** modify immune system function and are beneficial in moderate to severe CD refractory to other approaches, including immunosuppressives, and indicated both for induction and maintenance of remission. Benefit has also been demonstrated in moderate to severe UC (*Gut 2011;60:780*). **Infliximab** (**Remicade**; 5 mg/kg IV infusions at weeks 0, 2, and 6, followed by maintenance infusions every 8 weeks), **adalimumab** (**Humira**; 160 mg SC at week 0, then 80 mg SC at week 2, followed by 40 mg SC every 2 weeks), and **certolizumab pegol** (**Cimzia**; 400 mg SC at weeks 0, 2, and 4, followed by maintenance doses every 4 weeks) are the available anti-TNF-α agents. Combination therapy with infliximab and azathioprine is more effective than monotherapy with either agent in UC (*Gastroenterology 2014;146:392*). In addition to its role as an option for first-line therapy, adalimumab is also safe and effective for CD patients who have failed

infliximab therapy (*Aliment Pharmacol Ther 2010;32:1228*). However, because elective switching from IV infliximab to SC adalimumab is associated with loss of tolerance and efficacy, adherence to the first anti-TNF-α agent is encouraged (*Gut 2012;61:229*). In moderate to severe CD, infliximab plus azathioprine or infliximab monotherapy is more likely to attain steroid-free clinical remission than azathioprine monotherapy (*N Engl J Med 2010;362:1383*).

- Anti-TNF-α therapy has been associated with reactivation of latent TB; hence, placement of a purified protein derivative (PPD) skin test and CXR are essential prior to initiation of therapy (*Am J Gastroenterol 2010;105:501*). **Hepatitis B status** should also be assessed and vaccination

provided prior to therapy. Opportunistic infections as well as infectious complications can develop, and congestive heart failure may worsen during therapy.
    - Acute and delayed hypersensitivity reactions, or antibodies to infliximab and anti-double-stranded DNA antibodies, can develop with infliximab infusions. Local injection site reactions have been reported with adalimumab and certolizumab pegol therapy.
  - **Natalizumab** (**Tysabri**; 300-mg infusions at weeks 0, 4, and 8, followed by monthly infusions thereafter) is a humanized monoclonal antibody to α-4 integrin, a cellular adhesion molecule, used for moderate to severe CD refractory to all other approaches including anti-TNF-α antibodies. This agent may induce reactivation of human JC polyomavirus, causing progressive multifocal leukoencephalopathy (PML). Risk for PML can be minimized by avoiding concomitant immunosuppressive agents and close monitoring (*Am J Gastroenterol 2009;104:465*). Other infectious complications and acute hypersensitivity reactions are also possible.
  - **Vedolizumab** (**Entyvio**; 300-mg infusions at weeks 0 and 2, followed by infusions every 4-8 weeks), an α4β7 integrin antibody, has emerged as a new option for induction and maintenance of remission in both CD and UC (*N Engl J Med 2013;369:699*).
- **Severe or fulminant disease** describes patients typically hospitalized due to the severity of their symptoms. Fulminant CD patients have persistent symptoms despite conventional glucocorticoids or anti-TNF-α therapy or have high fevers, persistent vomiting, intestinal obstruction, intra-abdominal abscess, peritoneal signs, or cachexia (*Am J Gastroenterol 2009;104:465*). Fulminant colitis (both CD and UC) can present with profuse bloody bowel movements, significant anemia, systemic signs of toxicity (fever, sepsis, electrolyte disturbances, dehydration), and elevated laboratory markers of inflammation. **Toxic megacolon** occurs in 1-2% of UC patients, wherein the colon becomes atonic and modestly dilated, with significant systemic toxicity.
  - Supportive therapy consists of NPO status with NG suction if there is evidence of small bowel ileus. Dehydration and electrolyte disturbances are treated vigorously, and blood is transfused for severe anemia. Anticholinergic and opioid medication should be discontinued in toxic megacolon.
  - Initial investigation includes cross-sectional imaging to evaluate for intra-abdominal abscess. Blood cultures and stool studies to exclude *C. difficile* colitis are performed. Cautious flexible sigmoidoscopy may be done to determine severity of colonic inflammation and for biopsies to exclude CMV colitis.
  - Once infection is excluded, intensive medical therapy with IV **corticosteroids** (methylprednisolone 1 mg/kg body weight or equivalent to 40-60 mg of prednisone) and broad-spectrum antimicrobials should be initiated.
  - If response is not seen, **cyclosporine** infusion (2-4 mg/kg/d, to achieve blood levels of 200-400 ng/mL) and tacrolimus infusion represent options in fulminant UC colitis.
  - Nutritional support is administered as appropriate after 5-7 days; TPN is often indicated if enteral nutrition is not tolerated.
  - Clinical deterioration/lack of improvement despite 7-10 days of intensive medical management, evidence of bowel perforation, and peritoneal signs are indications for urgent total colectomy.

Surgical Management

- Surgery is generally reserved for fistulas, obstruction, abscess, perforation, or bleeding; medically refractory disease; and neoplastic transformation (*Gut 2011;60:571*). Stricturoplasty is an option for focal tight strictures; biopsies should be obtained to rule out cancer at stricture sites.

- In CD, recurrence close to the resected margins is common after bowel resection. Efforts should be made to avoid multiple resections in CD because of the risk of short bowel syndrome. Immunosuppressive agents should be discontinued before surgery and reinstituted if necessary during the postoperative period.
- **In UC, total colectomy is curative** and may be preferred over long-term immunosuppressive or biologic therapy.

Lifestyle/Risk Modification

- A low-roughage diet often can provide symptomatic relief in patients with mild to moderate disease or in patients with strictures.
- Patients with Crohn ileitis or ileocolonic resection may need vitamin B_{12} supplementation. Specific oral replacement of calcium, magnesium, folate, iron, vitamins A and D, and other micronutrients may be necessary in patients with small bowel CD.
- **TPN** can be administered in patients with food intolerance for greater than 4 or 5 days. Bowel rest has not been shown to reduce time to remission but can be used for nutritional maintenance and symptom relief while waiting for the effects of medical treatment or as a bridge to surgery.

SPECIAL CONSIDERATIONS

- In patients with both UC and Crohn colitis lasting longer than 8-10 years, annual or biennial **colonoscopic surveillance for neoplasia** with four-quadrant mucosal biopsies every 5-10 cm is recommended. Histopathologic evidence of any grade of dysplasia is an indication for total colectomy. Narrow-band imaging during colonoscopy may represent an alternative to chromoendoscopy for targeted biopsies in IBD (*Gastrointest Endosc 2011;74:840*).
- **Smoking cessation** is generally warranted for all patients with IBD. There is epidemiologic evidence of a protective effect on a limited number of patients with UC. However, nicotine has been shown to increase metabolism of many medications routinely used to treat IBD, decreasing their efficacy.
- **Venous thromboembolism.** Patients with IBD are at increased risk for both first and recurrent venous thromboembolism (*Gastroenterology 2011;139:779*).
- **Symptom control** is important as adjunct to therapy but must be used cautiously.
  - **Antidiarrheal agents** may be useful as an adjunctive therapy in selected patients with mild exacerbations or postresection diarrhea. They are contraindicated in severe exacerbations and toxic megacolon.
  - **Narcotics** should be used sparingly for pain control, because the chronicity of symptoms can lead to potential for dependence.

Functional Gastrointestinal Disorders

GENERAL PRINCIPLES

Definition

- Functional GI disorders are characterized by the presence of abdominal symptoms in the absence of a demonstrable organic disease process. Symptoms can arise from any part of the luminal gut.

- **Irritable bowel syndrome (IBS)**, primarily characterized by abdominal pain linked to altered bowel habits of at least 3 months in duration, is the best-recognized functional bowel disease.

DIAGNOSIS

- Clinical evaluation and investigation should be directed toward prudently excluding organic processes in the involved area of the gut while initiating therapeutic trials when functional symptoms are suspected.
- **Serologic tests for celiac sprue** are recommended in IBS patients. The prevalence of celiac sprue in diarrhea-predominant IBS patients is estimated at 3.6%, compared to 0.7% of the general population (*Am J Gastroenterol 2009;104:S1*).
- Patients >50 years old with new-onset bowel symptoms, patients with alarm symptoms (GI bleeding, anemia, weight loss, early satiety), and patients with symptoms not responding to empiric treatment need further workup with endoscopy. Routine cross-sectional imaging is not recommended with typical functional symptoms without alarm features.
- In young individuals with short-lived symptoms and no other explanation for dyspepsia, noninvasive testing for *H. pylori* can be considered (*BMJ 2008;337:a1400*).

TREATMENT

Patient education, reassurance, and help with diet and lifestyle modification are key to an effective physician-patient relationship. The psychosocial contribution to symptom exacerbation should be determined, and its management may be sufficient for many patients. Diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) appear to reduce functional GI symptoms in patients with IBS (*Gastroenterology 2014;146:67*).

Medications

- **Symptomatic management**
  - **Antiemetic agents** are useful in functional nausea and vomiting syndromes, in addition to neuromodulators.
  - When pain and bloating are the predominant symptoms, **antispasmodic** or **anticholinergic** medications (hyoscyamine, 0.125-0.25 mg PO/sublingual up to qid; dicyclomine, 10-20 mg PO qid) may provide short-term relief.
  - Stool frequency, but not abdominal pain, improves with increased dietary fiber (25 g/d) supplemented with PRN laxatives in constipation-predominant IBS.
  - **Loperamide** (2-4 mg, up to qid/PRN) can reduce stool frequency, urgency, and fecal incontinence.
  - Short-term nonabsorbable **antibiotic** therapy may improve bloating and diarrhea in IBS; long-term treatment has not been adequately studied. **Probiotics** (e.g., bifidobacteria) are sometimes beneficial (*Am J Gastroenterol 2009;104:S1*).
  - **Lubiprostone** (8 µg bid), a selective chloride channel activator, and **linaclotide** (290 µg daily), a guanylate cyclase C agonist, improve constipation-predominant IBS symptoms (*Gastroenterology 2014;147:1146*; *Clin Gastroenterol Hepatol 2014;12:616*). Moreover, polyethylene glycol 3350 plus electrolytes is suitable for use in constipation-predominant IBS (*Am J Gastroenterol 2013;108:1508*).
  - **Alosetron** (Lotronex, 1 mg daily to bid), a 5-HT3 antagonist, is useful in women with diarrhea-

predominant IBS (*Am J Gastroenterol 2009;104:1831*). However, its use is restricted to refractory diarrhea because of the rare potential for ischemic colitis.

- **Neuromodulators**
  - Low-dose **TCAs** (e.g., amitriptyline, nortriptyline, imipramine, doxepin: 25-100 mg at bedtime) have neuromodulatory and analgesic properties that are independent of their psychotropic effects. These can be beneficial, especially in pain-predominant functional GI disorders.
  - **Selective serotonin reuptake inhibitors (SSRIs)** (e.g., fluoxetine, 20 mg; paroxetine, 20 mg; sertraline, 50 mg; duloxetine, 20-60 mg) may also have efficacy, sometimes with better side effect profiles compared to TCAs.
  - **Cyclic vomiting syndrome (CVS)** is an increasingly recognized condition with stereotypic episodes of vigorous vomiting and asymptomatic intervals between episodes (*Aliment Pharmacol Ther 2011;34:263*). Treatment with low-dose TCAs or antiepileptic medications (zonisamide, levetiracetam) has prophylactic benefits (*Clin Gastroenterol Hepatol 2007;5:44*). Sumatriptan (25-50 mg PO, 5-10 mg transnasally, or 6 mg SC) or other triptans may abort an episode, especially if administered during a prodrome or early in the episode (*Cephalalgia 2011;31:504*). Established episodes may require IV hydration, scheduled IV antiemetics (ondansetron, prochlorperazine), benzodiazepines (lorazepam), and pain control with IV narcotics.

Acute Intestinal Pseudo-Obstruction (Ileus)

GENERAL PRINCIPLES

Definition

- **Acute intestinal pseudo-obstruction or ileus** consists of impaired transit of intestinal contents and obstructive symptoms (nausea, vomiting, abdominal distension, lack of bowel movements) without a mechanical explanation.
- **Acute colonic pseudo-obstruction** or **Ogilvie syndrome** describes massive colonic dilation without mechanical obstruction in the presence of a competent ileocecal valve, resulting from impaired colonic peristalsis (*Br J Surg 2009;96:229*).

Etiology

Ileus is frequently seen in the postoperative period. Narcotic analgesics administered for postoperative pain control may contribute, as can other medications that slow intestinal peristalsis (calcium channel blockers, anticholinergic medications, TCAs, antihistamines). Other predisposing causes include virtually any medical insult, particularly life-threatening systemic diseases, infection, vascular insufficiency, and electrolyte abnormalities. Etiology is similar for acute colonic pseudo-obstruction.

DIAGNOSIS

- A careful history and physical exam is essential in the initial evaluation.
- Conventional laboratory studies (CBC, complete metabolic profile, amylase, lipase) help in assessing for a primary intra-abdominal inflammatory process.
- **Obstructive series** (supine and upright abdominal radiograph with a CXR) determines the distribution of

intestinal gas and assesses for the presence of free intraperitoneal air.

- **Additional imaging studies** assess for mechanical obstruction and inflammatory processes and include CT, contrast enema, and small bowel series.

TREATMENT

- Basic **supportive measures** consist of NPO, fluid replacement, and correction of electrolyte imbalances. Medications that slow GI motility (adrenergic agonists, TCAs, sedatives,

narcotic analgesics) should be withdrawn or dose reduced. The ambulatory patient is encouraged to remain active and to undertake short walks.

- **Intermittent NG suction** prevents swallowed air from passing distally. In protracted cases, gastric decompression, either using an NG tube or a percutaneous endoscopic gastrostomy (PEG) tube, vents upper GI secretions and decreases vomiting and gastric distension.
- **Rectal tubes** help decompress the distal colon; more proximal colonic distension may necessitate **colonoscopic decompression**, especially when the cecal diameter approaches 9 cm. A flexible decompression tube can be left in the proximal colon during colonoscopy. Turning the patient from side to side may potentiate the benefit of colonoscopic decompression.

Medications

- **Neostigmine** (2 mg IV administered slowly over 3-5 minutes) is beneficial in selected patients with acute colonic distension. This can induce rapid reestablishment of colonic tone and is contraindicated if mechanical obstruction remains in the differential diagnosis. Side effects include abdominal pain, excessive salivation, symptomatic bradycardia, and syncope. A trial of neostigmine may be warranted before colonoscopic decompression in patients without contraindications (*N Engl J Med 1999;341:137*).
- **Methylnaltrexone** (**Relistor**; 8-12 mg SC per dose every other day) can be administered in settings where opioid medication use contributes to pseudo-obstruction.
- **Erythromycin** (200 mg IV) acts as a motilin agonist and stimulates upper gut motility; it has been used with some success in refractory postoperative ileus.
- **Alvimopan** is a peripherally acting μ-opioid receptor antagonist that enhances return of bowel function after abdominal surgery but has not been shown to shorten hospital stay (*Am Surg 2011;77:1460*).
- **Mosapride citrate** (15 mg PO tid), a 5-HT_4 receptor agonist, may reduce the duration of postoperative ileus when administered postoperatively (*J Gastrointest Surg 2011;15:1361*).
- **Prucalopride**, also a selective 5-HT_4 agonist, can relieve symptoms in patients with chronic intestinal pseudo-obstruction (*Aliment Pharmacol Ther 2012;35:48*).

Surgical Management

- **Surgical consultation** is required when the clinical picture is suggestive of mechanical obstruction or if peritoneal signs are present. Surgical exploration is reserved for acute cases with peritoneal signs, ischemic bowel, or other evidence for perforation.
- **Cecostomy** treats acute colonic distension when colonoscopic decompression fails.

PANCREATOBILIARY DISORDERS

Acute Pancreatitis

GENERAL PRINCIPLES

Definition

Acute pancreatitis consists of inflammation of the pancreas and peripancreatic tissue from activation of potent pancreatic enzymes within the pancreas, particularly trypsin.

Etiology

The most common causes are alcohol and gallstone disease, accounting for 75-80% of all cases. Less common causes include abdominal trauma, hypercalcemia, hypertriglyceridemia, and a variety of drugs. Post-endoscopic retrograde cholangiopancreatography

(ERCP) pancreatitis occurs in 5-10% of patients undergoing ERCP; prophylaxis with rectal NSAIDs or topical epinephrine and placement of prophylactic pancreatic duct stents can help prevent post-ERCP pancreatitis (*Aliment Pharmacol Ther 2013;38:1325*).

DIAGNOSIS

Clinical Presentation

Typical symptoms consist of acute onset of epigastric abdominal pain, nausea, and vomiting often exacerbated by food intake. Systemic manifestations can include fever, shortness of breath, altered mental status, anemia, and electrolyte imbalances, especially with severe episodes.

Diagnostic Testing

Laboratories

- Serum **lipase** is more specific and sensitive than serum **amylase**, although both are usually elevated beyond three times the upper limits of normal. These values do not correlate with severity or outcome of pancreatitis. Patients with renal insufficiency may have elevated enzymes at baseline from impaired clearance.
- Hepatic function testing may identify biliary obstruction as a possible etiology, and a lipid panel may suggest hypertriglyceridemia as the cause of acute pancreatitis.

Imaging

- **Dual-phase (pancreatic protocol) CT scan** is useful in the initial evaluation of severe acute pancreatitis but should be reserved for patients in whom the diagnosis is unclear, who fail to improve clinically within 48-72 hours, or in whom complications are suspected (*Am J Gastroenterol 2013;108:1400*). CT scan early in presentation may underestimate the severity of acute pancreatitis.
- **MRI with gadolinium** can also be used with at least similar efficacy, especially when CT is contraindicated. Magnetic resonance cholangiopancreatography (MRCP) is useful to detect a biliary source for pancreatitis before ERCP is performed (*Med Clin North Am 2008;92:889*).

TREATMENT

- **Aggressive volume repletion** with IV fluids must be undertaken, with careful monitoring of fluid balance, urine output, serum electrolytes (including calcium and glucose), and awareness of the potential

for significant fluid sequestration within the abdomen. Intensive care unit monitoring may be necessary.

- Patients should receive **nothing PO** until they are free of pain and nausea. NG suction is reserved for patients with ileus or protracted emesis. TPN may be necessary when inflammation is slow to resolve (around 7 days) or if an ileus is present. However, early enteral feeding is preferred over TPN.
- Acid suppression may be necessary in severely ill patients with risk factors for stress ulcer bleeding, although it has not been shown to decrease symptom duration or severity (*Gastroenterology 2007;132:2022*).

Medications

- **Narcotic analgesics** are usually necessary for pain relief.
- Routine use of prophylactic antibiotics is not recommended in the absence of systemic infection (*Am J Gastroenterol 2013;108:1400*).

Other Nonoperative Therapies

Urgent **ERCP and biliary sphincterotomy** within 72 hours of presentation can improve the outcome of severe gallstone pancreatitis in the presence of biliary obstruction and is associated with fewer complications (*Ann Surg 2009;250:68*). This is thought to result from reduced biliary sepsis rather than true improvement of pancreatic inflammation.

Surgical Management

Cholecystectomy. A delay in cholecystectomy after gallstone pancreatitis carries a substantial risk of recurrent biliary events (*Br J Surg 2011;98:1446*).

COMPLICATIONS

- **Necrotizing pancreatitis** represents a severe form of acute pancreatitis, usually identified on dynamic dual-phase CT scanning with IV contrast. The presence of radiologically identified pancreatic necrosis increases the morbidity and mortality of acute pancreatitis. Increasing abdominal pain, fever, marked leukocytosis, and bacteremia suggest infected pancreatic necrosis that requires broad-spectrum antibiotics and often surgical debridement. CT-guided percutaneous aspiration for Gram stain and culture can confirm the diagnosis of infected necrosis. **Carbapenems** or a combination of a **fluoroquinolone** and **metronidazole** have good penetration into necrotic tissue.
- The presence of **pseudocysts** is suggested by persistent pain or high amylase levels. Complications include infection, hemorrhage, rupture (pancreatic ascites), and obstruction of adjacent structures. Asymptomatic nonenlarging pseudocysts can be followed clinically with serial imaging studies to resolution. Decompression of symptomatic or infected pseudocysts can be performed by percutaneous, endoscopic, or surgical techniques (*Gastrointest Endosc Clin N Am 2007;17:559*).
- **Infection.** Potential sources of fever include pancreatic necrosis, abscess, infected pseudocyst, cholangitis, and aspiration pneumonia. Cultures should be obtained, and broad-spectrum antimicrobials appropriate for bowel flora should be administered. In the absence of fever or other clinical evidence for infection, prophylactic antimicrobial therapy has no clear role in acute pancreatitis.
- **Pulmonary complications.** Atelectasis, pleural effusion, pneumonia, and acute respiratory distress syndrome can develop in severely ill patients (see Chapter 10, Pulmonary Diseases).
- **Renal failure** can result from intravascular volume depletion or acute tubular necrosis.
- **Other complications.** Metabolic complications include hypocalcemia, hypomagnesemia, and

hyperglycemia. GI bleeding can result from stress gastritis, pseudoaneurysm rupture, or gastric varices from splenic vein thrombosis.

Chronic Pancreatitis

GENERAL PRINCIPLES

- Chronic pancreatitis represents inflammation, fibrosis, and atrophy of acinar cells resulting from recurrent acute or chronic inflammation of the pancreas.
- Most commonly seen with **chronic alcohol abuse**, it can also result from dyslipidemia, hypercalcemia, autoimmune disease, and exposure to various toxins. An inherited form (**hereditary pancreatitis**) is rarely seen; this can be associated with mutations in

genes encoding cationic trypsinogen (*PRSS1*) or pancreatic secretory trypsin inhibitor (*SPINK1*) (*Gastroenterology 2007;132:1557*).

- **Autoimmune pancreatitis (AIP)** represents an increasingly recognized subtype of chronic pancreatitis characterized by infiltration of IgG4-positive plasma cells in a classically sausage-shaped pancreas. AIP can be difficult to distinguish from pancreatic cancer on CT, but typically features diffuse narrowing of the main pancreatic duct without dilation. Initial treatment has traditionally been with high-dose steroids, although low-dose steroids may be similarly effective (*Pancreas 2014;43:261*). Relapses may occur in the pancreas or biliary tree, although retreatment with steroids is effective at inducing remission (*Gut 2013;62:1771*).

DIAGNOSIS

Clinical Presentation

Chronic abdominal pain, **exocrine insufficiency** from acinar cell injury and fibrosis (manifesting as weight loss and steatorrhea), and **endocrine insufficiency** from destruction of islet cells (manifesting as brittle diabetes) are the main clinical manifestations.

Diagnostic Testing

Laboratories

- Lipase and amylase may be elevated but are frequently normal and are nonspecific. Bilirubin, alkaline phosphatase, and transaminases may be elevated if there is concomitant biliary obstruction. A lipid panel and serum calcium should also be assessed.
- Indirect pancreatic function testing (such as secretin stimulation, fecal fat, and fecal elastase) can be performed but are not widely available and difficult to perform.

Imaging

- **Calcification** of the pancreas can be seen on imaging. Contrast-enhanced CT has a sensitivity of 75-90% and a specificity of 85% for the diagnosis of chronic pancreatitis, whereas MRCP is equivalent and a suitable alternative (*Gastroenterology 2007;132:1557*).
- **Endoscopic ultrasound (EUS)** has higher sensitivity for the diagnosis of chronic pancreatitis and is particularly useful for evaluating lesions concerning for neoplasia in the setting of chronic pancreatitis.

TREATMENT

Medications

- **Narcotic analgesics** are frequently required for control of pain, and narcotic dependence is common. **Neuromodulators** (TCAs, SSRIs) and **pregabalin** may improve symptoms and decrease reliance on narcotics (*Gastroenterology 2011;141:536*). In patients with mild to moderate exocrine insufficiency, the addition of oral pancreatic enzyme supplements may be beneficial for pain control.
- **Pancreatic enzyme supplements** are the mainstay of management of pancreatic exocrine insufficiency in conjunction with a low-fat diet (<50 g fat per day), facilitating weight gain and reduced stool frequency (*Aliment Pharmacol Ther 2011;33:1152*). Enteric-coated preparations (Pancrease or Creon, one to two capsules with meals) are stable at acid pH.
- **Fat-soluble vitamin** supplementation may be necessary.
- **Insulin** therapy is generally required for endocrine insufficiency, because the resultant diabetes mellitus is characteristically brittle and thus unresponsive to oral agents.
- When identified, treatment of the underlying disorder (e.g., hyperparathyroidism, dyslipidemia) is indicated. Alcohol cessation should be advised.

Other Nonoperative Therapies

- Patients with pancreatic duct obstruction from stones, strictures, or papillary stenosis may benefit from **ERCP and sphincterotomy**.
- Intractable pain may necessitate **celiac or splanchnic plexus block** (often EUS-guided) for short-term relief in selected patients or even surgery, such as a **Whipple procedure** or lateral pancreaticojejunostomy, in cases of a dilated pancreatic duct (*Aliment Pharmacol Ther 2009;29:979*).

Gallstone Disease

GENERAL PRINCIPLES

- **Asymptomatic gallstones (cholelithiasis)** are a common incidental finding for which no specific therapy is generally necessary (*J Gastroenterol Hepatol 2010;25:719*). Cholesterol stones are the most common type, but pigmented stones can be seen with hemolysis or infection. Risk factors include obesity, female gender, parity, rapid weight loss, ileal disease, and maternal family history.
- **Symptomatic cholelithiasis**, when upper abdominal symptoms are linked to gallstones, is typically treated surgically with cholecystectomy.
- **Acute cholecystitis** is caused most often by obstruction of the cystic duct by gallstones, but acalculous cholecystitis can occur in severely ill or hospitalized patients.

DIAGNOSIS

Clinical Presentation

- Cholelithiasis may present as **biliary colic**, a constant pain lasting for several hours, located in the right upper quadrant, radiating to the back or right shoulder, and sometimes associated with nausea or vomiting.
- Other presentations of gallstone disease include acute cholecystitis, acute pancreatitis, and cholangitis. Gallstone disease may rarely be associated with gallbladder cancer.
- Two-thirds of patients with **acute ascending cholangitis** present with right upper quadrant pain, fever

with chills and/or rigors, and jaundice (**Charcot triad**), usually in the setting of biliary obstruction (choledocholithiasis, neoplasia, sclerosing cholangitis, biliary stent occlusion). The presence of hypotension and altered mentation defines the **Reynolds pentad**, which is seen less commonly.

Diagnostic Testing

- **Ultrasound scans** have a high degree of accuracy in diagnosis (sensitivity and specificity >95%) and are the preferred initial test.
- **Hydroxy iminodiacetic acid (HIDA)** scan can demonstrate nonfilling of the gallbladder in patients with acute cholecystitis, although false-negative results may be seen in acalculous cholecystitis.

TREATMENT

Medications

- **Supportive measures** include IV fluid resuscitation and broad-spectrum antimicrobial agents, especially in the event of complications such as acute cholecystitis with sepsis, perforation, peritonitis, abscess, or empyema formation.
- **Ursodeoxycholic acid** (8-10 mg/kg/d PO in two to three divided doses for prolonged periods) might be prudent in a select group of patients with small cholesterol stones in

normally functioning gallbladders who are at high risk for complications from surgical therapy. Side effects include diarrhea and reversible elevation in serum transaminases.

Other Nonpharmacologic Therapies

Percutaneous cholecystostomy can be performed under fluoroscopy in severely ill patients with acute cholecystitis who are not surgical candidates, especially for acalculous cholecystitis (*Am J Surg 2013;206:935*).

Surgical Management

Cholecystectomy is the therapy of choice for symptomatic gallstone disease and acute cholecystitis. Laparoscopic cholecystectomy compares favorably with the open procedure, with lower morbidity, lower cost, shorter hospital stay, and better cosmetic results (*Lancet 2006;368:230*).

COMPLICATIONS

- **Acute pancreatitis.** See Acute Pancreatitis section.
- **Choledocholithiasis.** Common bile duct obstruction, jaundice, biliary colic, cholangitis, or pancreatitis can result from stones retained in the common bile duct. The diagnosis can be made on ultrasonography, CT, or magnetic resonance cholangiography. ERCP with sphincterotomy and stone extraction is curative.
- **Acute ascending cholangitis** represents a medical emergency with high morbidity and mortality if biliary decompression is not performed urgently. The condition should be stabilized with IV fluids and broad-spectrum antibiotics. Drainage of the biliary tree can be performed through endoscopic (ERCP with sphincterotomy) or percutaneous approaches under fluoroscopic guidance.

OTHER GASTROINTESTINAL DISORDERS

Anorectal Disorders

- **Defecatory disorders** present with difficulty evacuating stool from the rectum or outlet constipation. The diagnosis is ideally made in the setting of compatible symptoms and abnormal testing, including DRE, balloon expulsion testing, barium defecography, MRI, anorectal manometry, and/or pelvic floor electromyography (*Am J Gastroenterol 2014;109:1141*). Management includes biofeedback therapy (*Gastroenterology 2014;146:37*).
- **Thrombosed external hemorrhoids** present as acutely painful, tense, bluish lumps covered with skin in the anal area. The thrombosed hemorrhoid can be surgically excised under local anesthesia for relief of severe pain. In less severe cases, oral analgesics, sitz baths (sitting in a tub of warm water), stool softeners, and topical ointments may provide symptomatic relief (*BMJ 2008;336:380*).
- **Internal hemorrhoids** commonly present with either bleeding or a prolapsing mass with straining. Bulk-forming agents such as fiber supplements are useful in preventing straining at defecation. Sitz baths and Tucks pads may provide symptomatic relief. Ointments and suppositories that contain topical analgesics, emollients, astringents, and hydrocortisone (e.g., Anusol-HC Suppositories, one per rectum bid for 7-10 days) may decrease edema but do not reduce bleeding. Hemorrhoidectomy or band ligation can be curative and is indicated in patients with recurrent or constant bleeding (*BMJ 2008;336:380*).
- **Anal fissures** present with acute onset of pain during defecation and are often caused by hard stool. Anoscopy reveals an elliptical tear in the skin of the anus, usually in

the posterior midline. Acute fissures heal in 2-3 weeks with the use of stool softeners, oral or topical analgesics, and sitz baths. The addition of oral or topical nifedipine to these conservative measures can improve pain relief and healing rates (*Am J Surg 2013;206:748*).
- **Perirectal abscess** commonly presents as a painful induration in the perianal area. Patients with IBD and immunocompromised states are particularly susceptible. Prompt drainage is essential to avoid the serious morbidity associated with delayed treatment. Antimicrobials directed against bowel flora (metronidazole, 500 mg PO tid, and ciprofloxacin, 500 mg PO bid) should be administered in patients with significant inflammation, systemic toxicity, or immunocompromised states.

Celiac Sprue

GENERAL PRINCIPLES

- Celiac sprue consists of chronic inflammation of proximal small bowel mucosa from an immunologic sensitivity to **gluten** (protein found in wheat, barley, and rye), resulting in malabsorption of dietary nutrients.
- Clinical presentation can vary greatly from asymptomatic iron deficiency anemia to significant diarrhea and weight loss. Other presenting features can include osteoporosis, dermatitis herpetiformis, abnormal liver enzymes, and abdominal pain; incidental recognition at endoscopy can also occur (*N Engl J Med 2007;357:1731*).
- More than 7% of patients with nonconstipated IBS have celiac-associated antibodies, suggesting that gluten sensitivity may trigger symptoms resembling IBS (*Gastroenterology 2011;141:1187*).

DIAGNOSIS

- Noninvasive serologic tests are highly sensitive and specific and should be checked while the patient is on a gluten-containing diet. Both **IgA anti-tissue transglutaminase (TTG) and antiendomysial antibodies** have accuracies close to 100%. Quantitative IgA levels should also be checked; IgG antibodies against TTG are checked if the patient is IgA deficient (*Am J Gastroenterol 2013;108:656*).
- EGD with small bowel biopsies is performed to confirm diagnosis with positive serologic testing or if

suspicion remains high despite negative noninvasive testing. Classic biopsy findings include blunting or absence of villi and prominent intraepithelial lymphocytosis.

- Almost all patients with celiac sprue carry HLA-DQ2 and HLA-DQ8 molecules, so absence of these alleles has high negative predictive value when the diagnosis is in question or if patients are on a gluten-free diet.
- Nonceliac gluten sensitivity should only be considered after exclusion of celiac disease with appropriate testing; differentiation is important for risk identification for nutrient deficiency, complications, and family member risk.

TREATMENT

Medications

- Patients may require iron, folate, vitamin D, and vitamin B12 supplements.
- **Corticosteroids** (prednisone, 10-20 mg/d) may be required in refractory cases once inadvertent gluten ingestion has been excluded; immunosuppressive drugs have also been used (*N Engl J Med 2007;357:1731*).

Lifestyle/Risk Modification

- A **gluten-free diet** is first-line therapy and results in prompt improvement in symptoms. Dietary nonadherence is the most frequent cause for persistent symptoms.
- If symptoms persist despite a strict gluten-free diet, radiologic and endoscopic evaluation of the small bowel should be performed to rule out complications including collagenous colitis and **small bowel lymphoma**. However, the prognosis of adults with unrecognized celiac disease is good despite positive celiac antibodies; therefore, mass screening appears unnecessary (*Gut 2009;58:643*).

Diverticulosis and Diverticulitis

GENERAL PRINCIPLES

Definition

- **Diverticula** consist of outpouchings in the bowel, most commonly in the colon, but can also be seen elsewhere in the gut.
- **Diverticular bleeding** can occur from an artery at the mouth of the diverticulum.
- **Diverticulitis** results from microperforation of a diverticulum and resultant extracolonic or intramural inflammation.

DIAGNOSIS

Clinical Presentation

- Diverticulosis is most frequently asymptomatic. Although diverticulosis may be found in patients being investigated for symptoms of abdominal pain and altered bowel habits, a causal link is difficult to establish.

- Typical symptoms of diverticulitis include left lower quadrant abdominal pain, fevers and chills, and alteration of bowel habits. Localized left lower quadrant abdominal tenderness may be elicited on physical examination.

Diagnostic Testing

Laboratories

Diverticulitis may be associated with an elevated white blood cell (WBC) count with a left shift.

Imaging

- Diverticula are frequently seen on screening colonoscopy.
- Imaging studies, most commonly CT scans, can be useful in the diagnosis of diverticulitis.
- **Colonoscopy is contraindicated for 4-6 weeks after an episode of acute diverticulitis**, but should be performed after that interval to exclude a perforated neoplasm.

TREATMENT

- Increased dietary fiber is generally recommended in patients with diverticulosis, although no hard data exist to support its benefit (*Curr Opin Gastroenterol 2015;31:50*).
- A low-residue diet is recommended for mild diverticulitis, although no evidence exists to support this practice (*JAMA 2008;300:907*).

Medications

- Oral **antibiotics** (e.g., ciprofloxacin, 500 mg PO bid, and metronidazole, 500 mg PO tid for 10-14 days) may suffice for mild diverticulitis.

- Despite optimistic initial reports, mesalamine does not appear to be effective in preventing recurrence of diverticulitis in phase III controlled trials; no therapy has been proven to prevent recurrent diverticulitis (*Gastroenterology 2014;147:793*).
- Hospital admission, bowel rest, IV fluids, and broad-spectrum IV antimicrobial agents are typically required in moderate to severe cases.

Surgical Management

- Surgical consultation should be obtained early in moderate to severe diverticulitis, because operative intervention may be necessary should complications arise.
- Surgical resection may also be necessary in recurrent diverticulitis, typically after three or more recurrences at the same location.

Gastroparesis

GENERAL PRINCIPLES

Definition

Gastroparesis consists of abnormally delayed emptying of stomach contents into the small bowel in the absence of gastric outlet obstruction or ulceration, usually as a result of damage to the nerves or smooth muscle involved in gastric emptying.

Etiology

- **Mechanical obstruction should always be excluded.**
- In addition to evaluating for acute metabolic derangements and potential offending medications (narcotics, anticholinergic agents, chemotherapeutic agents, glucagon-like peptide-1 and amylin analogs), patients with gastroparesis should be screened for **diabetes mellitus**, thyroid dysfunction, neurologic disease, prior gastric or bariatric surgery, and autoimmune disorders (e.g., scleroderma).
- If no predisposing cause is identified, gastroparesis is designated **idiopathic**.

DIAGNOSIS

Clinical Presentation

Symptoms include nausea, bloating, and vomiting, usually hours after a meal.

Diagnostic Testing

- A **gastric-emptying study** (gamma camera scan after a radiolabeled meal) can confirm the diagnosis; medications that can delay gastric emptying should be stopped at least 48 hours prior to testing.
- Endoscopic evidence of retained food debris in the stomach after an overnight fast may be an indirect indicator of delayed gastric emptying.

TREATMENT

- First steps in management include fluid restoration, correction of electrolytes, nutritional support, and optimization of glucose control for diabetic patients. Indications for enteral feeding, preferably postpyloric, include unintentional loss of >10% of usual body weight and/or refractory symptoms requiring repeated hospitalizations (*Am J Gastroenterol 2013;108:18*).

- Nutritional consultation can help address nutritional deficiencies and optimize diet, especially to decrease dietary fat and insoluble fiber (*Gastroenterology 2011;141:486*). Small-particle-size diets reduce symptoms in patients with diabetic gastroparesis (*Am J Gastroenterol 2014;109:375*).

Medications

- **Metoclopramide** (10 mg PO qid half an hour before meals) often represents the first line of prokinetic therapy but has variable efficacy, and side effects (drowsiness, tardive dyskinesia, parkinsonism) may be limiting.
- **Domperidone** (20 mg PO qid before meals and at bedtime) does not cross the blood-brain barrier, but hyperprolactinemia can result. ECGs should be checked at baseline and on follow-up given the risk of QT prolongation.
- **Erythromycin** (125-250 mg PO tid or 200 mg IV) is a motilin receptor agonist and stimulates gastric motility, but tachyphylaxis limits long-term therapy.
- **Antiemetics** may improve associated nausea and vomiting but will not improve gastric emptying.

Surgical Management

- **Enteral feeding** through a jejunostomy feeding tube may be required for supplemental nutrition and is favored over TPN.
- **Gastric electrical stimulation** using a surgically implanted stimulator (Enterra) may reduce symptoms of

nausea and vomiting in half of medically refractory patients, but gastric emptying is typically not enhanced by this approach (*Gastrointest Endosc 2011;74:496*).

Ischemic Intestinal Injury

GENERAL PRINCIPLES

- **Acute mesenteric ischemia** results from arterial (or rarely venous) compromise to the superior mesenteric circulation.
- Emboli and thrombus formation are the most common causes of acute mesenteric ischemia, although **nonocclusive mesenteric ischemia** from vasoconstriction can also give rise to the disorder.
- **Ischemic colitis** results from mucosal ischemia in the inferior mesenteric circulation during a low-flow state (hypotension, arrhythmias, sepsis, aortic vascular surgery) in patients with atherosclerotic disease. Vasculitis, sickle cell disease, vasospasm, and marathon running can also predispose to ischemic colitis.

DIAGNOSIS

Clinical Presentation

- Patients with acute mesenteric ischemia may present with abdominal pain, but physical examination and imaging studies can be unremarkable until infarction has occurred. As a result, diagnosis is late and mortality is high.
- Ischemic colitis may manifest as transient bleeding or diarrhea; severe insults can lead to stricture formation, gangrene, and perforation. The heterogeneity of clinical presentation of ischemic colitis helps explain why clinical suspicion is often low. Although recurrences of ischemic colitis are infrequent (<10% at 5 years), mortality is high (one-third at 5 years) and driven by unrelated causes (*World J Gastroenterol 2013;19:8042*).

Diagnostic Testing

- **Urgent angiography** is indicated if the suspicion for acute mesenteric ischemia is high.
- CT with contrast has high sensitivity and specificity for the diagnosis of primary acute mesenteric ischemia (*Radiology 2010;256:93*), whereas Doppler EUS may help exclude chronic mesenteric ischemia (*Dig Liver Dis 2011;43:470*).
- In patients with ischemic colitis, characteristic "**thumb-printing**" of the involved colon may be seen on plain radiographs of the abdomen.
- Colonoscopy may reveal mucosal erythema, edema, and ulceration, sometimes in a linear configuration; evidence of gangrene or necrosis is an indication for surgical intervention.

TREATMENT

- Treatment of acute mesenteric ischemia is essentially surgical and increasingly **endovascular**, whereas both arterial bypass and percutaneous angioplasty represent options for chronic mesenteric ischemia (*Br J Surg 2014;101:e100*).
- In patients with ischemic colitis, in the absence of peritoneal signs or evidence of gangrene or perforation, expectant management with fluid and electrolyte repletion, broad-spectrum antimicrobials,

and maintenance of stable hemodynamics usually suffices.

- Evidence of gangrene or necrosis in the setting of ischemic colitis represents an indication for surgery.

19
Liver Diseases

Maria Samuel

Kristen Singer

Mauricio Lisker-Melman

Evaluation of Liver Disease

GENERAL PRINCIPLES

- Liver disease can present as a spectrum of clinical conditions that ranges from asymptomatic disease to end-stage liver disease (ESLD).
- A comprehensive investigation combining thorough history and physical examination with diagnostic tests, liver histology, and imaging can often establish a precise diagnosis.

DIAGNOSIS

Clinical Presentation

History

History taking should be focused on the following:

- History of present illnesses
- Medicine usage and toxin exposure (including alcohol)
- Associated signs and symptoms—development of jaundice, ascites, edema, pruritus, encephalopathy, gastrointestinal (GI) bleeding
- Family history of liver disease
- Comorbid conditions: obesity, diabetes, hyperlipidemia, inflammatory bowel disease, systemic hypotension
- Risk factors for infection: IV/intranasal drug use, body piercings, tattooing, sexual history, travel to foreign countries, occupation

Physical Examination

- Detailed physical exam is necessary. Physical stigmata of acute and chronic liver disease may be subtle or absent.
  - Jaundice
  - Ascites, peripheral edema, pleural effusions
  - Hepatomegaly and splenomegaly
  - Gynecomastia, testicular hypotrophy
  - Muscle wasting
  - Telangiectasias, palmar erythema, pubic hair changes
- Specific liver disorders may be associated with distinctive physical abnormalities: arthritis, acne, skin color changes, Kayser-Fleischer rings, clubbing, platypnea, orthodeoxia, dyspnea, or S_3 gallop.

Diagnostic Testing

Laboratories

- **Serum enzymes.** Hepatic disorders associated predominantly with elevation in aminotransferases are referred to as hepatocellular; hepatic disorders with predominant elevation in alkaline phosphatase (ALP) are referred to as cholestatic.
  - Elevation of **aspartate aminotransferase (AST) and alanine aminotransferase (ALT)** indicates hepatocellular injury and necrosis.
  - **ALP** is an enzyme that is present in a variety of tissues (bone, intestine, kidney, leukocytes, liver, and placenta). The concomitant elevation of other hepatic enzymes

(e.g., γ-glutamyl transpeptidase [GGT] or 5′-nucleotidase) assists in establishing the hepatic origin of ALP. Serum ALP level is often elevated in biliary obstruction, spaceoccupying lesions or infiltrative disorders of the liver, and conditions that cause intrahepatic cholestasis (primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC], drug-induced cholestasis).

- **Excretory products**
  - **Bilirubin** is a degradation product of hemoglobin and nonerythroid hemoproteins (e.g., cytochromes, myoglobin, catalases, and endothelial nitric oxide synthase). Total serum bilirubin is composed of conjugated (direct) and unconjugated (indirect) fractions. Unconjugated hyperbilirubinemia occurs as a result of excessive bilirubin production (hemolysis and hemolytic anemias, ineffective erythropoiesis, and resorption of hematomas), reduced hepatic bilirubin uptake (Gilbert syndrome and drugs such as rifampin and probenecid), or impaired bilirubin conjugation (Gilbert or Crigler-Najjar syndrome). Elevation of conjugated and unconjugated fractions occurs in Dubin-Johnson and Rotor syndromes and in conditions associated with intrahepatic (from hepatocellular, canalicular, or ductular damage) and extrahepatic (from mechanical obstruction) cholestasis.
  - **α-Fetoprotein (AFP)** is normally produced by fetal liver cells. Its production falls to normal adult levels of <10 ng/mL within 1 year of life. AFP is an insensitive and nonspecific biomarker for hepatocellular carcinoma (HCC), with a sensitivity and specificity of 61% and 81%, respectively, at a cutoff of 20 ng/mL, and 22% and 100%, respectively, at a cutoff of 200 ng/mL (*Gastroenterology 2010;138:493*). Levels of >400 ng/mL or a rapid doubling time are suggestive of HCC; mild to moderate elevations can also be seen in acute and chronic liver inflammation.

Imaging

- **Ultrasonography** is used to screen for dilation of the biliary tree and to detect gallstones and cholecystitis in patients with right-sided abdominal pain associated with abnormal liver blood tests. It can reveal and characterize liver masses, abscesses, and cysts. Color flow Doppler ultrasonography can assess patency and direction of blood flow in the portal and hepatic veins and is therefore used to monitor shunt patency following transjugular intrahepatic portosystemic shunt (TIPS). Ultrasonography is a frequently used modality for screening of HCC; however, this modality is less sensitive (tumors with diameters <2 cm) for the detection of HCC compared with CT or MRI. This technique is very operator dependent.
- **Helical CT scan** with IV contrast is useful in the evaluation of parenchymal liver disease. It has the added feature of contrast enhancement to define space-occupying lesions (e.g., abscess and tumor) and allows calculation of liver volume. Triple-phase CT (arterial, venous, and delayed phases) is indicated for liver mass evaluation. A delayed phase is useful when cholangiocarcinoma is suspected.
- **MRI** offers information similar to that provided by CT scan with the additional advantage of better characterization of liver lesions, fatty infiltration, and iron deposition. It is the modality of choice in patients

with an allergy to iodinated contrast. This modality should not be used in patients with renal failure (glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) due to the very low risk of gadolinium-associated nephrogenic systemic fibrosis. Of all the cross-sectional imaging techniques, MRI provides the highest tissue contrast. This, in conjunction with various contrast agents (especially hepatobiliary contrast agents), allows for definitive noninvasive characterization of liver lesions.

- **Magnetic resonance cholangiopancreatography (MRCP)** is a specialized version of MRI that provides an alternative noninvasive diagnostic modality for visualizing the intrahepatic and extrahepatic bile ducts. MRCP does not require contrast material to be administered into the ductal system.

Diagnostic Procedures

- **Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP)** involve the instillation of contrast into the biliary tree. They are most useful after the preliminary determination of abnormalities detected by ultrasonography, CT, or MRI/MRCP. These procedures allow for diagnostic and therapeutic maneuvers including biopsy, brushings, stenting, and placement of drains.
- **Percutaneous liver biopsy** is an invasive procedure that can be performed with or without radiographic (ultrasound or CT) guidance. Bleeding, pain, infection, injury to adjacent organs, and (rarely) death are potential complications. In the presence of coagulopathy, thrombocytopenia, and/or ascites, a biopsy can be obtained by the transjugular route. Suspicious liver lesions are usually biopsied with ultrasonographic or CT guidance. Laparoscopy is an alternative method for obtaining liver tissue.
- **Transjugular assessment of portal pressure** is an invasive procedure to measure the hepatic venous pressure gradient (HVPG), which is the difference between the wedged (representing the portal venous pressure) and the free hepatic venous pressures. The normal HVPG pressure is <6 mm Hg. HVPG >6 mm Hg is considered portal hypertension. Complications of portal hypertension such as ascites and esophageal varices usually manifest with HVPG >10 mm Hg.
- Noninvasive tests to assess fibrosis/cirrhosis, including AST-to-platelet ratio index (APRI), FibroScan, FibroTest/Fibrosure, transient elastography, and magnetic resonance spectroscopy, are being considered as alternative options to liver biopsy. Studies evaluating the combination of radiologic and serologic modalities to accurately detect the degree of fibrosis are under evaluation.

VIRAL HEPATITIS

The hepatotropic viruses include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV) (Tables 19-1 and 19-2). Nonhepatotropic viruses (viruses that indirectly affect the liver) include Epstein-Barr virus, cytomegalovirus, herpesvirus, measles, Ebola, and others.

Acute viral hepatitis is defined by an array of symptoms that may vary from mild, nonspecific symptoms to acute or fulminant hepatic failure. This condition may resolve or progress to chronic hepatitis, in certain cases, or to liver failure as a consequence of diffuse necroinflammatory liver injury.

Acute or fulminant hepatic failure (FHF) is defined as the rapid development of severe liver injury with encephalopathy and coagulopathy in a patient without preexisting liver disease within <6 months from the onset

of the acute illness.

Chronic viral hepatitis is defined as the presence of persistent (>6 months) virologic replication, as determined by serologic and molecular studies, with necroinflammatory and fibrotic injury. Symptoms and biochemical abnormalities may vary from none to moderate. Histopathologic classification of chronic viral hepatitis is based on etiology, grade, and stage. Grading and staging are measures of the severity of the inflammatory process and fibrosis, respectively. Chronic viral hepatitis may lead to cirrhosis and HCC.

Hepatitis A Virus

GENERAL PRINCIPLES

- HAV is an **RNA virus** that belongs to the **picornavirus family**. It is transmitted via the fecal-oral route and is the most common cause of acute viral hepatitis worldwide.
- Large-scale outbreaks due to contamination of food and drinking water can occur.
- The period of greatest infectivity is 2 weeks before the onset of clinical illness; virus shedding in infected patients' feces continues for 2-3 weeks after the onset of symptoms.

TABLE 19-1 Clinical and Epidemiologic Features of Hepatotropic Viruses

Organism	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Incubation	15-45 d	30-180 d	15-150 d	30-150 d	30-60 d
Transmission	Fecal-oral	Blood Sexual Perinatal	Blood Sexual (rare) Perinatal (rare)	Blood Sexual (rare)	Fecal-oral Organ transplantation
Risk groups	Residents of and travelers to endemic regions Children and caregivers in daycare centers	Injection drug users Multiple sexual partners Men who have sex with men Infants born to infected mothers Health care workers	Injection drug users Transfusion recipients	Any person with hepatitis B virus Injection drug users	Residents of and travelers to endemic regions Zoonosis: workers in pig farms
Fatality rate	1.0%	1.0%	<0.1%	2-10%	1%

Carrier state	No	Yes	Yes	Yes	No
Chronic hepatitis	None	2-10% in adults; 90% in children <5 yr	70-85%	Variable	Rare
Cirrhosis	No	Yes	Yes	Yes	No

TABLE 19-2 Viral Hepatitis Serologies[a]

Hepatitis	Acute	Chronic	Recovered/Latent	Vaccinated
HAV	IgM anti-HAV+	NA	IgG anti-HAV+	IgG anti-HAV+
HCV	All tests possibly negative HCV RNA+ Anti-HCV Ab+ in 8 wk after infection	Anti-HCV Ab+ HCV RNA+	Anti-HCV Ab+ HCV RNA-[b]	NA
HDV	IgM anti-HDV+[c] HDV Ag+[c]	IgG anti-HDV+[c]	IgG anti-HDV+[c]	Vaccination against HBV
HEV	IgM anti-HEV	NA	IgG anti-HEV	NA

Ab, antibody; HAV, hepatitis A virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; NA, not applicable.

[a]For hepatitis B virus serologies, see Table 19-3.

[b]Negative HCV RNA results should be interpreted with caution. Differences are found in thresholds for detection among assays and among laboratories.

[c]Markers of HBV infection are also present because HDV cannot replicate in the absence of HBV.

DIAGNOSIS

- HAV can be silent (subclinical), especially in children and young adults. Symptoms vary from mild illness to FHF and commonly include malaise, fatigue, pruritus, headache, abdominal pain, myalgias, arthralgias, nausea, vomiting, anorexia, and fever.
- **Physical examination** may reveal jaundice, hepatomegaly, and in rare cases, lymphadenopathy, splenomegaly, or a vascular rash.

- **Aminotransferase** elevations range from 10-100 times the upper limit of normal.
- The diagnosis of acute HAV is made by the detection of **IgM anti-HAV antibodies**.
- The **recovery phase** and **immunity phase** are characterized by the presence of **IgG anti-HAV antibodies and the decline of IgM anti-HAV antibodies**.
- Liver biopsy is rarely needed.
- **FHF** is rare, but the risk increases with age: 0.1% in patients younger than 15 years to >1% in patients older than 40 years.

TREATMENT

- Supportive symptomatic treatment is recommended.
- Liver transplantation is an option for FHF.

OUTCOME/PROGNOSIS

- Almost all cases of acute HAV hepatitis will resolve in 4-8 weeks. HAV does not progress to chronicity.
- A prolonged cholestatic disease, characterized by persistent jaundice and waxing and waning of liver enzymes, is more frequently seen in adults.

Hepatitis B Virus

GENERAL PRINCIPLES

- **HBV** is a **DNA virus** that belongs to the **hepadnavirus family**. The United States is considered an area of low prevalence for the infection. Eight genotypes of HBV have been identified (A through H). The prevalence of HBV genotypes varies depending on the geographic location. Genotypes A, B, and C are the most prevalent in the United States.
- Modes of transmission include vertical (mother to infant) and horizontal (person to person) via the following routes: parenteral or percutaneous (e.g., injection drug use, needlestick injuries), direct contact with blood or open sores of an infected person, and sexual contact with an infected individual.
- The rate of progression from acute to chronic HBV is approximately 90% for a perinatalacquired infection, 20-50% for infections acquired between the age of 1-5 years, and <5% for an adult-acquired infection.

DIAGNOSIS

Clinical Presentation

- According to the natural history of chronic HBV infection, three different **clinical phases** have been defined (Table 19-3):
  - Immune tolerant
  - Immune active (hepatitis B envelope antigen [HBeAg] positive and HBeAg negative)
  - Low replication
- **Extrahepatic manifestations** include polyarteritis nodosa, glomerulonephritis, cryoglobulinemia, serum sickness-like illness, membranous nephropathy, membranoproliferative glomerulonephritis, and papular

acrodermatitis (predominantly in children).

Diagnostic Testing

- HBV antigens (hepatitis B surface antigen [HBsAg] and HBeAg) can be detected in the serum. In the liver tissue, **HBsAg** stains in the hepatocyte cytoplasm, and **hepatitis B core antigen (HBcAg)** stains in the hepatocyte nuclei.
- **HBV DNA** is the most accurate marker of viral replication. It is detected by polymerase chain reaction (PCR). Large population-based studies have demonstrated a correlation between HBV DNA levels and disease progression to cirrhosis, decompensation, and development of HCC (*Gastroenterology 2006;130:678*; *JAMA 2006;295:65*).
- For use of HBV markers in clinical practice, see Table 19-3.
- **Liver biopsy** is useful to assess the degree of inflammation (grade) and fibrosis (stage) as well as other potential histologic abnormalities in patients with chronic hepatitis. Liver histology is an important adjuvant diagnostic test in guiding treatment decisions.

TREATMENT

- The treatment goal is viral eradication or suppression to prevent progression to ESLD and HCC. End points of treatment include:
  - Maintained suppression of serum HBV DNA levels to undetectable levels
  - HBsAg clearance and seroconversion to antibody anti-HBs
  - HBeAg clearance and seroconversion to antibody anti-HBe
  - Normalization of serum ALT
  - Improvement in liver histology
- There are several treatment guidelines for patients with HBV. In general, all the guidelines (referred to in Table 19-4) recommend that patients with compensated cirrhosis

P.582

P.583

P.584

with HBV DNA levels >2000 IU/mL should be treated independently of the ALT level; those with HBV DNA levels <2000 IU/mL should be treated only if the ALT is elevated. Patients with decompensated cirrhosis should be treated regardless of HBV DNA level or serum ALT (*J Hepatol 2009;50:227*).

TABLE 19-3 Use of Hepatitis B Virus (HBV) Markers in Clinical Practice

	Acute	Resolved Acute	Immune-Tolerant Chronic	Immune-Active Chronic HBV (wild-	Immune-Active Chronic HBV (pre-core or basal core promoter	Low-Replication Chronic	Vaccine

Test	HBV	HBV	HBV	type)	mutant)	HBV	Immunity
HBsAg	+	-	+	+	+	+	-
HBeAg	+	-	+	+	-	-	-
Anti-HBs	-	+	-	-	-	-	+
Anti-HBe	-	+	-	-	+	+	-
IgM anti-HBc	+	-	-	-	-	-	-
IgG anti-HBc	-	+	-	+	+	+	-
HBV DNA	$>10^6$ IU/mL	Neg	>106-10 IU/mL	>106 IU/mL	$>10^{3-4}$ IU/mL	$<10^2$ IU/mL	Neg
ALT/AST	++++	Nor	Nor	+++	++	Nor	Nor

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBc, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; Neg, negative; Nor, normal.

TABLE 19-4 Treatment Guidelines for Chronic Hepatitis B

	HBeAg Positive			HBeAg Negative		
Guideline	HBV DNA	ALT	Liver Biopsy	HBV DNA	ALT	Liver Biopsy
AASLD (2009)	>20,000	>2× ULN	___	>20,000	>2× ULN	___
	>20,000	≤2× ULN	Biopsy[a]	2,000-20,000	<2× ULN	Biopsy[b]
EASL (2012)	>2,000	>ULN	Optional[c]	>2,000	>ULN	Optional[c]
	>20,000	>ULN	____	>20,000	>ULN	____
APASL (2012)	>20,000	>2× ULN	_____	>2,000	>2× ULN	____

	>20,000	<2× ULN	Biopsy[a]	>2,000	< 2× ULN	Optional[d]

AALSD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ULN, upper limit of normal (ULN for AALSD: 30 units/L for males, 19 units/L for females; ULN for EASL and APASL: 40 units/L).

[a]Biopsy indicated for >40 years of age, ALT persistently 1-2× ULN, and family history of hepatocellular carcinoma.

[b]Treat if abnormal.

[c]Biopsy may be substituted with noninvasive markers of fibrosis.

[d]Biopsy indicated for patients >40 years of age.

- Chronic hepatitis B immune-tolerant patients and chronic hepatitis B with low replication should not be treated.
- Indications for stopping treatment, as per the current guidelines, include the following. For HBeAg-positive patients, treatment can be discontinued after 6 months (American Association for the Study of Liver Diseases [AASLD]) or 12 months (European Association for the Study of the Liver [EASL] and Asian Pacific Association for the Study of the Liver [APASL]) after the induction of negative HBV DNA and seroconversion to anti-HBe. For HBeAg-negative patients, the treatment can be stopped after the loss of HBsAg (EASL and AASLD), whereas APASL recommends a minimum of 2 years of HBV DNA negativity at three testing points obtained 6 months apart.

Medications

Medications for the treatment of hepatitis B are divided into three main groups: nucleoside analogs (entecavir), nucleotide analogs (tenofovir), and the interferons (IFNs).

- **Entecavir** is a potent anti-HBV oral nucleoside (guanosine) analog and is well tolerated. Dose is 0.5-1.0 mg daily in naïve and lamivudine (LAM)-resistant patients. Entecavir has a high genetic barrier for resistance (1.2%) over several years. However, in patients resistant to LAM, the resistance to entecavir could be as high as 40%. In patients with renal impairment, dose adjustment is needed. Side effects include headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, and abdominal pain. Entecavir is pregnancy category C.
- **Tenofovir** is a potent anti-HBV oral nucleotide (acyclic) analog and is well tolerated. Dose is 300 mg daily. Tenofovir has a high genetic barrier for resistance; no clinical resistance has been identified thus far. It is rarely reported to induce renal failure and Fanconi syndrome and may also lead to decreased bone density. Tenofovir is pregnancy category B.
- **IFNs** (α2a and α2b, in their pegylated form) are antiviral, immunomodulatory, and antiproliferative glycoproteins that have been used in the treatment of chronic HBV for several years. IFNs are parenteral agents and associated with a poor tolerability profile, especially in patients with advanced liver disease.

Long-term studies have shown a durable benefit in responders. Neither IFN nor pegylated IFN-α induces antiviral resistance. The IFNs are pregnancy category C.

PREVENTION

- **Preexposure prophylaxis**
  - **HBV vaccine** should be considered for everyone but particularly for individuals who belong to high-risk groups. HBV vaccines are safe.
  - HBV vaccination schedule includes three IM injections at 0, 1, and 6 months in infants or healthy adults. Protective antibody response (anti-HBs positive) is observed in >90% after the third dose.
- **Postexposure prophylaxis**
  - **Infants born to HBsAg-positive mothers should receive HBV vaccine and hepatitis B immunoglobulin (HBIg), 0.5 mL, within 12 hours of birth.** Immunized infants should be tested at approximately 12 months of age for HBsAg, anti-HBs, and anti-HBc.
  - Susceptible sexual partners of individuals with HBV and those with needlestick injury should receive HBIg (0.04-0.07 mL/kg) and the first dose of HBV vaccine at different sites as soon as possible (preferably within 48 hours but no more than 7 days after exposure). A second dose of HBIg should be administered 30 days after exposure, and the vaccination schedule should be completed.

  - Postexposure prophylaxis with HBIg plus a nucleotide or nucleoside analog should be used initially after liver transplantation to prevent HBV recurrence in certain patients.

OUTCOME/PROGNOSIS

Chronic hepatitis B

- Morbidity and mortality in chronic HBV are linked to level and persistence of viral replication. Spontaneous clearance of HBsAg occurs in 0.5% of patients annually.
- Once the diagnosis of chronic HBV is established, the 5-year cumulative incidence of developing cirrhosis ranges from 8-20%.
- Of patients with chronic HBV, 5-10% progress to HCC **with or without preceding cirrhosis**.

Hepatitis C

BASIC PRINCIPLES

- HCV is an RNA virus that belongs to the **flavivirus** family. There are six HCV genotypes with multiple subtypes. Genotype 1 accounts for about 75% and genotypes 2 and 3 account for about 20% of HCV infections in the United States.
- **HCV** is the most common chronic bloodborne infection and is a global health problem, with approximately **180 million carriers worldwide**.
- The most frequent mode of transmission is parenteral. Less common modes of transmission include high-risk sexual practices including men who have sex with men and perinatal transmission. Transmission by transfusion of blood products (and their derivatives) and organ transplantation has been reduced to near zero in developed countries due to sensitive screening methods.

DIAGNOSIS

Clinical Presentation

- The incubation period varies from 15-150 days.
- **Acute HCV hepatitis** is defined as presenting within 6 months of the exposure to HCV. During this time, there is a 20-50% chance of spontaneous resolution of infection (*Am J Gastroenterol 2008;103:1283*). Symptoms may vary from mild illness to FHF. Malaise, fatigue, pruritus, headache, abdominal pain, myalgias, arthralgias, nausea, vomiting, anorexia, and fever are nonspecific symptoms.
- **Chronic HCV hepatitis** runs an indolent course, sometimes for decades. Fatigue is a common symptom. The disease may only become clinically apparent late in the natural course, when symptoms are associated with advanced liver disease.
- **Extrahepatic manifestations** include mixed cryoglobulinemia (10-25% of patients with HCV), glomerular diseases (mixed cryoglobulinemia syndrome, membranous nephropathy, polyarteritis nodosa), porphyria cutanea tarda, cutaneous necrotizing vasculitis, lichen planus, lymphoma, diabetes mellitus, and other autoimmune disorders.

Diagnostic Testing

- **Antibodies against HCV (anti-HCV)** may be undetectable for the first 8 weeks after infection. These antibodies are detected by enzyme immunoassay (EIA). **Antibodies do not confer immunity.** The test has a sensitivity of 95-99% and a lower specificity. A false-positive test (anti-HCV positive with HCV RNA negative) may be detected in

  the setting of autoimmune hepatitis (AIH) or hypergammaglobulinemia. A false-negative test (anti-HCV negative with HCV RNA positive) may be seen in immunosuppressed individuals and in patients on hemodialysis.
- **HCV RNA** can be detected by **PCR** in serum as early as **1-2 weeks after infection** (qualitative and quantitative assays). It is expressed in IU/mL, with lower limits of detection approaching 10 IU/mL. HCV RNA determination is useful for both diagnosis and treatment purposes.
- **HCV genotypes and subtypes** can be detected by commercially available serologic and molecular assays. HCV genotype influences the response to treatment.
- **Liver biopsy** is useful to score the degree of inflammation (grade) and fibrosis (stage) in the liver of chronically infected patients. It is useful to grade the amount of liver steatosis and guide treatment decisions.
- Noninvasive markers of fibrosis are increasingly being used as an alternative to liver biopsy.

TREATMENT

- Acute infection: Monitor for spontaneous clearance, which is rare after 4 months. Although pegylated IFN monotherapy induces a sustained virologic response (SVR) in 80-94% of patients without ribavirin for a 24-week period independent of the genotype, current AASLD guidelines recommend to treat as described for chronic HCV infection.
- Treatment should be considered for patients with chronic HCV. Patients with limited life expectancy due to non-liver-related comorbid conditions do not require treatment.
- The highest priority for treatment should be given to patients with advanced liver disease, co-infected

(HIV and HBV) patients, patients with extrahepatic manifestations, and those with recurrent HCV after liver transplantation.

- The **goal of treatment** of HCV-infected persons is eradication of HCV, as determined by an SVR. SVR is defined as absence of detectable HCV RNA 12 weeks after completion of therapy. SVR reduces morbidity and end-stage complications of HCV infection including cirrhosis, HCC, and mortality (*Ann Intern Med 2013;158:3297*).

Medications

- Current regimens for the treatment of chronic HCV are IFN-free regimens. Medications for HCV treatment include the following:
  - **Ribavirin** is a guanosine analog antiviral agent (nucleoside inhibitor). It is generally not effective when used alone but plays an important role in combination treatment.
  - **Direct-acting antivirals (DAAs)** target specific nonstructural proteins of the virus, resulting in disruption of viral replication. Current treatment regimens for HCV include the combination of more than one DAA with or without ribavirin.
    - **Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs)** include the firstgeneration PIs telaprevir and boceprevir, which are no longer in use. Currently approved NS3/4A PIs include simeprevir and paritaprevir. Paritaprevir is boosted with ritonavir in for HCV treatment.
    - **NS5A inhibitors** include ledipasvir and ombitasvir.
    - **NS5B nucleos(t)ide polymerase inhibitors (NPIs)** include sofosbuvir and dasabuvir.
- The selection of a particular treatment regimen is dependent on several factors that are determined by a combination of clinical, biochemical, serologic, molecular, and imaging modalities and fibrosis score:
  - Treatment naïve (those who have never received any treatment for HCV) or treatment experienced (those who have failed an HCV treatment regimen)
  - HCV genotype and subtype
  - Stage or degree of liver fibrosis
  - Potential drug interactions
  - Comorbid conditions

TABLE 19-5 Treatment for Genotype 1 Chronic Hepatitis C Virus Infection

Drug Regimen	Dose	Duration of Treatment	Efficacy (%) Sustained Virological Response	
			Naïve	Experienced
Sofosbuvir + Ledipasvir	1 tab/d	12 wk	Cirrhotic 94 Noncirrhotic[a] 99	Cirrhotic[b] 100 Noncirrhotic 95
			Naïve	Experienced

Sofosbuvir (SOF)	1 tab/d (SOF)	12 wk	93[c]	F0-F1 97
Simeprevir (SMV)	1 tab/d (SMV)			F2 96 F3-F4[d] 93
			Genotype 1b Noncirrhotic	Genotype 1a[e] Noncirrhotic
Paritaprevir + Ritonavir + Ombitasvir (3D)	2 tab/d (3D)	12 wk	*Experienced* 100 *Naïve* 100	*Experienced* 94-100 *Naïve* 96
Dasabuvir (DSV)	1 tab BID (DSV) +/-Ribavirin		Cirrhotic *Experienced* 86-100 *Naïve* 100	Cirrhotic *Experienced* 80-100 *Naïve* 92

SVR, sustained virologic response.

[a]Naïve, noncirrhotic, viral load <6 million → treat for 8 weeks; SVR 95%.

[b]24 weeks of treatment, SVR 98%.

[c]24 weeks of treatment, SVR 100%.

[d]Treatment for 12 and 24 weeks resulted in similar efficacy for regimen containing ribavirin. For nonribavirin regimen, treatment for 24 weekly yielded SVR of 100%.

[e]For cirrhosis, genotype 1a, 24 weeks of treatment resulted in an SVR of 96% for naïve and experienced patients.

- **Chronic infection:** Treatment options vary depending on genotype and subtype, all with similar efficacy.
- **Genotypes 1-3** are the most commonly encountered genotypes in North America and Europe. Refer to Tables 19-5, 19-6, and 19-7 for specific treatment recommendations for genotypes 1a, 1b, 2, and 3. **Current treatments are all oral and IFN free.**
- **Genotypes 4-6** are rarely encountered in North America, and data on treatment are limited, particularly for genotypes 5 and 6. Current recommendations suggest the following treatments for **treatment-naïve** individuals:
  - **Genotype 4:** similar for genotype 1 (see Table 19-5)
  - Genotype 5: sofosbuvir plus peginterferon and weight-based ribavirin for 12 weeks
  - Genotype 6: ledipasvir-sofosbuvir for 12 weeks or sofosbuvir plus peginterferon and weight-based ribavirin for 12 weeks

PREVENTION

No preexposure prophylaxis or vaccine exists. Prevention of high-risk behaviors and lifestyle modifications should be encouraged.

OUTCOME/PROGNOSIS

HCC develops in approximately **1-2% of patients per year** and rarely occurs in the absence of cirrhosis.

TABLE 19-6 Treatment for Genotype 2 Chronic Hepatitis C Virus Infection

	Dose	Length of Treatment	Efficacy (SVR in %)
Sofosbuvir (SOF) + RBV			
Naïve	1 tab SOF + RBV	12 wk	97 (noncirrhotic) 83-100 (cirrhotic)
Experienced	1 tab SOF + RBV	12 wk	92-96 (noncirrhotic) 88-94 (cirrhotic)
SOF + daclatasvir (DAC)	1 tab SOF + 1 tab DAC	24 wk	92

RBV, ribavirin; SVR, sustained virologic response.

OTHER HEPATITIS VIRUSES

Hepatitis D

HDV is a circular RNA virus and is the only member of the genus *Delta virus*. It is found throughout the world and is endemic to the Mediterranean basin, the Middle East, and portions of South America (Amazon basin). Outside these areas, infections occur primarily in individuals who have received transfusions or in injection drug users. In countries such as the United States where HDV infection is rare, testing for HDV infection is not necessary in all patients with HBV infection. **HDV requires the presence of HBV for infection and replication.** In patients with coinfection (acute hepatitis B and D), the course is transient and self-limited. The rate of progression to chronicity is similar to the one reported for acute HBV. **IFN-α** is the **treatment of choice** for chronic hepatitis D.

TABLE 19-7 Treatment for Genotype 3 Chronic Hepatitis C Virus Infection

	Dose	Length of Treatment	Efficacy (SVR in %)
Sofosbuvir (SOF) + RBV +/-			

interferon (IFN)			
Naïve	1 tab SOF + RBV	24 wk	94 (noncirrhotic) 92 (cirrhotic)
Naïve, noncirrhotic	1 tab SOF + RBV + IFN	12 wk	97
Experienced	1 tab SOF + RBV	24 wk	87 (noncirrhotic) 60 (cirrhotic)
SOF + daclatasvir (DAC)			
Naïve	1 tab SOF + 1 tab DAC	12 wk	97 (noncirrhotic) 58 (cirrhotic)
Experienced	1 tab SOF + 1 tab DAC	12 wk	94 (noncirrhotic) 69 (cirrhotic)

RBV, ribavirin; SVR, sustained virologic response.

Hepatitis E

HEV is an **RNA virus** that belongs to the Hepeviridae family. Hepatitis E is considered a zoonotic disease, and reservoirs include pigs, wild boar, deer, and potentially other species. Transmission closely resembles that of HAV (i.e., **fecal-oral route**). Acute hepatitis E is clinically indistinguishable from other acute viral hepatitis and is usually a self-limited illness. Hepatitis E can cause chronic infection (HEV RNA for >6 months). Most cases have occurred in solid organ transplant recipients or immunosuppressed individuals (e.g., HIV). In a recent retrospective, multicenter study of 59 transplant recipients with chronic hepatitis E, the use of ribavirin monotherapy for 3 months achieved an SVR of 78% (*N Engl J Med 2014;370(12):1111*).

DRUG-INDUCED LIVER INJURY

GENERAL PRINCIPLES

- The National Institutes of Health (NIH) maintains a searchable database of drugs, herbal medications, and dietary supplements that have been associated with drug-induced liver injury (DILI) at *http://livertox.nih.gov/*. Over 1000 drugs and herbals have been associated with DILI.
- There are three major classifications of DILI that occur as a result of both intrinsic and idiosyncratic hepatotoxicity:
  - Hepatocellular injury refers to injury to the liver cell.
  - Cholestatic injury refers to injury to the biliary system or to hepatocytes with resulting intrahepatic cholestasis
  - Mixed hepatocellular and cholestatic injury refers to injury to both the liver cell and the biliary system.
- DILI is associated with approximately 50% of all the cases of FHF in the United States, with acetaminophen

being the most common causative agent. Acute DILI can progress to chronic injury in 5-10% of cases. Patients with chronic DILI may go on to develop significant fibrosis or cirrhosis and have signs and symptoms associated with cirrhosis or hepatic decompensation.

- Other less common types of DILI include chronic hepatitis, chronic cholestasis, granulomatous hepatitis, fibrosis or cirrhosis, and carcinogenesis.

DIAGNOSIS

Clinical Presentation

- The acute presentation can be clinically silent. When symptoms are present, they are nonspecific and include nausea/vomiting, general malaise, fatigue, jaundice, pruritus, and abdominal pain. In the acute setting, the majority of patients will recover after cessation of the offending drug.
- Fever and rash may also be seen in association with hypersensitivity reactions.

Diagnostic Criteria

- Clinical suspicion
- Temporal relation of liver injury to drug usage
- Resolution of liver injury after the suspected agent has been discontinued (except in cases of chronic DILI)

Diagnostic Testing

Biochemical abnormalities

- **Hepatocellular injury:** AST and ALT elevation more than two times the upper limit of normal.

- **Cholestatic injury:** ALP and conjugated bilirubin elevation more than two times the upper limit of normal.
- **Mixed injury** includes increases in all of the mentioned biochemical abnormalities to more than two times the upper limit of normal.

Diagnostic Procedures

Liver biopsy is sometimes needed.

TREATMENT

Nonpharmacologic Therapies

- Treatment includes cessation of offending drug and institution of supportive measures.
- An attempt to remove the agent from the GI tract should be made in most cases of acute toxic ingestion using lavage or cathartics (see Chapter 28, Toxicology).
- Management of acetaminophen overdose is a medical emergency (see Chapter 28, Toxicology).

Surgical Management

Liver transplantation may be an option for patients with drug-induced FHF.

OUTCOME/PROGNOSIS

Prognosis of DILI is often unique to the offending medication.

ALCOHOLIC LIVER DISEASE

GENERAL PRINCIPLES

- Alcoholism is a significant medical and socioeconomic problem.
- In 2012, 3.3 million deaths, or 5.9% of all global deaths, were attributable to alcohol consumption. Approximately 17 million US adults age 18 and older (7.2% of this age group) had an alcohol use disorder in 2012.
- The spectrum of alcoholic liver disease includes fatty liver, alcoholic hepatitis, and alcoholic cirrhosis.
- Fatty liver is the most commonly observed abnormality and occurs in up to 90% of alcoholics.
- In all of the excessive alcohol users, between 10-20% develop cirrhosis and 35% develop alcoholic hepatitis. More than half of the latter will progress to cirrhosis.
- Alcoholic cirrhosis is a common cause of ESLD and HCC.

DIAGNOSIS

Clinical Presentation

- **Fatty liver**
  - Patients are usually asymptomatic.
  - Clinical findings include hepatomegaly and mild liver enzyme abnormalities.
- **Alcoholic hepatitis**
  - Alcoholic hepatitis may be clinically silent or severe enough to lead to rapid development of hepatic failure and death.
  - Clinical features include fever, abdominal pain, anorexia, nausea, vomiting, weight loss, and jaundice.
  - In severe cases, patients may develop transient portal hypertension.

- **Alcoholic cirrhosis**
  - The presentation is variable, from clinically silent disease to decompensated cirrhosis.
  - Patients frequently give a history of drinking until the onset of symptoms.
  - Alcoholics may underestimate or minimize their reported alcohol abuse.

Diagnostic Testing

Laboratories

- In alcoholic fatty liver, laboratory tests may be normal or demonstrate **mild elevation in serum aminotransferases** (AST greater than ALT) and ALP.
- In alcoholic hepatitis, laboratory tests typically demonstrate elevation in serum aminotransferases (AST greater than ALT with a 2:1 ratio) and ALP. Hyperbilirubinemia (conjugated) and elevated prothrombin time (PT)/international normalized ratio (INR) may also be observed.
  - Laboratory abnormalities associated with a poor prognosis include renal failure, leukocytosis, a markedly elevated total bilirubin, and elevation of PT/INR that does not normalize with subcutaneous or IV vitamin K. Administration of oral vitamin K is not recommended due to poor gut absorption in

patients with jaundice (*Clin Liver Dis 2012;16:371*).

- A number of classification systems have been developed to risk stratify patients with alcoholic hepatitis and assess response to treatment:
  - **Discriminant function (DF)** = 4.6 x ($PT_{patient}$ - $PT_{control}$) + serum bilirubin. Scores <32 and >32 have 93% and 68% 1-month survival, respectively.
  - **The Glasgow Alcoholic Hepatitis Score (GAHS)** incorporates patient age, white blood cell count, blood urea, PT/INR, and serum bilirubin (Table 19-8). A score <9 has no difference in survival between untreated and steroid-treated patients. A score >9 has a difference in 1-month survival between untreated (52% 1-month survival) and steroid-treated (78% 1-month survival) patients (*Gut 2007;56:1743*).
  - The **Lille model** incorporates age, renal insufficiency, albumin, PT, bilirubin, and the evolution of bilirubin at day 7 (bilirubin on day 7 - bilirubin on day 0) to predict 6-month mortality in patients with severe alcoholic hepatitis who have received corticosteroid therapy. In a prospective study, a score of ≥ 0.45 was associated with a lower 6-month survival compared to a score >0.45 (25% vs. 85%). A score > 0.45 suggests that a patient is not responding to glucocorticoid therapy (*Hepatology 2007;45:1348*).

Diagnostic Procedures

- The typical histopathologic findings in alcoholic liver disease include hepatocyte ballooning with and without Mallory-Denk bodies, lobular inflammation, necrosis of hepatocytes, periportal fibrosis, perivenular and pericellular fibrosis, ductal proliferation, and fatty changes.

TABLE 19-8 The Glasgow Alcoholic Hepatitis Score

	Points Given		
Variable	1	2	3
Age	<50	> 50	—
WBC (× 109/L)	<15	≥15	—
Urea (mmol/L)	<5	≥5	—
INR	<1.5	1.5-2.0	>2.0
Bilirubin (µol/L)	<125	125-250	>250

INR, international normalized ratio; WBC, white blood cell.

- The indication of liver biopsy depends on the clinical assessment of the patient. It may be helpful if alternate diagnoses are being considered.

TREATMENT

- The cornerstone of treatment is abstinence from alcohol.
- Nutritional status should be evaluated and corrected accordingly. Nutrition should be oral or by a small-bore feeding tube. Peripheral parenteral nutrition (PPN) and total parenteral nutrition (TPN) are alternative options. Good nutrition improves nitrogen balance, may improve liver tests, and may decrease hepatic fat accumulation, but generally does not enhance survival.

Medications

Treatment of acute alcoholic hepatitis with corticosteroids is controversial. However, there is evidence that patients with a DF >32 and GAHS >9 may have a short-term benefit from steroid therapy. An early decrease in bilirubin levels after 1 week of treatment portends a better prognosis (Lille score).

- **Oral prednisolone** (40 mg/d PO for 4 weeks, followed by a taper over 2-4 weeks) is a steroid treatment for patients with severe alcoholic hepatitis. Prednisolone is preferred (but not demonstrated to be better) over prednisone as the latter requires conversion to its active form, prednisolone, within the liver. In a recent trial, prednisolone demonstrated a beneficial effect on short-term mortality (28 days), but not on the medium- or long-term mortality (90 days and 1 year, respectively) (*N Engl J Med 2015;372:1619*).
- **Pentoxifylline** (400 mg PO tid for 4 weeks) is a nonselective phosphodiesterase inhibitor that, in a recent trial, did not show improved outcomes in this patient group (*N Engl J Med 2015;372:1619*).

Surgical Management

Patients with cirrhosis and ESLD can be evaluated for liver transplantation but are required to abstain from alcohol for 6 months prior to evaluation, maintain abstinence, and be part of a rehabilitation program.

OUTCOME/PROGNOSIS

- Fatty liver may be reversible with abstinence.
- In alcoholic hepatitis, prognosis depends on the severity of presentation and alcohol abstinence. The in-hospital mortality for severe cases is approximately 50% due to complications including sepsis and renal failure.
- In alcoholic cirrhosis, prognosis is variable and depends on the degree of liver decompensation. Abstinence from alcohol may promote significant liver chemistry improvement.

IMMUNE-MEDIATED LIVER DISEASES

Autoimmune Hepatitis

GENERAL PRINCIPLES

AIH is a chronic unresolving inflammation of the liver of unknown cause, associated with circulating autoantibodies and hyperglobulinemia.

- Women are affected more than men (gender ratio, 3.6:1).
- Extrahepatic manifestations may be found in 30-50% of patients and include synovitis, celiac disease, Coombs-positive hemolytic anemia, autoimmune thyroiditis, Graves disease, rheumatoid arthritis, ulcerative colitis, and other immune-mediated processes.

Two types of AIH have been proposed based on differences in their immunologic markers. They have a good response to corticosteroid therapy.

- **Type I AIH** is the most common form of the disease and constitutes 80% of AIH cases. It is associated with antinuclear antibodies (ANAs) and anti-smooth muscle antibodies (SMAs).
- **Type 2 AIH** is characterized by antibodies to liver/kidney microsome type 1 (anti-LKM1) and/or liver cytosol type 1 (anti-LC1). This type is predominately seen in children and young adults (*J Hepatol 2015;62:S100*).

DIAGNOSIS

Clinical Presentation

- Aminotransferase elevations are generally more prominent than those of bilirubin and ALP, although a cholestatic picture marked by high levels of conjugated bilirubin and ALP can be seen.
- Elevation of serum globulins, particularly γ-globulins (IgG), is characteristic of AIH. Hyperglobulinemia is generally associated with circulating autoantibodies, which are helpful in identifying AIH.
- In approximately 30-40% of cases, the clinical presentation is similar to acute viral hepatitis. A smaller percentage of patients may present in FHF or with asymptomatic elevation of serum ALT. It presents with cirrhosis in at least 25% of patients.
- The most common symptoms at presentation include fatigue, jaundice, myalgias, anorexia, diarrhea, acne, abnormal menses, and right upper quadrant abdominal discomfort.
- Patients with AIH may overlap with clinical and histologic findings consistent with other liver diseases (e.g., PBC, PSC, Wilson disease, and autoimmune cholangitis).
- Diagnostic criteria have been codified by an international panel (*Hepatology 2002;36(2):479*). This same panel has since put forth simplified diagnostic criteria based on autoantibodies, IgG, histology, and the exclusion of viral hepatitis (*Hepatology 2010;51(6):7*).

Diagnostic Testing

Liver biopsy is recommended for definitive diagnosis.

- **"Piecemeal necrosis" or interface hepatitis** with lobular or panacinar inflammation (lymphocytic and plasmacytic infiltration) are the histologic hallmarks of the disease.
- Histologic changes, such as ductopenia or destructive cholangitis, may indicate overlap syndromes combining characteristics of AIH, PSC, PBC, or autoimmune cholangitis.

TREATMENT

Treatment should be started in patients with elevated serum aminotransferase levels (>5 times upper limit of normal), hyperglobulinemia, and histologic features of interface hepatitis, bridging, or multiacinar necrosis.

Medications

- Therapy consists of prednisone (50-60 mg/d PO) as monotherapy or at a lower dose (30 mg/d PO) in conjunction with azathioprine (50 mg or up to 1-2 mg/kg). The dose of prednisone is tapered down every 10-15 days, whereas the dose of azathioprine remains unchanged. As the AIH biochemical abnormalities subside, the maintenance regimen with combination therapy is continued for 1 year. The prednisone is then gradually stopped, and during the second year, treatment is with azathioprine monotherapy. At the end of the second year, a liver biopsy is obtained to reassess histologic regression. If the histology has

normalized, in association with biochemical remission, options include discontinuation of the immunosuppression with close follow-up to assess new flares or continuing the maintenance therapy.

- The combination of prednisone and azathioprine decreases corticosteroid-associated side effects; however, azathioprine should be used with caution in patients with pretreatment cytopenias or thiopurine methyltransferase deficiency.
- **Budesonide** (6-9 mg/d PO), in combination with azathioprine (1-2 mg/kg/d PO), may also result in normalization of AST and ALT, with fewer steroid-specific side effects, in **noncirrhotic** adults with AIH (*Gastroenterology 2010;139(4):1198*).
- Other treatment alternatives for suboptimal response or treatment failures include mycophenolate mofetil, tacrolimus, cyclosporine, and budesonide.

Surgical Management

- Liver transplantation should be considered in patients with ESLD and those with AIH-mediated FHF.
- After transplantation, recurrent AIH is seen in approximately 15% of patients. De novo AIH or immunologically mediated hepatitis, defined as hepatitis with histologic features similar to AIH in patients transplanted for nonautoimmune diseases, has been described in about 5% of transplant recipients.

MONITORING/FOLLOW-UP

- About 90% of adults have improvements in the serum aminotransferase, bilirubin, and γ-globulin levels within the first 2 weeks of treatment.
- Histologic improvement lags behind clinical and laboratory improvement by 3-8 months.

OUTCOME/PROGNOSIS

- The overall goal of treatment is normalization of aminotransferases, hyperglobulinemia (IgG), and liver histology.
- Remission is achieved in 65% and 80% of patients within 1.5 and 3.0 years of treatment, respectively.
- Relapses occur in at least 20-50% of patients after cessation of therapy and require retreatment.

Primary Biliary Cirrhosis

GENERAL PRINCIPLES

Primary biliary cirrhosis or primary biliary cholangitis (PBC) is a cholestatic hepatic disorder of unknown etiology with autoimmune features.

- It most often affects middle-aged women (>90%) and is more commonly described in Caucasians. It is caused by granulomatous destruction of the interlobular bile ducts, which leads to progressive ductopenia and cholestasis.
- Cholestasis is generally slowly progressive and can lead to cirrhosis and eventually liver failure.
- Extrahepatic manifestations include keratoconjunctivitis sicca (Sjögren), renal tubular acidosis, gallstones, thyroid disease, scleroderma, Raynaud phenomenon, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), and celiac disease.

DIAGNOSIS

Clinical Presentation

- Fatigue, jaundice, and pruritus are often the most troublesome symptoms.
- Patients may present de novo with manifestations of ESLD.

- Although there are no exam findings that are specific for PBC, xanthomata and xanthelasma can be a clue to underlying cholestasis.

Diagnostic Testing

- Antimitochondrial antibodies are present in >90% of patients.
- Typical features include elevated levels of ALP, total bilirubin, cholesterol, and IgM.

Diagnostic Procedures

Liver biopsy is helpful for both diagnosis and staging.

TREATMENT

Medications

- No curative therapy is available; treatment aims to slow progression of disease.
- **Ursodeoxycholic acid (UDCA)** (13-15 mg/kg/d PO) is a bile acid derivative with hepatocyte cytoprotective properties that stimulates hepatocellular and ductular secretions. Traditionally, UDCA has been suggested to reduce mortality when given long term. However, recent meta-analyses have suggested an advantage of using a combination of UDCA plus steroids or UDCA plus bezafibrates over UDCA monotherapy (outcomes measured were all-cause mortality and liver transplantation). UDCA plus bezafibrates had a greater side effect profile compared to the other treatment options (*Medicine 2015;94(11):1*).
- **Obeticholic acid** (OCA; 10-50 mg/d PO) is a derivative of the primary bile acid chenodeoxycholic acid and affects bile acid homeostasis. This agent is expected to be approved by the US Food and Drug Administration (FDA) soon. In a trial of patients with PBC who had an inadequate response to UDCA, a 3-month treatment with OCA plus UDCA significantly reduced levels of ALP, GGT, and ALT when compared to UDCA plus placebo (*Gastroenterology 2015;148:751*).

Surgical Management

- Liver transplantation is an option in advanced disease.
- Recurrent PBC after transplantation has been documented at a rate of 20% over 10 years.

OUTCOME/PROGNOSIS

- PBC progresses along a path of increasingly severe histologic damage (florid bile duct lesions, ductular proliferation, fibrosis, and cirrhosis).
- Progression to cirrhosis and liver failure may occur years from diagnosis.

Primary Sclerosing Cholangitis

GENERAL PRINCIPLES

PSC is a cholestatic liver disorder characterized by inflammation, fibrosis, and obliteration of the extrahepatic and/or intrahepatic bile ducts.

- Patients with PSC can be subdivided into those with **small duct** and **large duct involvement**. Small duct disease is defined as typical histologic features of PSC with a normal cholangiogram. In classic PSC, characteristic strictures of the biliary tree can be detected by cholangiography. Patients with small duct disease have a more favorable prognosis (*Hepatology 2002;35:1494*).
- The peak incidence is at about age 40 years. Most patients are middle-aged men, and the male-to-female ratio is 2:1.
- PSC is frequently associated with inflammatory bowel disease (70% of patients have concomitant ulcerative colitis). The clinical course of these conditions is not correlated.

DIAGNOSIS

Clinical Presentation

- Clinical manifestations include intermittent episodes of jaundice, hepatomegaly, pruritus, weight loss, and fatigue. Patients slowly progress to cirrhosis.
- Acute cholangitis is defined as an infection of the biliary ductal system usually caused by bacteria ascending from its junction with the duodenum and is a frequent complication in patients with strictures of the biliary ducts. Symptoms of acute cholangitis include fever, chills, rigors, jaundice, and right upper quadrant pain.
- Cholangiocarcinoma is the most frequent neoplasm associated with PSC. Patients with PSC have a 15% lifetime risk of developing cholangiocarcinoma (*Curr Gastroenterol Rep 2015;17:17*).

Diagnostic Testing

- The diagnosis of PSC should be considered in individuals with inflammatory bowel disease who have increased levels of ALP even in the absence of symptoms of hepatobiliary disease.
- **ANA** is positive in up to 50% of cases, and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is positive in 80% of cases.
- MRCP is the preferred diagnostic study of choice.

Diagnostic Procedures

- ERCP can confirm the diagnosis of PSC by demonstrating strictures or irregularities of the intrahepatic or extrahepatic bile ducts. It also allows duct brushings and biopsies to be obtained to evaluate for associated malignancy. Intraductal endoscopy provides direct visualization of the biliary ducts with the advantage of direct tissue sampling.
- Liver biopsy is helpful in the diagnosis of small-duct PSC, in the exclusion of other diseases, and in staging. Characteristic histologic findings include concentric periductal fibrosis (“onion skinning”), degeneration of bile duct epithelium, ductular proliferation, ductopenia, and cholestasis.
- Fluorescent in situ hybridization (FISH) allows for molecular assessment of malignancy from tissue obtained by brushing or biopsy.

TREATMENT

Medications

- At this time, there is no established medical treatment for PSC. Clinical trials for the utilization of nuclear receptor ligands (fibrates, OCA, and TGR5 receptor ligand), novel bile acid therapies, and simtuzumab are under investigation.
- Several randomized, placebo-controlled trials comparing the use of UDCA (13-23 mg/kg/d) showed improvement of liver tests in the UDCA group compared to placebo. However, there was no difference in long-term survival or time to liver transplantation between both groups. UDCA (>28 mg/kg/d) was associated with a higher risk of serious adverse events including death and transplantation and is **not** currently recommended for **PSC therapy** (*Gastroenterology 2013;145:521*).
- Episodes of cholangitis should be managed with IV antibiotics and endoscopic therapy.

Other Nonpharmacologic Therapies

- ERCP can be useful to dilate and stent dominant strictures.
- Surgical management
  - Colectomy for ulcerative colitis does not affect the course of PSC.
  - Patients with decompensated cirrhosis or recurrent cholangitis should be referred for liver transplantation.
  - Selected hilar cholangiocarcinomas may be considered for liver transplantation.
  - Recurrent PSC after liver transplantation has been documented.

COMPLICATIONS OF CHOLESTASIS

Nutritional Deficiencies

GENERAL PRINCIPLES

Any condition that blocks bile excretion (at the level of the liver cell level or the biliary ducts) is defined as cholestasis. Laboratory manifestations of cholestasis include elevated levels of ALP and bilirubin.

- **Nutritional deficiencies** result from fat malabsorption.
- **Fat-soluble vitamin deficiency** (vitamins A, D, E, and K) is often present in advanced cholestasis and is particularly common in patients with steatorrhea.

DIAGNOSIS

Clinical Presentation

- Characteristic manifestations of vitamin deficiencies are discussed in Chapter 2, Nutrition Support.
- Patients with steatorrhea may give a history of oily, foul-smelling diarrhea that may stick to the toilet bowl or be difficult to flush.

Diagnostic Testing

- 25-Hydroxyvitamin D serum concentrations reflect the total body stores of vitamin D. Vitamin D deficiency in the setting of malabsorption and steatorrhea is a good surrogate clinical marker for total body concentrations of other fat-soluble vitamins.

- Stool can be tested for fecal fat. Both spot tests and 24-hour collections can be done.

TREATMENT

Medications

Vitamin supplements are available to correct deficiencies.

Osteoporosis

GENERAL PRINCIPLES

- Osteoporosis is defined as a decrease in the amount of bone (mainly trabecular bone), leading to a decrease in its structural integrity and increase in the risk of fractures.
- The relative risk of osteopenia in cholestasis is 4.4 times greater than the general population, matched for age and gender. Osteoporosis is more commonly seen in clinical cholestasis due to PBC.

DIAGNOSIS

Bone mineral density should be measured by dual-energy X-ray absorptiometry (DEXA) in all patients at the time of diagnosis and during follow-up (every 1-2 years).

TREATMENT

Treatment of bone disease includes weight-bearing exercise, oral calcium supplementation (1.0-1.5 g/d), bisphosphonate therapy, and vitamin D supplementation.

Pruritus

GENERAL PRINCIPLES

The pathophysiology is debated and may be due to the accumulation of bile acid compounds or endogenous opioid agonists.

DIAGNOSIS

Patients with cholestasis may present with itching in the setting of a normal or elevated bilirubin level.

TREATMENT

Medications

First Line

- Pruritus is best treated with cholestyramine, a basic anion exchange resin. It binds bile acids and other anionic compounds in the intestine and inhibits their absorption. The dose is 4 g mixed with water before and after the morning meal, with additional doses before lunch and dinner. The maximum recommended dose is 16 g/d. Cholestyramine should be administered apart from other vitamins or medications to

prevent impaired absorption.

- Colestipol, another similar resin, is also available.

Second Line

- Antihistamines (hydroxyzine, diphenhydramine, or doxepin, 25 mg PO at bedtime) and petrolatum may provide symptomatic relief.
- Rifampin (150-600 mg/d) and naltrexone (25-50 mg/d) are reserved for intractable pruritus. Long-term therapy with rifampin is associated with minor, transient elevations in serum aminotransferase levels in 10-20% of patients—abnormalities that usually do not require dose adjustment or discontinuation. In rare instances, it can induce severe forms of DILI.

METABOLIC LIVER DISEASES

GENERAL PRINCIPLES

Wilson disease (WD) is an autosomal recessive disorder (*ATP7B* gene on chromosome 13) that results in progressive copper overload.

- Female-to-male ratio is 2:1.
- Absent or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and deposited in other organs, notably the brain, kidneys, and cornea.
- Extrahepatic manifestations include Kayser-Fleischer rings in the Descemet membrane in the periphery of the cornea due to copper deposition (diagnosed on slit-lamp examination), Coombs-negative hemolytic anemia, renal tubular acidosis, arthritis, and osteopenia.

DIAGNOSIS

Clinical Presentation

- The average age at presentation of liver dysfunction is 6-20 years, but it can manifest later in life. Liver disease can be highly variable, ranging from asymptomatic with only mild biochemical abnormalities to FHF.

- Most patients with the FHF presentation of WD have a characteristic pattern of clinical findings including Coombs-negative hemolytic anemia with features of acute intravascular hemolysis, rapid progression to renal failure, a rise in serum aminotransferases from the beginning of clinical illness (typically <2000 IU/L), and normal or markedly subnormal serum ALP (typically <40 IU/L) (*Hepatology 2008;47:2090*).
- The diagnosis of WD should be considered in patients with unexplained liver disease with or without neuropsychiatric symptoms, first-degree relatives with WD, or individuals with FHF (with or without hemolysis).
- Neuropsychiatric disorders usually occur later, most of the time in association with cirrhosis. The manifestations include asymmetric tremor, dysarthria, ataxia, and psychiatric features.

Diagnostic Testing

- Low serum ceruloplasmin level (<20 mg/dL), elevated serum free copper level (>25 µg/dL), and elevated 24-hour urinary copper level (>100 µg) are seen in patients with WD.
- The liver histology (massive necrosis, steatosis, glycogenated nuclei, chronic hepatitis, fibrosis, cirrhosis)

findings are nonspecific and depend on the presentation and stage of the disease. Elevated hepatic copper levels of >250 µg/g dry weight (normal <40 µg/g) on biopsy are highly suggestive of WD.

- Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing. Many patients are compound heterozygotes for mutations in the *ATP7B* gene, making identification of mutations difficult.

TREATMENT

Medications

Treatment is with the copper-chelating agents penicillamine and trientine. Zinc salts that block the intestinal absorption of copper are also used.

- **Penicillamine** 1-2 g/d (in divided doses bid or qid) and pyridoxine 25 mg/d (to avoid vitamin B_6 deficiency during treatment) are indicated in patients with hepatic failure. Use may be limited by side effects (e.g., hypersensitivity, bone marrow suppression, proteinuria, systemic lupus erythematosus, Goodpasture syndrome). Penicillamine should never be given as initial treatment to patients with neurologic symptoms.
- **Trientine** 1-2 g/d (in divided doses bid or qid) may also be used in hepatic failure. This has similar side effects as penicillamine but at a lower frequency. The risk of neurologic worsening with trientine is less than with penicillamine.
- **Zinc salts** 50 mg tid are indicated in patients with chronic hepatitis and cirrhosis in the absence of hepatic failure. Other than gastric irritation, zinc has an excellent safety profile.

Surgical Management

Liver transplantation is the only therapeutic option in FHF or in patients with progressive dysfunction despite chelation therapy.

MONITORING/FOLLOW-UP

- For monitoring, serum copper and ceruloplasmin, liver biochemistries, INR, complete blood cell count, urinalysis (especially for those on chelation therapy), and physical examination should be performed regularly, at least twice annually.
- The 24-hour urinary excretion of copper should be measured annually while on medication. More frequent monitoring may be needed if there is suspicion of noncompliance or if dose adjustment is required. The estimated serum free copper may be elevated or low in situations of nonadherence and overtreatment, respectively.
- First-degree relatives of any newly diagnosed patient with WD should be screened for WD.

OUTCOME/PROGNOSIS

After liver transplantation, in the absence of neurologic symptoms, patients require no further medical treatment.

Hereditary Hemochromatosis

GENERAL PRINCIPLES

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron overload.

- This is the most common inherited form of iron overload affecting Caucasian populations. One in 200-400 Caucasian individuals are homozygous for hemochromatosis (*HFE*) gene mutations. It rarely manifests clinically before middle age (40-60 years).
- HH is most frequently caused by a missense mutation (C282Y) in the *HFE* gene located on chromosome 6. **Approximately 90% of patients with HH are homozygote for the C282Y mutation.** Less frequent mutations that lead to HH include H63D and S65C and the compound heterozygous C282Y/H63D and C282Y/S65C mutations.
- Secondary iron overload states include thalassemia major, sideroblastic anemia, chronic hemolytic anemias, iatrogenic parenteral iron overload, chronic hepatitis B and C, alcohol-induced liver disease, porphyria cutanea tarda, and aceruloplasminemia.

DIAGNOSIS

Clinical Presentation

- Presentation varies from **asymptomatic disease** to **cirrhosis** and HCC.
- Clinical findings include slate-colored skin, diabetes, cardiomyopathy, arthritis, hypogonadism, and hepatic dysfunction.

Diagnostic Testing

Diagnosis is based on laboratory testing, imaging, and liver biopsy.

- The diagnosis is suggested by **high fasting transferrin saturation (>45%) (serum iron divided by the total iron binding capacity)**. Other nonspecific laboratory tests include elevated serum iron and ferritin levels. **Ferritin level >1000 ng/mL is an accurate predictor of the degree of fibrosis in patients with HH.**
- If transferrin saturation is >45% and ferritin is elevated, then check for C282Y homozygosity. If patient is a C282Y homozygote, then:
  - If ferritin <1000 ng/mL and liver enzymes are normal, proceed to therapeutic phlebotomy.
  - If ferritin >1000 ng/mL or liver enzymes are elevated, proceed to liver biopsy for histology and hepatic iron concentration (HIC).
- The normal content of iron in the liver ranges from 250-1500 µg/g dry weight. In patients with HH, HIC ranges from 2000-30,000 µg/g dry weight.
- In patients with elevated transferrin saturation and heterozygosity of the C282Y mutation, exclude other liver or hematologic diseases and consider liver biopsy.
- **MRI** is the modality of choice for noninvasive quantification of iron storage in the liver and for noninvasive surveillance of HCC. It allows for repeated measures and minimizes sampling error.

TREATMENT

Therapy consists of **phlebotomy** every 7-15 days (500 mL blood) until iron depletion is confirmed by a ferritin level of 50-100 ng/mL and a transferrin saturation of <40%. Maintenance phlebotomy of one or two units of blood three to four times a year is continued for life, unless there are contraindications for rapid mobilization of iron stores (i.e., heart failure).

Medications

- **Iron chelation with deferoxamine** is an alternative to phlebotomy, but it is often more expensive and has side effects such as GI distress, visual and auditory impairments, and muscle cramps. Deferoxamine binds free iron, facilitates urinary excretion, and is recommended only when phlebotomy is contraindicated. Deferoxamine is only given IV, IM, or SC.
- Deferasirox is an oral iron chelator that selectively binds iron, forming a complex that is excreted through the feces.

Surgical Management

Liver transplantation may be considered in cases of HH with cirrhosis.

OUTCOME/PROGNOSIS

- The survival rate in appropriately treated noncirrhotic patients is identical to that of the general population.
- Patients who undergo liver transplantation for hemochromatosis have better survival rates if they are iron depleted via phlebotomy prior to transplantation compared to patients who are iron overloaded prior to transplantation (*Gastroenterology 2010;139:393*).
- The relative risk for HCC is approximately 20, with an annual incidence of 3-4%. Patients with HH and advanced fibrosis or cirrhosis should be screened annually for HCC (*Hepatology 2011;54(1):328*).

α1-Antitrypsin Deficiency

GENERAL PRINCIPLES

- α_1-Antitrypsin (α_1AT) deficiency is an autosomal recessive disease associated with accumulation of misfolded α_1AT in the endoplasmic reticulum of hepatocytes. The most common allele is protease inhibitor M (PiM—normal), followed by PiS and PiZ (deficient variants). African Americans have a lower frequency of these alleles.
- The most prevalent deficiency alleles Z and S are derived from European ancestry (*Am J Gastroenterol 2008;103:2136*).
- α_1AT deficiency can also be associated with emphysema in early adulthood, as well as other extrahepatic manifestations including panniculitis, pancreatic fibrosis, and membranoproliferative glomerulonephritis.

DIAGNOSIS

Clinical Presentation

- The disease may present as neonatal cholestasis or, later in life, as chronic hepatitis, cirrhosis, or HCC.
- The presence of significant pulmonary and hepatic disease in the same patient is rare (1-2%).

Diagnostic Testing

- Low serum α_1AT level (10-15% of normal) will flatten the α_1-globulin curve on serum electrophoresis.
- Deficient α_1AT phenotype (PiSS, PiSZ, and PiZZ).
- Elevated AST and ALT.

Diagnostic Procedures

Liver biopsy shows characteristic periodic acid-Schiff-positive diastase-resistant globules in the periportal hepatocytes.

TREATMENT

Currently, there is no specific medical treatment for liver disease associated with α_1AT deficiency.

Gene therapy for α_1AT deficiency is a potential future alternative.

Surgical Management

Liver transplantation is an option for those with cirrhosis and is curative, with survival rates of 90% at 1 year and 80% at 5 years.

OUTCOME/PROGNOSIS

- Chronic hepatitis, cirrhosis, or HCC may develop in 10-15% of patients with the PiZZ phenotype during the first 20 years of life.
- Controversy exists as to whether liver disease develops in heterozygotes (PiMZ, PiSZ, PiFZ).

MISCELLANEOUS LIVER DISORDERS

Nonalcoholic Fatty Liver Disease

GENERAL PRINCIPLES

- Nonalcoholic fatty liver disease (NAFLD) is a clinicopathologic syndrome that encompasses several clinical entities that range from simple steatosis to steatohepatitis, fibrosis, ESLD, and HCC in the absence of significant alcohol consumption (*Gastroenterology 2002;123:1705*).
- Nonalcoholic steatohepatitis (NASH) is part of the spectrum of NAFLD and is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.
- NAFLD is associated with an increasing prevalence of type 2 diabetes, obesity, and the metabolic syndrome in the US population.

DIAGNOSIS

Clinical Presentation

The disease may vary from asymptomatic liver fatty infiltration to advanced fibrosis, cirrhosis, and HCC.

Diagnostic Testing

- When patients with hepatic steatosis detected on imaging have symptoms or signs attributable to liver disease or have abnormal liver biochemistries, they should be evaluated for NAFLD and worked up accordingly.
- In patients with hepatic steatosis detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries, it is reasonable to assess for metabolic risk factors (e.g., obesity, glucose intolerance, dyslipidemia) and alternate causes for hepatic steatosis such as significant alcohol consumption or medications.

- The distinction between NAFLD and NASH is determined by liver biopsy. Liver biopsy remains the

diagnostic gold standard. However, the decision to perform a liver biopsy should take into account the specific clinical questions that are relevant to each case.

- Noninvasive predictive models, serum biomarkers, and imaging studies are increasingly used as surrogate measures of liver fibrosis, inflammation, and steatosis, without replacing liver biopsy.
- Normal liver enzymes are observed in up to 80% of patients. When present, these elevations are mild. Aminotransferases greater than two times normal may be predictive of fibrosis across different populations.
- Imaging studies such as ultrasonography, CT scan, and MRI may detect moderate to severe steatosis.

TREATMENT

Nonpharmacologic Therapies

Therapies to correct or control associated conditions are warranted (weight loss through diet and exercise, tight control of diabetes and insulin resistance, appropriate treatment of hyperlipidemia, and discontinuation of possible offending agents).

Medications

Despite inconclusive data on a long-term therapy safety profile, guidelines support the use of pioglitazone (45 mg/d) and vitamin E (800 IU/d) in nondiabetics with biopsy-proven NASH (*Hepatology 2012;55(6):2005*).

Surgical Management

Liver transplantation should be considered in patients with cirrhosis.

OUTCOME/PROGNOSIS

- Approximately 25% of patients with simple steatosis will progress to NASH.
- Progression to NASH cirrhosis has been reported at a rate of 11% over a 15-year period (*Clin Liver Dis 2012;16:397*).

Ischemic Hepatitis

GENERAL PRINCIPLES

Ischemic hepatitis results from acute liver hypoperfusion. Clinical circumstances associated with acute hypotension or hemodynamic instability include severe blood loss, substantial burns, cardiac failure, heat stroke, sepsis, sickle cell crisis, and others.

DIAGNOSIS

Clinical Presentation

Ischemic hepatitis presents with an acute and frequently transient and severe rise of aminotransferases during or following an episode of liver hypoperfusion.

Diagnostic Testing

- Laboratory studies show a rapid rise in levels of serum AST, ALT (>1000 mg/dL), and lactate dehydrogenase (LDH) within 1-3 days of the insult.
- Total bilirubin, ALP, and INR may initially be normal but subsequently rise as a result of reperfusion injury.

Diagnostic Procedures

Liver biopsy is not routinely needed, because the diagnosis can usually be made with clinical history. Classic histologic features include variable degrees of zone 3 (centrilobular) necrosis with collapse around the central vein. Coexistent features may include passive congestion, sinusoidal distortion, fatty change, and cholestasis. Inflammatory infiltrates are rare.

TREATMENT

Treatment consists of supportive care and correction of the underlying condition that caused the circulatory collapse.

OUTCOME/PROGNOSIS

Prognosis is dependent on rapid and effective treatment of the underlying condition.

Hepatic Vein Thrombosis

GENERAL PRINCIPLES

Hepatic vein thrombosis (HVT), also known as Budd-Chiari syndrome, causes hepatic venous outflow obstruction. It has multiple etiologies and a variety of clinical consequences.

- Thrombosis is the main factor leading to obstruction of the hepatic venous system, frequently in association with myeloproliferative disorders, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, factor V Leiden, protein C and S deficiency, Jak-2 mutation, and contraceptive use (*Dig Liver Dis 2011;43:503*).
- Membranous obstruction of the inferior vena cava (IVC) and stenosis of the IVC anastomosis after liver transplantation are conditions that present clinically similar to HVT.
- Less than 20% of cases are idiopathic.

DIAGNOSIS

Clinical Presentation

Patients may present with acute, subacute, or chronic illness characterized by ascites, hepatomegaly, and right upper quadrant abdominal pain. Other symptoms may include jaundice, encephalopathy, GI bleeding, and lower extremity edema.

Diagnostic Testing

- Serum-to-ascites albumin gradient (SAAG) is >1.1 g/dL. Serum albumin, bilirubin, AST, ALT, and PT/INR are usually abnormal.
- Laboratory evaluation to identify a hypercoagulable state should be performed (see Chapter 20, Disorders of Hemostasis and Thrombosis).
- Doppler ultrasound can be used as a screening test. Definitive diagnosis is made with magnetic resonance venography, hepatic venography, or cavography.

TREATMENT

Medications

Nonsurgical treatment includes anticoagulation, thrombolytics, diuretics, angioplasty, stents, and TIPS.

Surgical Management

Liver transplantation is an option in selected patients.

Portal Vein Thrombosis

GENERAL PRINCIPLES

Portal vein thrombosis (PVT) is seen in a variety of clinical settings, including abdominal trauma, cirrhosis, malignancy, hypercoagulable states, intra-abdominal infections, pancreatitis, and after portocaval shunt surgery and splenectomy.

DIAGNOSIS

Clinical Presentation

- PVT can present as an acute or chronic condition.
- The acute phase may go unrecognized. Symptoms include abdominal pain/distension, nausea, anorexia, weight loss, diarrhea, or features of the underlying disorder.
- Chronic PVT may present with variceal hemorrhage or other manifestations of portal hypertension.

Diagnostic Testing

- In patients with no obvious etiology, a hypercoagulable workup should be performed.
- **Ultrasonographic Doppler** examination is sensitive and specific for establishing the diagnosis. Portal venography, CT, or magnetic resonance venography can also be used.

TREATMENT

Medications

- In patients with acute PVT with or without cirrhosis, anticoagulation is recommended in the absence of any obvious contraindications. Treatment is aimed to prevent further thrombosis and recanalization, to treat complications and concurrent disease, and to identify underlying risk factors (*Neth J Med 2009;67:46*).
- In patients with chronic PVT, anticoagulation is not recommended.

Other Nonpharmacologic Therapies

In the setting of chronic PVT, treatment should focus on the complications of portal hypertension and include nonselective β-blockers, endoscopic banding for varices, and diuretics for ascites.

Surgical Management

Portosystemic derivative surgery carries a high morbidity and mortality, especially in patients with cirrhosis. In some instances where surgery is precluded or the thrombus expands despite adequate anticoagulation, interventional radiology may be able to deploy a TIPS. This may then theoretically resolve symptomatic

portal hypertension and prevent the thrombus recurrence or extension by the creation of a portosystemic shunt (*Nat Rev Gastroenterol Hepatol 2014;11:435*).

FULMINANT HEPATIC FAILURE

GENERAL PRINCIPLES

- FHF is a condition that includes evidence of a combination of coagulation abnormalities and any degree of mental alteration (encephalopathy) in a patient without preexisting liver disease and with an illness of <26 weeks in duration.

- Terms signifying length of illness in FHF such as hyperacute (<7 days), acute (7-21 days), and subacute (>21 days to <26 weeks) are not frequently used because they do not have prognostic significance (*Gastroenterol Clin North Am 2011;40:523*).
- In 20% of cases, no clear cause is identified. Acetaminophen hepatotoxicity and viral hepatitis are the most common causes of FHF. Other causes include AIH, drug and toxin exposure, ischemia, acute fatty liver of pregnancy, WD, and Reye syndrome.
- Acute inflammation with varying degrees of necrosis and collapse of the liver's architectural framework are the typical histologic changes seen in FHF.

DIAGNOSIS

Clinical Presentation

- Patients may present with mild to severe mental status changes in the setting of moderate to severe acute hepatitis and coagulopathy.
- Patients may develop cardiovascular collapse, acute renal failure, cerebral edema, and sepsis.

Diagnostic Testing

- Aminotransferases are typically elevated and, in many cases, are >1000 IU/L.
- INR >1.5 that does not correct with the administration of vitamin K is characteristic.
- Workup to determine the etiology of FHF should include acute viral hepatitis panel, serum drug screen (including acetaminophen level), ceruloplasmin, AIH serologies, and pregnancy test.
- Right upper quadrant ultrasound with Doppler may be obtained to evaluate obstruction of hepatic venous inflow or outflow.
- CT of the head may be obtained to evaluate and track progression of cerebral edema; however, the radiologic findings may lag behind its development and do not substitute for serial bedside assessments of neurologic status.
- Liver biopsy is seldom used to establish etiology or prognosis. Given the presence of coagulopathy, a transjugular approach to liver biopsy may be attempted if necessary.

TREATMENT

- Supportive therapy (quiet dark room, avoid patient stimulation, maintain head of bed elevation to 30 degrees) in the intensive care unit (ICU) setting with liver transplant capabilities is essential.
- Precipitating factors, such as infection, should be identified and treated. Blood glucose, electrolytes, acid-

base balance, coagulation parameters, and fluid status should be serially monitored.

- Sedatives should be avoided to appropriately gauge the patient's mental status.
- *N*-acetylcysteine (NAC) may be used in cases of FHF in which acetaminophen ingestion is suspected or when circumstances surrounding admission is inadequate. NAC also appears to improve spontaneous survival when given during early hepatic encephalopathy stages (grades I and II) even in the setting of nonacetaminophen FHF.
- Fresh frozen plasma and the use of recombinant activated factor VIIa should be considered in the setting of active bleeding or when invasive procedures are required.
- Cerebral edema and intracranial hypertension are related to the severity of encephalopathy. In patients with grade III or IV encephalopathy, intracranial pressure monitoring should be considered (intracranial pressure should be maintained below 20 mm Hg and cerebral perfusion pressure should be maintained above 50 mm Hg). Management of cerebral edema, when identified by CT imaging, includes intubation with sedation to avoid overstimulation, elevation of the head of the bed,

use of mannitol (0.5-1.25 g/kg of 20% solution), and/or use of hypertonic saline (30% hypertonic saline at a rate of 5-20 mL/h to maintain a serum sodium of 145-155 mmol/L) (*Hepatology 2004;39(2):464*). Lactulose is not indicated for encephalopathy in this setting. Its use may result in increased bowel gas that can interfere with the surgical approach for liver transplantation.
- Therapeutic hypothermia (chilled to 32°C) is an adjunct therapy in patients with grade III or IV hepatic encephalopathy or uncontrolled intracranial hypertension; it may be used as a bridge to liver transplantation in some patients.
- Liver transplantation should be urgently considered in cases of severe FHF. Poor prognostic indicators in acetaminophen-induced FHF include arterial pH <7.3, INR >6.5, creatinine >2.3 mg/dL, and encephalopathy grades III through IV (King's College Criteria).

OUTCOME/PROGNOSIS

- In the United States, 45% of adults with FHF have a spontaneous recovery, 25% undergo liver transplantation, and 30% die without liver transplantation (*Curr Opin Organ Transplant 2011;16:289*).
- Death often results from progressive liver failure, GI bleeding, cerebral edema, sepsis, or arrhythmia.
- A rapid decline in aminotransferases correlates poorly with prognosis and does not always indicate an improved response to therapy.

CIRRHOSIS

- Cirrhosis is a chronic condition characterized by diffuse replacement of liver cells by fibrotic tissue, which creates a nodular-appearing distortion of the normal liver architecture. Advanced fibrosis represents the end result of many etiologies of liver injury.
- Cirrhosis affects nearly 5.5 million Americans, and in 2009, it was the 12th leading cause of death in the United States.
- The most common etiologies are alcohol-related liver disease, chronic viral infection, and NASH (diagnosis and treatment discussed earlier in respective sections).
- Main complications of cirrhosis include portal hypertension with various clinical manifestations (ascites, esophageal and gastric varices, portal hypertensive gastropathy and colopathy, hypersplenism, gastric antral

vascular ectasia, spontaneous bacterial peritonitis [SBP], hepatorenal syndrome [HRS], hepatic encephalopathy, and HCC). Frequent laboratory abnormalities encountered in a patient with cirrhosis include anemia, leukopenia, thrombocytopenia, hypoalbuminemia, coagulopathy, and hyperbilirubinemia.

Portal Hypertension

GENERAL PRINCIPLES

- Portal hypertension is the main complication of cirrhosis and is characterized by increased resistance to portal flow and increased portal venous inflow. Portal hypertension is established by measuring the pressure gradient between the hepatic vein and the portal vein (normal portosystemic pressure gradient is approximately 3 mm Hg).
- Direct and indirect clinical consequences of portal hypertension appear when the portosystemic pressure gradient exceeds 10 mm Hg (*Dig Liver Dis 2011;43:762*).

- Causes of portal hypertension in patients without cirrhosis include idiopathic portal hypertension, schistosomiasis, congenital hepatic fibrosis, sarcoidosis, cystic fibrosis, arteriovenous fistulas, splenic and portal vein thrombosis, HVT (Budd-Chiari syndrome), myeloproliferative diseases, nodular regenerative hyperplasia, and focal nodular hyperplasia.

DIAGNOSIS

Portal hypertension frequently complicates cirrhosis and presents with ascites, splenomegaly, and GI bleeding from varices (esophageal or gastric), portal hypertensive gastropathy (PHG), gastric antrum vascular ectasia (GAVE), or portal hypertensive colopathy.

- Ultrasonography, CT, and MRI showing cirrhosis, splenomegaly, collateral venous circulation, and ascites are suggestive of portal hypertension.
- Upper endoscopy may show varices (esophageal or gastric), PHG, or GAVE.
- Transjugular portal pressure measurements may be performed to calculate the portosystemic pressure gradient.

TREATMENT

Treatment of GI bleeding due to portal hypertension is covered in Chapter 18, Gastrointestinal Diseases.

Ascites

GENERAL PRINCIPLES

Ascites is the abnormal (>25 mL) accumulation of fluid within the peritoneal cavity. Other causes of ascites, unrelated to portal hypertension, include cancer (peritoneal carcinomatosis), heart failure, tuberculosis, myxedema, pancreatic disease, nephrotic syndrome, surgery or trauma to the lymphatic system or ureters, and serositis.

DIAGNOSIS

- Presentation ranges from ascites detected only by imaging methods to a distended, bulging, and sometimes tender abdomen. Percussion of the abdomen may reveal shifting dullness.

- **SAAG** is calculated as serum albumin minus the ascites albumin; a gradient > 1.1 indicates portal hypertension-related ascites (97% specificity). A SAAG of <1.1 is found in nephrotic syndrome, peritoneal carcinomatosis, serositis, TB, and biliary or pancreatic ascites.
- Ultrasonography, CT, and MRI are sensitive methods to detect ascites.
- **Diagnostic paracentesis** (60 mL) should be performed in the setting of new-onset ascites, suspicion of malignant ascites, or to rule out SBP. **Therapeutic paracentesis** (large volume) should be performed when tense ascites causes significant discomfort or respiratory compromise or when suspecting abdominal compartment syndrome.
- Routine diagnostic testing should include SAAG calculation, red and white blood cell counts and differential, total protein, and culture. Amylase and triglyceride measurement, cytology, and mycobacterial smear/culture can be performed to confirm specific diagnoses.
- Bleeding, infection, persistent ascites leak, and intestinal perforation are possible complications.

- Large-volume paracentesis (>7 L) may lead to circulatory collapse, encephalopathy, and renal failure. Concomitant administration of IV albumin (5-8 g/L ascites removed) can be used to minimize these complications, especially in the setting of renal insufficiency or the absence of peripheral edema.

TREATMENT

Medications

- **Diuretic therapy** is initiated along with **salt restriction** (<2 g sodium or 88 mmol Na^+/d). Diuretics should be used with caution, or their use should be discontinued in patients with an increasing serum creatinine level.
- **Spironolactone** 100 mg PO daily is indicated. The daily dose can be increased by 50-100 mg every 7-10 days to a maximum dose of 400 mg until satisfactory weight loss or side effects occur. Hyperkalemia and gynecomastia are common side effects. Other potassium-sparing diuretics such as amiloride, triamterene, or eplerenone are substitutes that can be used in patients in whom painful gynecomastia develops.
- **Loop diuretics**, such as furosemide (20-40 mg, increasing to a maximum dose of 160 mg PO daily) or bumetanide (0.5-2.0 mg PO daily), can be added to spironolactone.
- Patients should be observed closely for signs of dehydration, electrolyte disturbances, encephalopathy, muscle cramps, and renal insufficiency. Nonsteroidal anti-inflammatory agents may blunt the effect of diuretics and increase the risk of renal dysfunction.

Other Alternative Therapies

- TIPS is effective in the management of refractory or hard-to-treat ascites.
- Complications of TIPS include shunt occlusion, bleeding, infection, cardiopulmonary compromise, hepatic encephalopathy, hepatic failure, and death.

Spontaneous Bacterial Peritonitis

GENERAL PRINCIPLES

- SBP is an infectious complication of portal hypertension-related ascites defined as >250 neutrophils/μL in the

ascites fluid.

- Bacterascites is defined as culture-positive ascites in the presence of normal neutrophil counts (<250 neutrophilsμ/L) in the ascites fluid. This condition may be spontaneously reversible or the first step in the development of SBP. In the presence of signs or symptoms of infection, bacterascites should be treated like SBP.
- Risk factors for SBP include ascites fluid protein concentration <1 mg/dL, acute GI bleeding, and a prior episode of SBP.

DIAGNOSIS

Clinical Presentation

SBP may be asymptomatic. Clinical manifestations include abdominal pain and distention, fever, decreased bowel sounds, and worsening hepatic encephalopathy. Cirrhotic patients with ascites and evidence of any clinical deterioration should undergo diagnostic paracentesis to exclude SBP.

Diagnostic Testing

The diagnosis is confirmed when >250 neutrophils/μL are found in the ascites fluid. Gram stain reveals the organism in only 10-20% of samples.

- Ascites cultures are more likely to be positive when 10 mL of the fluid is inoculated into two blood culture bottles at the bedside.
- The most common organisms are *Escherichia coli*, *Klebsiella*, and *Streptococcus pneumoniae*. Polymicrobial infection is uncommon and should lead to the suspicion of secondary bacterial peritonitis. Checking total protein, LDH, and glucose on ascites fluid is helpful in distinguishing secondary bacterial peritonitis from SBP.

TREATMENT

Medications

- Patients with SBP should receive empiric antibiotic therapy with IV third-generation cephalosporins (ceftriaxone, 1 g IV daily, or cefotaxime, 1-2 g IV q6-8h, depending on renal function). Therapy should be tailored based on culture results and antibiotic susceptibility. Paracentesis should be repeated if no clinical improvement occurs in 48-72 hours, especially if the initial fluid culture was negative (*Hepatology 2009;49:2087*).
- Oral quinolones can be considered a substitute for IV third-generation cephalosporins in the absence of vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine >3 mg/dL (*Hepatology 2009;49:2087*).
- Patients with <250 neutrophils/μL in the ascites fluid and signs or symptoms of infection (fever or abdominal pain or tenderness) should also receive empiric antibiotic therapy (*Hepatology 2009;49:2087*).
- Concomitant use of albumin 1.5 g/kg body weight at time of diagnosis and 1.0 g/kg body weight on day 3 improves survival and prevents renal failure in SBP (*Am J Gastroenterol 2009;104:1802*).

Primary Prophylaxis (No Prior History of SBP)

Patients with severe liver disease with ascitic fluid protein <1.5 mg/dL along with impaired renal function (creatinine ≥1.2, blood urea nitrogen ≥25, or serum Na <130) or liver failure (Child score ≥9 and bilirubin ≥3) should be treated with long-term norfloxacin 400 mg PO daily.

Secondary Prophylaxis (After the First Episode of SBP)

Norfloxacin 400 mg PO daily is the treatment of choice for prevention of recurrent SBP (*Hepatology 1990;12:716*). Alternative treatments include Bactrim double strength, levofloxacin, or ciprofloxacin.

Acute Kidney Injury in Patients with Cirrhosis and Hepatorenal Syndrome

GENERAL PRINCIPLES

Acute kidney injury (AKI) in decompensated cirrhosis is a common complication. Revised consensus recommendations define AKI as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or a percentage increase of serum creatinine ≥50% from a known or presumed baseline within the prior 7 days (*J Hepatol 2015;62:968*). HRS results from severe peripheral vasodilatation, which leads to renal vasoconstriction. The definition of HRS-AKI (type I HRS) is provided in Table 19-9. Common precipitating factors include systemic bacterial infections, SBP, GI hemorrhage, and large-volume paracentesis without volume expansion. HRS is a diagnosis of exclusion.

TABLE 19-9 Diagnostic Criteria of HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI (an increase in serum creatinine ≥0.3 mg/dL within 48 hours or a percentage increase of serum creatinine ≥50% from a known or presumed baseline within the prior 7 days)
    - Stage 1: increase in serum creatinine ≥0.3 mg/dL or an increase ≥1.5- to 2-fold from baseline
    - Stage 2: increase in serum creatinine >2- to 3-fold from baseline
    - Stage 3: increase in serum creatinine >3-fold from baseline, >4 mg/dL with an acute increase ≥0.3 mg/dL, or initiation of renal replacement therapy
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury, defined as:
    - Absence of proteinuria (>500 mg/d)
    - Absence of microhematuria (>50 RBCs per high-power field)
    - Normal findings on renal ultrasonography

AKI, acute kidney injury; HRS, hepatorenal syndrome; RBC, red blood cell.
Adapted from Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015;62:968-74.

DIAGNOSIS

HRS is observed in cirrhotic patients with ascites, with and without hyponatremia. HRS has been divided into two types.

- **Type I** HRS is characterized by the acute onset of rapidly progressive renal failure (<2 weeks) unresponsive to volume expansion.
- **Type II** HRS progresses more slowly but relentlessly and often clinically manifests as diuretic-resistant ascites.

TREATMENT

Medication

Specific medical therapy is only recommended for type I HRS.

- Terlipressin (vasopressin analog) is not FDA approved for use in the United States. In a placebo-controlled trial, 34% of patients who received terlipressin had a reversal of their HRS in comparison to 13% who received placebo (*Gastroenterology 2008; 134:1360*).
- SC somatostatin analogs (octreotide) and oral β-adrenergic agonist (midodrine) with IV albumin is a commonly used regimen for the management of HRS in the United States.

Other Nonpharmacologic Therapies

Hemodialysis may be indicated in patients listed for liver transplantation.

Surgical Management

Liver transplantation may be curative. Patients receiving hemodialysis for more than 12 weeks should be considered for liver and kidney transplantation.

OUTCOME/PROGNOSIS

Without treatment, patients with type I HRS have a poor prognosis, with death occurring within 1 to 3 months of onset. Patients with type II HRS have a longer median survival.

Hepatic Encephalopathy

GENERAL PRINCIPLES

- Hepatic encephalopathy is the syndrome of disordered consciousness and altered neuromuscular activity that is seen in patients with acute or chronic hepatocellular failure or portosystemic shunting.
- The grades of hepatic encephalopathy are dynamic and can rapidly change.
  - Grade I: Sleep reversal pattern, mild confusion, irritability, tremor, asterixis
  - Grade II: Lethargy, disorientation, inappropriate behavior, asterixis
  - Grade III: Somnolence, severe confusion, aggressive behavior, asterixis
  - Grade IV: Coma
- **Precipitating factors** include medication noncompliance to lactulose, azotemia, FHF, opioids or sedative-hypnotic medications, acute GI bleeding, hypokalemia and alkalosis (diuretics and diarrhea), constipation,

infection, high-protein diet, progressive hepatocellular dysfunction, and portosystemic shunts (surgical or TIPS).

DIAGNOSIS

- Asterixis (flapping tremor) is present in stage I through III encephalopathy. This motor disturbance is not specific to hepatic encephalopathy.
- The electroencephalogram shows slow, high-amplitude, and triphasic waves.
- Determination of blood ammonia level is not a sensitive or specific test for hepatic encephalopathy.

TREATMENT

Medications include nonabsorbable disaccharides (lactulose, lactitol, and lactose in lactasedeficient patients) and antibiotics (neomycin, metronidazole, and rifaximin).

- **Lactulose**, 15-45 mL PO (or via nasogastric tube) bid-qid, is the first choice for treatment of hepatic encephalopathy. Lactulose dosing should be adjusted to produce three to five soft stools per day. Oral lactulose should not be given to patients with ileus or possible bowel obstruction. In the acute phase, a starting dose of 30 mL every 2 hours is recommended. This can then be transitioned to every 4 hours, 6 hours, and then 8 hours once the patient starts having bowel movements.
- **Lactulose enemas** (prepared by the addition of 300 mL lactulose to 700 mL distilled water) may also be administered in patients who cannot tolerate oral intake.
- **Rifaximin** is an oral nonsystemic broad-spectrum antibiotic that is used at a dose of 550 mg PO bid with no serious adverse events. In a placebo-controlled trial, rifaximin reduced the risk of hepatic encephalopathy and the time to first hospitalization over a 6-month period.
- **Neomycin** can be given by mouth (500-1000 mg q6h) or as a retention enema (1% solution in 100-200 mL isotonic saline). Approximately 1-3% of the administered dose of neomycin is absorbed with the attendant risk of ototoxicity and nephrotoxicity.
- In a randomized controlled trial, combination therapy with lactulose and rifaximin was more effective than lactulose alone for management of hepatic encephalopathy (*Am J Gastroenterol 2013;108(9):1458*).

Hepatocellular Carcinoma

GENERAL PRINCIPLES

HCC frequently occurs in patients with cirrhosis, especially when associated with viral hepatitis (HBV or HCV), alcoholic cirrhosis, α_1AT deficiency, and hemochromatosis.

DIAGNOSIS

Clinical Presentation

- Clinical presentation is directly proportional to the stage of disease. HCC may present with right upper quadrant abdominal pain, weight loss, and hepatomegaly.
- Suspect HCC in a cirrhotic patient who develops manifestations of liver decompensation.
- Surveillance for HCC should be performed every 6 months with a sensitive imaging study. The

combination of imaging with AFP is not recommended because it is unlikely to provide a gain in the detection rate. In patients with hepatitis B, surveillance should begin after age 40 years even in the absence of cirrhosis.

Diagnostic Testing

- AFP (see earlier section Evaluation of Liver Disease).
- Investigational serum markers for HCC include lens culinaris agglutinin-reactive AFP, des-γ-carboxyprothrombin (DCP), α-L-fucosidase, and glypican-3 (GPC3).
- Liver ultrasound, triple-phase CT, and MRI with contrast are sensitive and often used for detection of HCC (see Table 19-10 for Organ Procurement and Transplantation

Network criteria for diagnosis of HCC). Liver biopsy should be considered for patients at risk for HCC with suspicious liver lesions ≥1 cm with noncharacteristic imaging features (absence of arterial hypervascularity and venous or delayed phase washout).

TABLE 19-10 Organ Procurement and Transplantation Network (OPTN) Imaging Criteria for the Diagnosis of Hepatocellular Carcinoma (HCC)

OPTN Class 5	Meets all diagnostic criteria for HCC and may qualify for automatic MELD exception points.
Class 5A: ≥1 cm and <2 cm measured on late arterial or portal venous phase	Increased contrast enhancement in late hepatic arterial phase *and* washout during later phases *and* peripheral rim enhancement (capsule or pseudocapsule). A single solitary OPTN class 5A does not earn MELD exception points, but the combination of two or three OPTN class 5A nodules constitutes eligibility for transplantation.
Class 5A-g: same size as OPTN class 5A HCC	Increased contrast enhancement in late hepatic arterial phase *and* growth by ≥50% or more on serial CT or MRI obtained ≤6 months apart.
Class 5B: maximum diameter ≥2 cm and ≤5 cm	Increased contrast enhancement in late hepatic arterial phase *and* either washout *or* peripheral rim enhancement (capsule or pseudocapsule) *or* growth by ≥50% or more on serial CT or MRI obtained ≤6 months apart.
Class 5T	Prior regional treatment for HCC.
Class 5X: maximum diameter ≥5 cm	Increased contrast enhancement in late hepatic arterial phase *and* either washout *or* peripheral rim enhancement (capsule or pseudocapsule).

MELD, Model for End-Stage Liver Disease.
Adapted from *Radiology* 2013;266(2):376-82.

TREATMENT

Surgical Management

- Hepatic resection is the treatment of choice in noncirrhotic patients.
- Liver transplantation is the treatment of choice for select cirrhotic patients who fall into Milan criteria (single HCC <5 cm or up to three nodules <3 cm).
- Milan criteria are used by the United Network for Organ Sharing (UNOS) for priority status (exception points) for liver transplantation candidacy in patients with HCC.

Nonpharmacologic Therapies

- Transarterial chemoembolization (TACE) improves survival in selected patients. It is recommended as first-line palliative therapy for nonsurgical patients with large or multifocal HCC who do not have vascular invasion or metastatic disease (*Hepatology 2011;53:1020*).
- Selected patients with tumors beyond Milan criteria HCC can be downstaged to meet Milan criteria with TACE, radiofrequency ablation (RFA), and transarterial radioembolization (TARE) prior to liver transplantation

Medications

- **Sorafenib** is a small molecule that inhibits tumor cell proliferation and angiogenesis. In patients with advanced HCC, median survival and radiologic progression were 3 months longer for patients treated with sorafenib compared to placebo (*N Engl J Med 2008;359:378*). Currently, there are several new medications being investigated for the treatment of HCC that inhibit angiogenesis, epidermal growth factor receptor, and mammalian target of rapamycin (mTOR).
- **Chemotherapy.** There are no consistently effective combination cytotoxic agents for the management of HCC.

OUTCOME/PROGNOSIS

Early diagnosis is essential because surgical resection and liver transplantation can improve long-term survival (*Hepatology 2011;53:1020*). Liver transplantation has demonstrated, in patients meeting Milan criteria, a recurrence-free survival of 80-90% at 3-4 years. Advanced HCC that is beyond Milan criteria has a dismal prognosis, with a 5-year survival of 0-10%.

LIVER TRANSPLANTATION

GENERAL PRINCIPLES

- Liver transplantation is an effective therapeutic option for irreversible acute liver disease and ESLD for which available therapies have failed. Whole cadaveric livers and partial livers (split-liver, reduced-size, and living-related) are used in the United States as sources for liver transplantation. There continues to be a disparity between supply and demand of suitable livers for transplantation.
- The Model for End-Stage Liver Disease (MELD) score allows for prioritization for liver transplantation. It is calculated by a formula that takes into account serum bilirubin, serum creatinine, and INR. Patients are regularly evaluated for a liver transplantation

when they achieve a MELD of 15. Patients are considered for “exception MELD points” for conditions such as HCC within Milan criteria, hepatopulmonary syndrome, portopulmonary hypertension, polycystic liver disease, familial amyloidosis, and unusual tumors.

- Patients with cirrhosis should be considered for transplant evaluation when they have a decline in hepatic synthetic or excretory functions, ascites, hepatic encephalopathy, or complications such as HRS, HCC, recurrent SBP, or variceal bleeding.
- Candidates for liver transplantation are evaluated by a multidisciplinary team that includes hepatologists, transplant surgeons, transplant nurse coordinators, social workers, psychologists, and financial coordinators.
- General **contraindications** to liver transplant include severe and uncontrolled extrahepatic infection, advanced cardiac or pulmonary disease, extrahepatic malignancy, multiorgan failure, unresolved psychosocial issues, medical noncompliance issues, and ongoing substance abuse (e.g., alcohol and illegal drugs).

TREATMENT

Immunosuppressive, infectious, and long-term complications are discussed in Chapter 17, Solid Organ Transplant Medicine.

20
Disorders of Hemostasis and Thrombosis

Kristen M. Sanfilippo

Brian F. Gage

Tzu-Fei Wang

Roger D. Yusen

Hemostatic Disorders

GENERAL PRINCIPLES

Normal hemostasis involves a sequence of interrelated reactions that lead to platelet aggregation (primary hemostasis) and activation of coagulation factors (secondary hemostasis) to produce a durable vascular seal.

- **Primary hemostasis** consists of an immediate but temporary response to vessel injury, where platelets and von Willebrand factor (**vWF**) interact to form a primary hemostatic plug.
- **Secondary hemostasis** results in formation of a fibrin clot (Figure 20-1). Injury exposes extravascular tissue factor to blood, which initiates activation of factors VII and X and prothrombin. Subsequent activation of factors XI, VIII, and V leads to generation of thrombin, conversion of fibrinogen to fibrin, and formation of a durable clot (*Semin Thromb Hemost 2009;35:9*).

DIAGNOSIS

Clinical Presentation

History

A detailed history can assess bleeding risk or severity, determine congenital or acquired etiology, and evaluate for primary or secondary hemostatic defects.

- Prolonged bleeding after dental extractions, circumcision, menstruation, labor and delivery, trauma, or surgery may suggest an underlying bleeding disorder.
- Family history may suggest an inherited bleeding disorder.

Physical Examination

- Primary hemostasis defects often cause mucosal bleeding and excessive bruising.
  - Petechiae: <2 mm subcutaneous bleeding, do not blanch with pressure, typically present in areas subject to increased hydrostatic force (the lower legs and periorbital area)
  - Ecchymoses: >3 mm black-and-blue patches due to rupture of small vessels from trauma
- Secondary hemostasis defects can result in **hematomas**, hemarthroses, or delayed bleeding after trauma or surgery.

Diagnostic Testing

Laboratories

The history and physical exam guide test selection. Initial studies should include platelet count, prothrombin time (**PT**), activated partial thromboplastin time (**aPTT**), and a blood smear.

- **Primary hemostasis tests**
  - A low **platelet count** requires review of blood smear to rule out platelet clumping artifact or giant platelets.

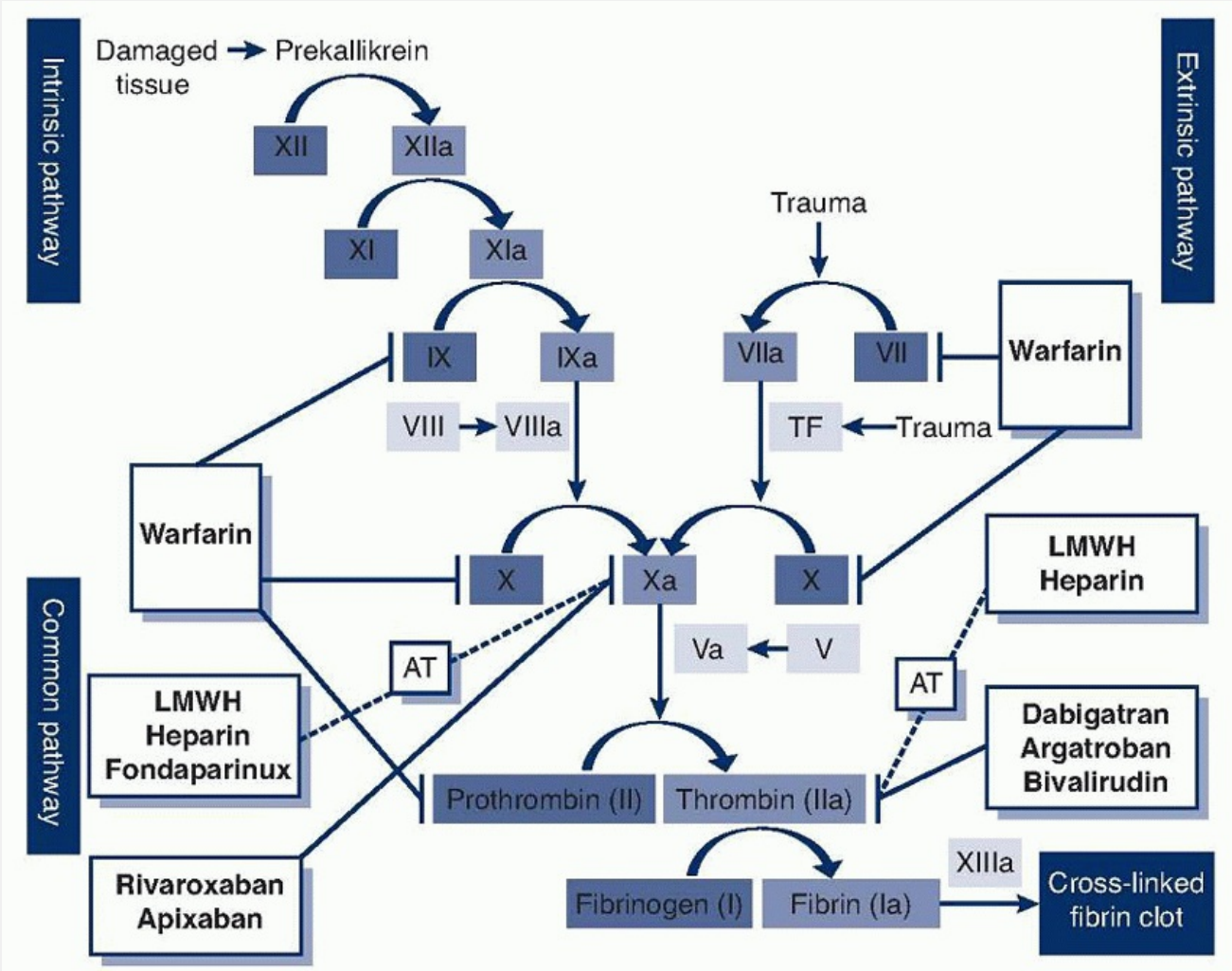


Figure 20-1. Coagulation cascade. *Solid arrows* indicate activation. *Solid* or *dashed lines* that run into a vertical line are associated with drugs represent a point of inhibition. Extrinsic pathway includes the right upper portion of cascade above factor X. Intrinsic pathway includes the left upper portion of the cascade above factor X. Common pathway includes the lower portion of the cascade from factor X and below. AT, antithrombin; LMWH, low-molecular-weight heparin; TF, tissue factor.

- The **platelet function assay-100 (PFA-100)** instrument assesses vWF-dependent platelet activation in flowing citrated whole blood. Patients with von Willebrand disease (**vWD**) and qualitative platelet disorders can have prolonged PFA-100 closure times. Anemia (hematocrit <30%) and thrombocytopenia (platelet $<100 \times 10^9$/L) can cause prolonged closure times.
- **In vitro platelet aggregation** studies measure platelet secretion and aggregation in response to platelet agonists (see Qualitative Platelet Disorders section).
- Laboratory evaluation of vWD includes measurement of vWF antigen (**vWF:Ag**) and **vWF activity** and **vWF multimer analysis**.

- **Secondary hemostasis** (Figure 20-1)
  - **PT:** Measures time to form a fibrin clot after adding thromboplastin (tissue factor and phospholipid) and calcium to citrated plasma. Sensitive (i.e., elevated PT) to deficiencies of **extrinsic pathway** (factor VII), **common pathway** (factors X and V and prothrombin), and **fibrinogen** and to use of vitamin K antagonists and direct factor Xa and thrombin (IIa) inhibitors. Reporting a PT ratio as an international normalized ratio (**INR**) reduces interlaboratory variation (*Thromb Haemost 1983;49:238*) in monitoring warfarin use.
  - **aPTT:** Measures the time to form a fibrin clot after activation of citrated plasma by calcium, phospholipid, and negatively charged particles. Besides heparin, low-molecular-weight heparin (**LMWH**), fondaparinux, and direct anti-Xa and thrombin (IIa) inhibitors, deficiencies

and inhibitors of coagulation factors of the **intrinsic pathway** (e.g., high-molecular-weight kininogen, prekallikrein, factor XII, factor XI, factor IX, and factor VIII), **common pathway** (e.g., factor V, factor X, prothrombin), and **fibrinogen prolong the aPTT**.

- **Thrombin time:** Measures time to form a fibrin clot after addition of thrombin to citrated plasma. Quantitative and qualitative deficiencies of fibrinogen, fibrin degradation products, heparin, LMWH, fondaparinux, and direct thrombin (IIa) inhibitors prolong thrombin time.
- **Fibrinogen:** Measured by adding thrombin to dilute plasma and measuring clotting time. Conditions causing hypofibrinogenemia include decreased hepatic synthesis, massive hemorrhage, and disseminated intravascular coagulation (**DIC**).
- **D-Dimers** result from plasmin digestion of fibrin (i.e., fibrin degradation products). Elevated D-dimer concentrations occur in many disease states (i.e., venous thromboembolism [**VTE**], DIC, trauma, and cancer).
- **Mixing studies** determine whether a factor deficiency or an inhibitor has prolonged the PT or aPTT. Mixing patient plasma 1:1 with normal pooled plasma (all factor activities = 100%) restores deficient factors sufficiently to normalize or nearly normalize the PT or aPTT (Table 20-1). If mixing fails to correct the PT or aPTT, a specific factor inhibitor, a nonspecific inhibitor (e.g., lupus anticoagulant [**LA**]), or an anticoagulant drug may have caused the prolongation.

PLATELET DISORDERS

Thrombocytopenia

- **Thrombocytopenia** is defined as a platelet count of <140 × 10^9/L.
- Thrombocytopenia occurs from decreased production, increased destruction, or sequestration of platelets (Table 20-2).

Immune Thrombocytopenia

GENERAL PRINCIPLES

Immune thrombocytopenia (ITP) is an acquired immune disorder in which antiplatelet antibodies cause shortened platelet survival and suppress megakaryopoiesis leading to thrombocytopenia and increased bleeding risk (*Blood 2009;113:6511*). Etiologies of ITP include idiopathic (primary), associated with coexisting conditions (secondary), or drug induced.

TABLE 20-1 Factor Deficiencies That Cause Prolonged Prothrombin Time and/or Activated Partial Thromboplastin Time and Correct with 50:50 Mix

Assay Result	Suspected Factor Deficiencies
↑ aPTT; normal PT	XII, XI, IX, VIII, HMWK, PK
↑ PT; normal aPTT	VII
↑ PT and ↑ aPTT	II, V, X, or fibrinogen

aPTT, activated partial thromboplastin time; HMWK, high-molecular-weight kininogen; PK, prekallikrein; PT,

prothrombin time.

TABLE 20-2 Classification of Thrombocytopenia

Decreased Platelet Production	Increased Platelet Clearance
Marrow failure syndromes	*Immune-mediated mechanisms*
Congenital	Immune thrombocytopenic
Acquired: Aplastic anemia, paroxysmal nocturnal hemoglobinuria	Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome
Hematologic malignancies	Posttransfusion purpura
Marrow infiltration: Cancer, granuloma	Heparin-induced thrombocytopenia
Myelofibrosis: Primary or secondary	*Non-immune-mediated mechanisms*
Nutritional: Vitamin B12 and folate deficiencies	DIC
Physical damage to the bone marrow: Radiation, alcohol, chemotherapy	Local consumption (aortic aneurysm)
	Acute hemorrhage
Increased Splenic Sequestration	**Infections Associated with Thrombocytopenia**
Portal hypertension	HIV, HHV-6, ehrlichiosis, rickettsia, malaria, hepatitis C, CMV, Epstein-Barr, *Helicobacter pylori*, *Escherichia coli* O157
Felty syndrome	
Lysosomal storage disorders	
Infiltrative hematologic malignancies	
Extramedullary hematopoiesis	

CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; HHV-6, human herpesvirus 6.

Epidemiology

Adult primary **ITP** has an incidence of 3.3 cases per 10^5 persons (*Am J Hematol 2010;85:174*).

Etiology

- In **primary ITP**, autoantibodies bind to platelet surface antigens and cause premature clearance by the reticuloendothelial system in addition to immune-mediated suppression of platelet production.
- **Secondary ITP** occurs in the setting of systemic lupus erythematosus (**SLE**), antiphospholipid antibody syndrome (**APS**), HIV, hepatitis C virus (**HCV**), *Helicobacter pylori*, and lymphoproliferative disorders (*Blood 2009;113:6511*).
- **Drug-dependent ITP** results from drug-platelet interactions prompting antibody binding (*N Engl J Med 2007;357:580*). Medications linked to thrombocytopenia include quinidine and quinine; platelet inhibitors abciximab, eptifibatide, tirofiban, and ticlopidine; antibiotics linezolid, rifampin, sulfonamides, and vancomycin; the anticonvulsants phenytoin, valproic acid, and carbamazepine; analgesics acetaminophen, naproxen, and diclofenac; cimetidine; and chlorothiazide (*Ann Intern Med 2005;142:474*).

DIAGNOSIS

Clinical Presentation

- **ITP** typically presents as mild mucocutaneous bleeding and petechiae or incidental thrombocytopenia. Occasionally, ITP can present as major bleeding.
- Risk of bleeding is highest with platelet counts <30 × 10^9/L (*Blood 2011;117:1490*).

Diagnostic Testing

Normalization of platelet counts with discontinuation of suspected drug and confirmation if thrombocytopenia recurs when rechallenged support the diagnosis of **drug-induced ITP**.

Laboratories

- Review a peripheral blood smear to confirm automated platelet count and assess for platelet clumping and to determine platelet, red cell, and white cell morphologies.
- Laboratory tests do not confirm the diagnosis of primary ITP, although they help to exclude secondary causes. Primary **ITP** often has the scenario of isolated thrombocytopenia in the absence of a likely underlying causative disease or medication.
- Test for infection-associated causes (e.g., HIV, HCV) (*Blood 2011;117:4190*).
- Serologic tests for antiplatelet antibodies generally do not help diagnose **ITP** because of poor sensitivity and low negative predictive value (**NPV**) (*Am J Hematol 2005;78:193*).

Diagnostic Procedures

Diagnosis of ITP does not typically require bone marrow examination, although it can help to exclude other causes in select patients with additional complete blood cell (**CBC**) abnormalities, unresponsiveness to immune suppression therapy, or atypical signs or symptoms (*Blood 2011;117:4190*).

TREATMENT

- The decision to treat **primary ITP** depends on the severity of thrombocytopenia and bleeding risk. The therapeutic goal is a safe platelet count to prevent major bleeding (typically ≥30 × 10^9/L) and minimization of treatment-related toxicities.
- Initial therapy, when indicated, consists of **glucocorticoids** (typically prednisone 1 mg/kg/d orally, followed by a slow taper over weeks to months). Nonresponders to glucocorticoids or patients with active bleeding may also receive IV immunoglobulin **(IVIG**; 1 g/kg for one to two doses). Rh-positive patients may also receive anti-D immunoglobulin (**WinRho**) (ineffective postsplenectomy). WinRho works by forming anti-D-coated red blood cell (**RBC**) complexes, which bind to splenic macrophages, saturate the reticuloendothelial system, and prevent platelet destruction. WinRho may cause severe hemolysis and requires postinfusion monitoring. Reduce WinRho dose if hemoglobin (**Hgb**) <10 g/dL and avoid when the Hgb is <8 g/dL. Most primary ITP cases respond to therapy within 1-3 weeks.
- 30-40% of patients will relapse during a steroid taper (**relapsed/refractory ITP**).
- Two-thirds of patients with refractory ITP will obtain a durable complete response following **splenectomy**. Administer pneumococcal, meningococcal, and *Haemophilus influenzae* type B vaccines before (preferred) or after splenectomy.
- Treatment options for those who fail splenectomy include single or combined therapies with prednisone, IVIG, androgen therapy with danazol, other immunosuppressive agents, **rituximab** (anti-CD20 monoclonal antibody) (*Blood 2011;117:4190*), and/or thrombopoietin receptor (**TPO-R**) agonists.
- There are two TPO-R agonists for treatment of refractory primary ITP patients with increased bleeding risk: **romiplostim** (Nplate), dosed SC weekly, and **eltrombopag** (Promacta), taken orally once a day. TPO-R

agonists produce durable platelet count improvements in a majority of refractory ITP patients beginning 5-7 days after initiation. Potential complications include thromboembolic events and bone marrow fibrosis (*Lancet 2011;377:393*; *Lancet 2008;371:395*).

- Management of **secondary ITP** may include a combination of treatment for the underlying disease and therapies similar to those used for management of primary ITP.
- Platelet transfusion for severe drug-induced thrombocytopenia may decrease risk of bleeding. IVIG, steroids, and plasmapheresis have uncertain benefit.

Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome

GENERAL PRINCIPLES

Definition

Thrombotic thrombocytopenic purpura (TTP) and **hemolytic-uremic syndrome (HUS)** are thrombotic microangiopathies (**TMAs**) caused by platelet-vWF aggregates and platelet-fibrin aggregates, respectively, resulting in thrombocytopenia, microangiopathic hemolytic anemia (**MAHA**), and organ ischemia. Usually, clinical and laboratory features permit differentiation of TTP from HUS. TMA may occur in association with DIC, HIV infection, malignant hypertension, vasculitis, organ and stem cell transplant-related toxicity, adverse drug reactions, and pregnancy-related complications of preeclampsia/eclampsia and **HELLP** (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets) syndrome.

Epidemiology

Sporadic TTP has an incidence of approximately 11.3 cases per 10^6 persons, occurring more frequently in women and African Americans (*J Thromb Haemost 2005;3:1432*). **Typical HUS** usually occurs in gastroenteritis outbreaks affecting children. Adults may present with both **typical** and **atypical** (non-gastroenteritis-associated) variants of **HUS**.

Etiology

- Autoantibody-mediated removal of plasma vWF-cleaving protease: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), leading to elevated levels of abnormally large vWF multimers, typically causes **sporadic TTP** (*N Engl J Med 1998;339:1578*). The abnormal vWF multimers spontaneously adhere to platelets and may produce occlusive vWF-platelet aggregates in the microcirculation and subsequent microangiopathy. Second-hit events may involve endothelial dysfunction or injury.
- Severe ADAMTS13 deficiency does not cause HUS and other types of TMA, with the exception of some cases associated with HIV and pregnancy.
- **Typical or enteropathic HUS** has an association with *Escherichia coli* (O157:H7) production of Shiga-like toxins in Shiga toxigenic *E. coli* HUS (**STEC-HUS**).
- **HUS** can also be associated with transplantation, endothelial-damaging drugs, and pregnancy (*Kidney Int Suppl 2009;112:S8*).
- Inherited or acquired defects in regulation of the alternative complement pathway are present in 30-50% of atypical HUS cases (*Annu Rev Path Mech Dis 2008;3:249*).

DIAGNOSIS

Clinical Presentation

- The complete clinical pentad of **TTP**, present in <30% of cases, includes **consumptive thrombocytopenia, MAHA, fever, renal dysfunction, and fluctuating neurologic deficits**.
- The findings of thrombocytopenia and MAHA should raise suspicion for **TTP-HUS** in the absence of other identifiable causes.
- Patients with autosomal recessive inherited ADAMTS13 deficiencies have relapsing TTP (Upshaw-Schulman syndrome).
- Diarrhea, usually bloody, and abdominal pain often precede STEC-HUS.
- Marked renal dysfunction usually occurs in HUS.

Diagnostic Testing

- TMAs produce schistocytes (fragmented red cells) and thrombocytopenia on blood smears. The findings of anemia, elevated reticulocyte count, low or undetectable haptoglobin, and elevated lactate dehydrogenase (**LDH**) support the presence of hemolysis.
- Sporadic TTP has TMA findings, normal PT and aPTT, mild to moderate azotemia, very low or undetectable ADAMTS13 enzyme activity, and often detectable ADAMTS13 inhibitory antibody.
- Typical HUS has TMA and acute renal failure. *E. coli* O157 stool culture has a higher sensitivity than Shiga toxin assays. However, stool samples obtained after diarrhea has resolved reduce the sensitivity of both tests (*Kidney Int 2009;75:S29*).
- In the absence of precipitating risk factors, testing for **atypical HUS** should include molecular and serologic tests for complement regulator factor H and I mutations or autoantibodies through reference laboratories.

TREATMENT

- The mainstay of therapy for **TTP** consists of rapid treatment with plasma exchange (**PEX**) of 1.0-1.5 plasma volumes daily. PEX is continued for several days after normalization of platelet count and LDH.
  - If PEX is not available or will be delayed, infuse **fresh frozen plasma (FFP)** immediately to replace ADAMTS13.
  - Common practice includes the administration of **glucocorticoids**: prednisone 1 mg/kg PO per day. Consider a brief course of high-dose corticosteroids (methylprednisolone 0.5-1.0 g/d IV) in critically ill or PEX nonresponding patients (*Blood 2010;116:4060*).
  - Platelet transfusion in the absence of severe bleeding is relatively contraindicated due to potential risk of additional microvascular occlusions.
  - 90% of treated patients have a remission; however, relapses may occur days to years later.
  - Therapy with **rituximab** can achieve durable remissions following TTP relapses (*Ann Intern Med 2003;138:105*; *Thromb Haemost 2009;101:233*).
  - **Immunosuppression** with cyclophosphamide, azathioprine, or vincristine and splenectomy may have success in the treatment of refractory or relapsing TTP (*Ann Hematol 2002;81:7*; *Blood 2000;96:1223*).
- **STEC-HUS** does not usually improve with PEX, and treatment remains supportive. Antibiotic therapy does not hasten recovery or minimize toxicity for STEC-HUS.
- **TMA associated with calcineurin inhibitors** (cyclosporine, tacrolimus), typically given in the transplant setting, usually responds to drug dose reduction or discontinuation of the offending agent.
- **Atypical HUS** often leads to chronic renal failure necessitating dialysis.
- In 2011, the US Food and Drug Administration (**FDA**) approved eculizumab for treatment of **atypical HUS**. Eculizumab is a humanized monoclonal antibody that binds to complement protein C5, blocking its cleavage

into C5a and the cytotoxic membrane attack complex C5b-9, thus inhibiting complement activation (*Blood 2011;118:3303*).

- *Neisseria meningitides* vaccination is recommended 2 weeks prior to starting eculizumab; however, in **atypical** HUS, this grace period is typically not possible.

Heparin-Induced Thrombocytopenia

GENERAL PRINCIPLES

Definition

Heparin-induced thrombocytopenia (HIT) is an acquired hypercoagulable disorder associated with use of heparin or heparin-like products and due to autoantibodies targeting

the anticoagulant and platelet factor 4 (**PF4**) complexes. HIT typically presents with thrombocytopenia or a decrease in platelet count by at least 50% from preexposure baseline. Major complications of HIT consist of arterial and venous thromboembolic events.

Epidemiology

The incidence of **HIT** ranges from 0.1-1.0% in medical and obstetric patients receiving prophylactic and therapeutic unfractionated heparin (**UFH**), to >1-5% in patients receiving prophylactic UFH after cardiothoracic surgery (*Chest 2012;141:e495s*). Patients exposed only to LMWH have a low incidence of HIT (*Thromb Res 2009;124:189*). HIT rarely occurs in association with the synthetic pentasaccharide fondaparinux (*N Engl J Med 2007;356:2653*).

Etiology

Immune-responsive patients produce autoantibodies that bind to PF4/heparin complexes, which can activate platelets, cause thrombocytopenia, and lead to clot formation through increased thrombin generation (*Blood 2003;101:31*).

DIAGNOSIS

Clinical Presentation

- **HIT** usually develops within 5-14 days of heparin exposure (**typical-onset HIT**). Exceptions include **delayed-onset HIT**, which occurs after stopping heparin, and **early-onset HIT**, which starts within the first 24 hours of heparin administration in patients with recent exposure to heparin (*Chest 2012;141:e495s*).
- Suspect HIT when thrombocytopenia occurs during heparin exposure by any route in the absence of other causes of thrombocytopenia.
- The **4T scoring system** (Table 20-3) determines HIT pretest probability and has an NPV of >95% (*J Thromb Haemost 2006;4:759*).

TABLE 20-3 4T Scoring System for Pretest Probability of Heparin-Induced Thrombocytopenia

T Category	0 Points	1 Point	2 Points
Thrombocytopenia	PLT fall <30% or nadir <10 × 10^9/L	PLT fall 30-50% or nadir 10-19 × 10^9/L	PLT fall >50% and nadir ≥20 × 10^9/L

Timing of thrombocytopenia	≤4 d without prior exposure	Likely within 5-10 d, not clear; >10 d; ≤1 d (with exposure 31-100 d)	Within 5-10 d of exposure or ≤1 d (with exposure in last 30 d)
Thrombotic event	No thrombus	Thrombus recurrence or progression; erythematous skin lesion; suspected thrombus	Confirmed thrombus; skin necrosis; acute reaction after UFH bolus
Other causes for thrombocytopenia	Definite	Possible	None apparent

PLT, platelets; UFH, unfractionated heparin.
Sum the points for each of the four categories to determine the clinical probability: high (6-8 points), intermediate (4-5 points), low (0-3 points).
Data from *J Thromb Haemost 2006;4:759-65* and *J Thromb Haemost 2010;8:1483-5.*

- HIT rarely causes severe thrombocytopenia (platelet count <20 × 10^9/L) and bleeding.
- **Thromboembolic complications** occur in 30-75% of HIT patients (i.e., heparininduced thrombocytopenia and thrombosis [**HITT**]). Thrombosis can precede, be concurrent with, or follow thrombocytopenia.
- HIT causing venous thrombi at heparin injection sites produces full-thickness skin infarctions, sometimes in the absence of thrombocytopenia.
- HIT can cause systemic allergic responses following an IV bolus of heparin characterized by fever, hypotension, dyspnea, and cardiac arrest.

Diagnostic Testing

- Obtain surveillance platelet counts every 2-3 days during heparin exposure in patients with >1% risk of HIT (*Chest 2012;141:e495s*).
- For suspected HIT, laboratory tests for PF4 antibodies improve diagnostic accuracy.
  - PF4 antibodies in patients' serum is a sensitive screening test but lacks specificity.
  - Specificity improves when a positive enzyme-linked immunosorbent assay (**ELISA**) is quantified in optical density (**OD**) units. The higher the OD, the more likely it is that the patient has HIT.
- There are two functional assays for HIT: serotonin release assay (**SRA**) and heparininduced platelet activation (**HIPA**; more common in Europe).
  - Both tests detect PF4 antibodies in patients' serum capable of activating control platelets in the presence of heparin.
  - Both tests have high specificity for HIT but lower sensitivity than ELISA.
  - Testing in reference laboratories typically delays results for days.
- For a low clinical probability of HIT, testing for HIT antibodies is *not* indicated.
  - For a moderate to high clinical probability of HIT, PF4 ELISA testing is indicated. A negative PF4 ELISA effectively rules out HIT.
  - A functional test (SRA or HIPA) should confirm a positive PF4 ELISA to improve testing specificity.

TREATMENT

- Because HIT test results are not often immediately available, clinical assessment should determine initial management.
- When HIT is strongly suspected or confirmed, **eliminate all heparin exposure**.
- Patients with HIT are at high risk for VTE and require alternative anticoagulation (*Blood 2012;119:2209*) with a parenteral direct thrombin inhibitor (**DTI**) (i.e., **argatroban or bivalirudin)**, although fondaparinux also has been used (*J Thromb Haemost 2011;9:2389*). Do not use LMWH in patients with HIT.
- Assess for symptomatic VTE, and screen (e.g., lower extremity venous compression ultrasound) to assess for asymptomatic VTE, because VTE warrants a full course of anticoagulation (*Blood 2003;101:31*).
- Start warfarin only after the platelet count normalizes, at an initial dose no greater than 5 mg daily, overlapping with a DTI for 5 days, to reduce the risk of limb gangrene due to ongoing hypercoagulable conditions and depletion of proteins C and S.
- DTIs prolong the INR and require careful monitoring when transitioning from DTI to warfarin (see Medications under Approach to Venous Thromboembolism).
- Avoid using oral DTI and anti-Xa inhibitors because they have not been adequately evaluated for safety and efficacy in HIT patients with or without thrombosis.
- The recommended duration of anticoagulation therapy for HIT depends on the clinical scenario: 4 weeks for **isolated HIT** (without thrombosis) and 3 months for **HIT-associated thrombosis** (*Chest 2012;141:e495s*) (see treatment duration in Approach to Venous Thromboembolism section).

Posttransfusion Purpura

GENERAL PRINCIPLES

Definition

Posttransfusion purpura (PTP), a rare syndrome characterized by the formation of alloantibodies against platelet antigens, most commonly HPA-1a, follows blood component transfusion and causes severe thrombocytopenia.

Epidemiology

PTP has an incidence of 1 in 50,000 to 100,000 blood transfusions, although approximately 2% of the population has a potential risk for PTP based on the frequency of HPA-1b/1b.

Etiology

Glycoprotein (GP) IIIa has a polymorphic epitope called HPA-1a/b, the antigen most commonly involved in PTP. **PTP** typically occurs in HPA-1a/1b-negative multiparous women or previously transfused patients when reexposed to HPA-1a by transfusion. An amnestic response produces alloantibodies to the HPA-1a, which appear to also recognize the patient's HPA-1a-negative platelets and cause thrombocytopenia via platelet destruction.

DIAGNOSIS

- In **PTP**, severe thrombocytopenia ($<15 \times 10^9$/L) usually occurs within 7-10 days of transfusion.
- Confirmation of suspected **PTP** requires detection of platelet alloantibodies.

TREATMENT

Although spontaneous platelet recovery eventually occurs, bleeding may require treatment. Effective therapies include IVIG and plasmapheresis. Transfusion with platelets from a donor who lacks the causative epitope (typically HPA-1a) does not clearly have higher efficacy than random platelet transfusion. Reserve transfusion for patients with PTP and severe bleeding (*Am J Hematol 2004;76:258*).

Gestational Thrombocytopenia

GENERAL PRINCIPLES

Definition

Gestational thrombocytopenia (platelet counts ≥70 × 10^9/L) is a benign, mild thrombocytopenia associated with pregnancy.

Epidemiology

Gestational thrombocytopenia spontaneously occurs in approximately 5-7% of otherwise uncomplicated pregnancies (*Clin Obstet Gynecol 1999;42:327*).

Etiology

The mechanism of gestational thrombocytopenia remains unknown.

DIAGNOSIS

Clinical Presentation

Gestational thrombocytopenia occurs in the third trimester of pregnancy. The mother has no symptoms, and the fetus remains unaffected.

Differential Diagnosis

Other causes of thrombocytopenia during pregnancy include **ITP, preeclampsia, eclampsia, HELLP syndrome, TTP, and DIC.**

Diagnostic Testing

To distinguish between gestational thrombocytopenia and other syndromes, diagnostic testing includes an evaluation for infection and hypertension and laboratory testing for hemolysis and liver dysfunction.

OUTCOME/PROGNOSIS

Gestational thrombocytopenia and thrombocytopenia associated with preeclampsia and eclampsia usually resolve promptly after delivery.

Thrombocytosis

GENERAL PRINCIPLES

Definition

Thrombocytosis is defined as a platelet count of >450 × 10^9/L by the World Health Organization (WHO).

Etiology

Thrombocytosis has reactive and clonal etiologies that may coexist.

- **Reactive thrombocytosis** may occur during recovery from thrombocytopenia; after splenectomy; or in response to iron deficiency, acute infectious or chronic inflammatory states, trauma, and malignancies.
  - Low risks of thrombosis or bleeding.
  - Platelets normalize after improvement of the underlying disorder.
  - If accompanied by thrombotic complications, evaluate for an underlying myeloproliferative disorder.
- **Essential thrombocytosis (ET)** is a chronic myeloproliferative disorder. Eventual progression to myelofibrosis, acute myeloid leukemia, or myelodysplastic syndrome occurs in a minority of ET patients (*Br J Haematol 2005;130:153*).

DIAGNOSIS

Clinical Presentation

History

ET may present as an incidental discovery or present with thrombotic or hemorrhagic symptoms. The risk of thrombosis increases with age, prior thrombosis, duration of disease, and other comorbidities (*Blood 1999;93:417*). Erythromelalgia, due to microvascular occlusive platelet thrombi, presents as intense burning or throbbing of the extremities, typically involving the feet. Cold exposure usually relieves symptoms. Hemorrhage typically occurs with platelet counts >1000 × 10^9/L, and acquired deficiencies of large vWF multimers often accompany hemorrhage patients with ET (*Blood 1993;82:1749*).

Physical Examination

Approximately 50% of ET patients develop mild splenomegaly. Typical signs of erythromelalgia include erythema and warmth of affected digits.

Diagnostic Criteria

In 2008, the **WHO** revised criteria (requires all four) included (*Curr Hematol Malig Rep 2007;4:33*):

- Sustained platelet count >450 × 10^9/L
- Bone marrow biopsy showing increased mature megakaryocytes and no increase in erythropoiesis or granulopoiesis
- Exclusion of chronic myelogenous leukemia (**CML**), polycythemia vera, and primary myelofibrosis according to WHO criteria
- Presence of *JAK2V617F* mutation or other clonal marker (*Lancet 2005;365:1054*), **or**, if clonal marker not present, no evidence for reactive thrombocytosis (*Leukemia 2008;22:14*)

TREATMENT

Patients requiring cytoreduction include those with high risk of thrombosis (age >60 years or a history of thrombosis). The majority of thrombotic complications occur at modest platelet count elevations. Treatment typically aims for a platelet count of ≤400 × 10^9/L. Platelet-lowering drugs include **hydroxyurea** and **anagrelide** or **interferon-α** in pregnant patients or females in their childbearing years (*Blood 2001;97:863*).

- Hydroxyurea and anagrelide provide equivalent platelet count control, but anagrelide causes more

complications (*N Engl J Med 2005;353:33*).

- Anagrelide side effects include palpitations, atrial fibrillation, fluid retention, and headache.
- Plateletpheresis rapidly lowers platelet counts, although it is reserved for patients who have acute arterial thrombosis.

Qualitative Platelet Disorders

GENERAL PRINCIPLES

Qualitative platelet disorders present with mucocutaneous bleeding and excessive bruising with an adequate platelet count, PT, and aPTT and normal screening tests for vWD. Most potent platelet defects produce prolonged PFA-100 closure times. However, a normal PFA-100 does not exclude qualitative platelet disorders, and high clinical suspicion of a disorder should lead to further testing.

Classification

- **Inherited disorders** of platelet function include receptor, signal transduction, cyclooxygenase, secretory (e.g., storage pool disease), adhesion, or aggregation defects. In vitro platelet aggregation studies can identify patterns of agonist responses consistent with a particular defect, such as the rare autosomal recessive disorders of adhesion in **Bernard-Soulier syndrome** (lack of GP Ib/IX [vWF receptor]) and aggregation in **Glanzmann thrombasthenia** (lack of GP IIb/IIIa [fibrinogen receptor]).
- **Acquired** platelet defects are more common than hereditary platelet qualitative disorders.
  - Conditions associated with acquired qualitative defects include metabolic disorders (uremia, liver failure), myeloproliferative diseases, myelodysplasia, acute leukemia, monoclonal gammopathy, and cardiopulmonary bypass platelet trauma.
  - **Drug-induced** platelet dysfunction is a side effect of many drugs, including high-dose penicillin, aspirin (ASA) and other **NSAIDs**, and ethanol. Other drug classes, such

as β-lactam antibiotics, β-blockers, calcium channel blockers, nitrates, antihistamines, psychotropic drugs, tricyclic antidepressants, and selective serotonin reuptake inhibitors, cause platelet dysfunction in vitro, but they rarely cause bleeding.

  - Certain **foods and herbal products** may affect platelet function including omega-3 fatty acids, garlic and onion extracts, ginger, gingko, ginseng, and black tree fungus. Patients should stop using herbal medications and dietary supplements ≥1 week before major surgery (*Thromb Res 2005;117:49*; *Anaesthesia 2002;57:889*).

TREATMENT

- Reserve platelet transfusions for major bleeding episodes. Anecdotal reports have described successful control of severe bleeding with recombinant factor VIIa (**rFVIIa**).
- Treatment of **uremic platelet dysfunctio**n can include dialysis to improve uremia; desmopressin (**DDAVP**) 0.3 μg/kg IV to stimulate release of vWF from endothelial cells; or conjugated estrogens (0.6 mg/kg IV daily for 5 days) (*Nat Clin Pract Nephrol 2007;3:138*) and platelet transfusions in actively bleeding patients, although transfused platelets rapidly acquire the uremic defect. Transfusion or erythropoietin (**EPO**) to increase a hematocrit toward 30% might assist in hemostasis (*Am J Kidney Dis 1991;18:44*; *Br J Haematol 1985;59:139*).
- **Reversal of drug-induced platelet dysfunction**
  - **NSAIDs** other than ASA reversibly inhibit cyclooxygenase (**COX**). Their effects only last several days. **COX-2 inhibitors** have antiplatelet activity in large doses, but they have a minimal effect on platelets at therapeutic doses.

- **Aspirin** irreversibly inhibits COX-1 and COX-2. Its effects diminish over 7-10 days due to new platelet production.
- **Thienopyridines** inhibit platelet aggregation by irreversibly (clopidogrel and prasugrel) or reversibly (ticagrelor) blocking platelet adenosine diphosphate (ADP) receptor P2Y12.
- **Dipyridamole**, alone or in combination with ASA (Aggrenox), inhibits platelet function by increasing intracellular cyclic adenosine monophosphate (**cAMP**).
- **Abciximab, eptifibatide, and tirofiban** block platelet IIb/IIIa-dependent aggregation (see Chapter 4, Ischemic Heart Disease).
- Platelet transfusion compensates for drug-induced platelet dysfunction, except immediately following tirofiban and eptifibatide therapy.
- Hold antiplatelet agents for 7 days before elective invasive procedures.

INHERITED BLEEDING DISORDERS

Hemophilia A

GENERAL PRINCIPLES

Definition

Hemophilia A is an X-linked recessive coagulation disorder due to mutations in the gene encoding factor VIII.

Epidemiology

Hemophilia A affects approximately 1 in 5000 live male births. Approximately 40% of cases occur in families with no prior history of hemophilia, reflecting the high rate of spontaneous germline mutations in the factor VIII gene (*N Engl J Med 2001;344:1773*).

DIAGNOSIS

Clinical Presentation

- Patients with severe hemophilia experience frequent spontaneous hemarthroses and hematomas, hematuria, and delayed posttraumatic and postoperative bleeding. Repeated bleeding into a “target” joint causes chronic synovitis and hemophilic arthropathy.
- Moderate hemophiliacs have fewer spontaneous bleeding episodes, and mild hemophiliacs may only bleed excessively after trauma or surgery.

Diagnostic Testing

Factor VIII activity: Severe (<1%), moderate (1-5%), and mild (>5-<40%). Mild hemophiliacs with factor VIII ≥30% may not have a prolonged aPTT.

TREATMENT

Medications

First Line

- Mild to moderate hemophilia A with minor bleeding:
  - **DDAVP** (0.3 μg/kg IV infused over 30 minutes, or 150 μg intranasally [Stimate, 1.5 mg/mL] each nostril)

increases factor VIII activity three- to fivefold. Because all patients do not have an expected response to DDAVP, they should undergo a DDAVP challenge to assess responsiveness. To avoid tachyphylaxis, no more than three consecutive doses should be given per week (*Blood 1997;90:2515*).

- Mild to moderate hemophilia A with major bleeding *or* severe hemophilia A with any bleeding:
  - **Factor VIII replacement** is the mainstay of therapy with many hemophiliac patients able to do home infusion.
  - **Factor VIII concentrate** increases factor VIII activity by 2% for every 1 IU/kg infused; thus a 50 IU/kg IV bolus raises factor VIII activity by 100% over baseline. Extended treatment should follow with 25 IU/kg IV bolus q12h to maintain sufficient levels.
  - One to three doses of **factor VIII** concentrates targeting peak plasma activities of 30-50% typically stop mild hemorrhages.
  - Major traumas and surgery require maintenance of levels >80%.
  - Adjust doses based on peak and trough factor VIII levels to achieve individualized targets based on bleeding risk.
  - Continuous infusion of factor VIII provides a safe and effective alternative to intermittent infusion (*Haemophilia 2006;12:212*; *Haemophilia 2012;18:753*).

Second Line

Second-line factor VIII sources include **cryoprecipitate** and **FFP**.

Hemophilia B

GENERAL PRINCIPLES

Definition

Hemophilia B is an X-linked recessive coagulation disorder secondary to mutations in the gene encoding factor IX.

Epidemiology

Hemophilia B affects approximately 1 in 30,000 male births.

Diagnostic Testing

Factor IX activity. Hemophilia A (factor VIII) and B (factor IX) use the same severity scale based on degree of decreased factor activity.

Clinical Presentation

Hemophilia B remains clinically indistinguishable from hemophilia A.

TREATMENT

Therapy of hemophilia B consists of **factor IX replacement** with either **plasma-derived factor IX** or **recombinant factor IX** (BeneFIX).

- DDAVP lacks efficacy because it does **not** increase factor IX levels.
- Postinfusion peak targets, duration of therapy, and laboratory monitoring for treatment of hemophilia B-related bleeding are similar to those for hemophilia A.
- Every 1 IU/kg of factor IX replacement typically raises plasma factor IX activity by 1%. Factor IX has a half-life

of 18-24 hours.

COMPLICATIONS OF HEMOPHILIA A AND B THERAPY

- Alloantibodies to factors VIII and IX in response to replacement therapy develop in approximately 20% and 12% of severe hemophilia A and B patients, respectively. These alloantibodies neutralize infused factor VIII or IX.
- Determining the titer of a factor VIII or IX inhibitor, using a laboratory assay that reports inhibitor strength in Bethesda units (**BUs**), predicts inhibitor behavior and guides therapy.
- Treatment options for factor VIII or IX inhibitors include the following (*Lancet 2012;379:1447*):
  - Large doses of factor VIII or IX concentrates overcome inhibitors for patients with weak inhibitors (BU <5).
  - Because factor VIII or IX concentrates will not overcome inhibitors in patients with high titers (BU >5), bypassing agents, such as recombinant factor VII or activated prothrombin complex concentrate (aPCC), need to be used (*Blood 2007;109:546*).
    - **rFVIIa** (NovoSeven) is dosed at 90 µg/kg every 2 hours until hemostasis occurs.
    - **aPCC** (most commonly used is Factor Eight Inhibitor Bypassing Activity [FEIBA]) is dosed at 75-100 IU/kg q12h. FEIBA contains activated factors VII, VIII, XI, and X and thrombin, and it can cause thrombosis or DIC.

von Willebrand Disease

GENERAL PRINCIPLES

Classification

vWD has three main types (*J Thromb Haemost 2006;4:2103*).

- **Type 1 vWD** is due to a quantitative deficiency of vWF (70-80% of cases).
- **Type 2 vWD**, due to a qualitative defect of vWF, includes four subtypes (2A, 2B, 2M, 2N).
  - Type 2A: reduced vWF high-molecular-weight multimer
  - Type 2B: pathologically enhanced platelet affinity to vWF
  - Type 2M: reduced platelet affinity to vWF
  - Type 2N: defective factor VIII binding to vWF
- **Type 3 vWD** has a virtual complete lack of vWF (*Blood 2001;97:1915*).

Epidemiology

vWD, the most common inherited bleeding disorder, affects around 0.1-1% of the population.

Etiology

Most forms of **vWD** have an autosomal dominant inheritance with variable penetrance, although autosomal recessive forms (types 2N and 3) exist. vWF circulates as multimers of variable size and facilitates adherence of platelets to injured vessel walls and stabilizes factor VIII in plasma.

DIAGNOSIS

Clinical Presentation

Clinical findings consist of mucocutaneous bleeding (epistaxis, menorrhagia, gastrointestinal bleeding), easy

bruising, and bleeding from trauma or surgery.

Diagnostic Testing

Testing for suspected vWD should include vWF:Ag, vWF ristocetin cofactor (vWF:RCo), and factor VIII activity. See the American Society of Hematology pocket guide on vWD.

TREATMENT

Goal of therapy is to raise vWF:RCo and factor VIII activity to ensure adequate hemostasis. vWF:RCo activities >50% control most hemorrhages.

- **DDAVP** 0.3 µg/kg IV can be used to treat type 1 vWD. Because only two-thirds of patients will respond, a test dose should assess for a response. For responders undergoing **minor invasive procedures**, infuse 1 hour before, followed by q12-24h for three more doses postoperatively, with or without oral antifibrinolytic drugs (i.e., aminocaproic acid or tranexamic acid).
  - DDAVP does not effectively treat most type 2 or type 3 vWD patients.
  - DDAVP is contraindicated in type 2B vWD because of the risk of thrombocytopenia.
  - Common side effects of DDAVP include hyponatremia, nausea, and flushing. Patients should limit fluid intake to 1200 mL/d within 24 hours of any dose.
- **vWF plasma-derived concentrate transfusions** (Alphanate, Humate-P, and Wilate) should aim to raise vWF:RCo activity to approximately 100% and maintain it between 50-100% until sufficient hemostasis occurs (typically 5-10 days). Cryoprecipitate is a second-line vWF source. Indications for concentrate transfusions:
  - Type 1 vWD-DDAVP nonresponders
  - Type 1 vWD with major bleeding or surgery
  - All other vWD types requiring hemostasis treatment

ACQUIRED COAGULATION DISORDERS

Vitamin K Deficiency

GENERAL PRINCIPLES

Vitamin K deficiency is usually caused by malabsorption states or poor dietary intake combined with antibiotic-associated loss of intestinal bacterial colonization. Hepatocytes require vitamin K to complete the synthesis (γ-carboxylation) of clotting factors (X, IX, VII, prothrombin) and the natural anticoagulant proteins C and S.

DIAGNOSIS

Vitamin K deficiency is suspected when an at-risk patient has a prolonged PT that corrects after a 1:1 mix with normal pooled plasma.

TREATMENT

Vitamin K replacement can be given by mouth (e.g., phytonadione 5 mg PO daily) in patients who have had poor dietary intake. When malabsorption is present, vitamin K can be repleted parenterally. IV administration of vitamin K has more reliable absorption than SC and is the preferred parenteral route.

Liver Disease

GENERAL PRINCIPLES

Liver disease can impair hemostasis (see Figure 20-1) because hepatocytes produce coagulation factors, with the exception of vWF and factor VIII. Coagulopathy is typically mild with stable liver disease until patients decompensate. Other hemostatic complications include thrombocytopenia due to splenic sequestration, DIC, hyperfibrinolysis, and cholestasis (which impairs vitamin K absorption). Although PT/INR and aPTT prolongations imply an increased risk of bleeding, they do not reflect concurrent reductions in protein C and protein S. Liver disease has a fragile balance of procoagulant and anticoagulant activities, which can easily be disrupted by infection, renal insufficiency, and vasomotor dysfunction (*Blood 2010;116:878*).

TREATMENT

- **Vitamin K** replacement may shorten a prolonged PT/INR due to a vitamin K antagonist, dietary deficiency, or cholestasis.
- **FFP** may be indicated for patients who are bleeding or require an invasive procedure and have abnormal coagulation parameters but may cause volume overload. A common threshold is PT >1.5 control despite limited supportive evidence.
- **Cryoprecipitate**, 1.5 units/10 kg body weight, corrects hypofibrinogenemia (<100 mg/dL).
- **Prothrombin complex concentrate (PCC)**, but safety and efficacy are unproven.
- Randomized controlled trials failed to show a hemostasis benefit for **recombinant factor VIIa** in GI bleeding (*Hepatology 2008;47:1604*).
- Reserve **platelet transfusions** for active bleeding or prior to invasive procedures, such as liver biopsy, in patients with thrombocytopenia (<50 × 10^9/L).

Disseminated Intravascular Coagulation

GENERAL PRINCIPLES

Etiology

DIC occurs in a variety of systemic illnesses that include sepsis, trauma, burns, shock, obstetric complications, and malignancies (notably, acute promyelocytic leukemia).

Pathophysiology

Exposure of tissue factor to the circulation generates excess thrombin, leading to platelet activation, consumption of coagulation factors (including fibrinogen) and regulators (antithrombin [**AT**] and proteins C and S), fibrin generation, generalized microthrombi, and reactive fibrinolysis.

DIAGNOSIS

Clinical Presentation

Consequences of **DIC** include bleeding, organ dysfunction secondary to microvascular thrombi and ischemia, and less often, large arterial and venous thrombosis (*Br J Haematol 2009;145:24*).

Diagnostic Testing

No one test confirms diagnosis of DIC. The International Society on Thrombosis and Haemostasis (**ISTH**) devised a clinical scoring system for objective detection of DIC (Table 20-4). Serial “DIC panels” help assess

clinical management and prognosis.

TREATMENT

Treatment consists of supportive care and correction of the underlying disorder if possible. **FFP**, **cryoprecipitate**, and **platelets** can be administered when needed clinically (e.g., bleeding or surgery), rather than strictly based on a laboratory threshold. Administer adjusted-dose IV **heparin** to patients with large-vessel venous or arterial thrombi. Nonbleeding patients who have DIC should receive thromboprophylaxis with heparin.

Acquired Inhibitors of Coagulation Factors

GENERAL PRINCIPLES

Acquired inhibitors of coagulation factors may occur de novo (autoantibodies) or may develop in hemophiliacs (alloantibodies) following factor VIII or IX infusions. The most common acquired inhibitor is directed against factor VIII. De novo cases often arise in patients with underlying lymphoproliferative or autoimmune disorders.

DIAGNOSIS

Patients with factor VIII inhibitors present with an abrupt onset of bleeding or bruising, prolonged aPTT that does not correct after 1:1 mixing with normal plasma, markedly decreased factor VIII activity, and a normal PT. Patients rarely develop autoantibodies that

inhibit other factors (II, V, X) and subsequently prolong aPTT and PT, which do not correct after mixing studies.

TABLE 20-4 International Society on Thrombosis and Haemostasis Disseminated Intravascular Coagulation Scoring System

Use only in patients with an underlying condition known to be associated with DIC.

	0 Points	1 Point	2 Points
Thrombocytopenia	>100 × 10^9/L	<100 × 10^9/L	≤50 × 10^9/L
D-Dimer	Normal	<10 × upper limit of normal	≥10 × upper limit of normal
PT Prolongation	<3 s	3-6 s	>6 s
Fibrinogen	>100 mg/dL	≤100 mg/dL	

DIC, disseminated intravascular coagulation.
Sum the points for each of the four categories to determine the clinical probability of having DIC: compatible with overt DIC ≥5 points, and suggestive of nonovert DIC <5 points.
Data from *Thromb Haemost 2001;86:132* and *Crit Care Med 2004;32:24167.*

TREATMENT

Bleeding complications in patients with factor VIII inhibitors (autoantibodies) are managed in the same manner as for hemophiliacs with alloantibodies to factor VIII (see Inherited Bleeding Disorders section). Long-term therapy consists of immunosuppression with prednisone or prednisolone ± cyclophosphamide to reduce production of the autoantibody (*Blood 2012;120:47*). The use of rituximab has become increasingly more common (*Br J Haematol 2014;165:600*).

VENOUS THROMBOEMBOLIC DISORDERS

Approach to Venous Thromboembolism

GENERAL PRINCIPLES

Definition

- **Thromboses** or blood clots may occur in veins, arteries, or chambers of the heart.
- **VTE** refers to **deep vein thrombosis (DVT)** or **pulmonary embolism (PE)**.
- **Thrombophlebitis** consists of inflammation in a vein due to a blood clot.
- **Superficial thrombophlebitis** may occur in any superficial vein.

Classification

The anatomic location of DVT/PE, clot burden, and sequelae may affect prognosis and treatment recommendations.

- Thromboses can be classified as **deep** or **superficial** and as **proximal** or **distal**.
  - Avoid using the term **superficial femoral vein** because it really refers to part of the **femoral vein (a deep vein)**.
  - **Proximal** lower extremity DVTs occur in or superior to the popliteal vein (or the confluence of tibial and peroneal veins), whereas **distal** DVTs occur inferiorly.
- Location in the pulmonary arterial system characterizes **PEs** as **central/proximal** (main pulmonary artery, lobar, or segmental) or **distal** (subsegmental).

Epidemiology

- Without treatment, half of patients with proximal lower extremity DVT develop PE.
- DVTs in the upper extremities are often related to an indwelling catheter and can cause PE.
- DVT may occur concomitantly with superficial thrombophlebitis.

Etiology

- Venous thromboemboli arise under conditions of **blood stasis**, **hypercoagulability** (changes in the soluble and formed elements of the blood), or venous **endothelial dysfunction/injury**.
- Hypercoagulable states may have an inherited or acquired etiology (see Risk Factors section).
- **Superficial thrombophlebitis** occurs in association with varicose veins, trauma, infection, and hypercoagulable disorders.
- Other causes of pulmonary arterial occlusion *include in situ* thrombi (e.g., sickle cell disease), marrow fat embolism, amniotic fluid embolism, pulmonary artery sarcoma, and fibrosing mediastinitis.

Risk Factors

- Risk factors for VTE can be categorized as inherited, acquired, or unknown (idiopathic).
- **Inherited thrombophilic disorders** are suggested by spontaneous VTE at a young age (<50 years), recurrent VTE, VTE in first-degree relatives, thrombosis in unusual anatomic locations (i.e., abdominal), and recurrent fetal loss.
- The most common inherited risk factors for VTE include gene mutations **(factor V Leiden and prothrombin gene G20210A)** and deficiencies of the natural anticoagulants **protein C, protein S, and AT**.
- **Homocystinuria**, a rare autosomal recessive disorder caused by deficiency of cystathionine-β-synthase, leads to extremely high plasma homocysteine and causes early onset arterial and venous thromboembolic events. Mild elevation of homocysteine may be caused by a mutation in methylenetetrahydrofolate reductase (**MTHFR**), but does not cause VTE (*Arch Intern Med 2007;167:497*; *Br J Haematol 2008;141:529*). Therefore, *MTHFR* mutation should not be included in the thrombophilia testing.
- Spontaneous VTE in unusual locations, such as cavernous sinus, mesenteric vein, or portal vein, may be the initial presentation of paroxysmal nocturnal hemoglobinuria **(PNH)** or myeloproliferative disorders.
- **Spontaneous (idiopathic) VTEs** have a high risk of recurrence (8-10% per year) regardless of the presence of an inherited thrombophilia (*N Engl J Med 2001;344:1222*).
- **Acquired hypercoagulable** states may arise secondary to malignancy, immobilization, infection, trauma, surgery, collagen vascular diseases, nephrotic syndrome, HIT, DIC, medications (e.g., estrogen), and pregnancy.
- Acquired **autoantibodies** associated with HIT and APS can cause arterial or venous thrombi.
- **APS** is a hypercoagulable disorder that requires the presence of at least one clinical **and** one laboratory criterion (*J Thromb Haemost 2006;4:295*).
  - **APS clinical criteria:**
    - Unprovoked arterial or venous thrombosis in any tissue or organ *or*
    - Pregnancy morbidities (unexplained late fetal death; premature birth complicated by eclampsia, preeclampsia, placental insufficiency; or ≥ three unexplained consecutive spontaneous abortions at <10 weeks of gestation or one at ≥10 weeks).
  - **APS laboratory criteria:**

    Presence of autoantibodies
    - **LA**, anticardiolipin, or β_2-glycoprotein-1 antibodies
    - Confirmation of positive autoantibody tests (must be done at least 12 weeks apart)
    - Approximately 10% of patients with SLE have an LA; however, most patients with an LA do not have SLE.
  - APS may include **other features**, such as thrombocytopenia, valvular heart disease, livedo reticularis, neurologic manifestations, and nephropathy.

Prevention

Identifying patients at high risk for VTE and instituting prophylactic measures should remain a high priority (see Chapter 1, Inpatient Care in Internal Medicine).

DIAGNOSIS

Clinical Presentation

- **Pain, edema, redness, and warmth** in an affected extremity **are the most common symptoms of a DVT**. Pretest assessment of the probability of a DVT provides useful information when combined with the results of compression ultrasound, D-dimer test, or both, in determining whether to exclude or accept the diagnosis of DVT or perform additional imaging studies (*Lancet 1997;350:1795*).
- **Superficial thrombophlebitis** presents as a tender, warm, erythematous, and often palpable thrombosed vein. Accompanying DVT may produce additional symptoms and signs.

- **PE** may produce shortness of breath, chest pain (pleuritic), hypoxemia, hemoptysis, pleural rub, new right-sided heart failure, and tachycardia (*Ann Intern Med 1998;129:997*). Validated clinical risk factors for a PE in outpatients who present to an emergency department include signs and symptoms of DVT, high clinical suspicion of PE, tachycardia, immobility in the past 4 weeks, history of VTE, active cancer, and hemoptysis (*Ann Intern Med 2001;135:98*).

Differential Diagnosis

- The **differential diagnoses of DVT** include cellulitis, Baker cyst, hematoma, venous insufficiency, postphlebitic syndrome, lymphedema, sarcoma, arterial aneurysm, myositis, rupture of the gastrocnemius, and abscess.
- **Symmetric, bilateral lower extremity edema** suggests heart, renal, or liver failure as the cause of the signs and symptoms.
- The **differential diagnosis of PE** includes dissecting aortic aneurysm, pneumonia, acute bronchitis, pericardial or pleural disease, heart failure, costochondritis, rib fracture, and myocardial ischemia.

Diagnostic Testing

Clinical Probability Assessment

Clinical decision rules help to exclude VTE when used in combination with other diagnostic tests (such as normal D-dimer).

- Clinical predictors of PE include prior VTE, heart rate ≥100 bpm, recent surgery/immobilization, hemoptysis, cancer, signs of a DVT (e.g., unilateral edema), and an alternative diagnosis less likely than PE. Patients who have one or fewer of these predictors (i.e., a low simplified Wells score) are unlikely to have a PE. The combination of a low Wells score and a normal D-dimer essentially rules out a PE (*Ann Intern Med 2011;154:709*).
- Clinical predictors of DVT from Wells criteria include heart rate ≥100 bpm, recent lower limb trauma/surgery/immobilization, bedridden state, cancer, lower extremity vein proximal tenderness, swelling of entire lower extremity, significant calf size asymmetry, pitting edema, dilated collateral lower extremity superficial veins, and alternative diagnoses less likely than DVT. Patients who have one or fewer of these predictors (i.e., low Wells score) are unlikely to have a DVT (*Lancet 1997;350:1795*).

Laboratories

- **D-Dimer** and fibrin degradation products may increase during VTE but are nonspecific.
  - D-Dimer testing for VTE has a low positive predictive value (**PPV**) and specificity; **patients with a positive test require further evaluation**.
  - A sensitive quantitative D-dimer assay has a high enough NPV to exclude a **DVT** when the objectively defined clinical probability is low and/or a noninvasive test is negative (*Ann Intern Med 2004;140:589*; *JAMA 2006;295:199*).
  - In the setting of a moderate to high clinical pretest probability (e.g., patients with cancer), a negative D-dimer

does not have sufficient NPV for excluding the presence of DVT or PE (*Ann Intern Med 1999;131:417*; *Arch Intern Med 2001;161:567*).
    - Compared to a fixed D-dimer cutoff of 500 µg/L, upward age adjustment of the cutoff (age × 10 in patients at least age 50 years) will increase the number of patients who can have PE excluded based on the combination of D-dimer testing and objective clinical probability assessment (*JAMA 2014;311:1117*).
- Signs and symptoms of the **APS** should lead to laboratory evaluation.
    - Serologic tests (e.g., IgG and IgM β_2-glycoprotein-1 antibodies, and IgG and IgM cardiolipin antibodies) or clotting assays (e.g., LA) detect APS, and performing both improves sensitivity.
    - LAs may prolong the aPTT or PT/INR, although they do not predispose to bleeding.
- In the setting of spontaneous VTE at unusual sites, use flow cytometry to assess for missing antigens on red cells and leukocytes and detect **PNH**.

Imaging

- **DVT-specific testing** (*Chest 2012;141:e351S*) Initial diagnostic imaging for suspected acute DVT typically consists of **compression ultrasound,** called **duplex examination** when performed with Doppler testing, of the veins (*Am J Respir Crit Care Med 1999;160:1043*), although some other diagnostic options include magnetic resonance venography, **CT** venography, and venography.
    - In addition to assessing for DVT, imaging may detect other pathology (see Differential Diagnosis section).
    - Compression ultrasound has a high sensitivity in **symptomatic** patients and a low sensitivity in **asymptomatic** patients.
    - Compression ultrasound has a low sensitivity for detecting **calf** DVT and may fail to visualize parts of the deep femoral vein, upper extremity venous system, and pelvic veins.
    - Compression ultrasound may have difficulty distinguishing between acute and **chronic** DVT.
    - **Lower extremity venous compression ultrasound** may help diagnose or exclude VTE in patients who have suspected PE and a nondiagnostic ventilation/perfusion (**V/Q**) scan, nondiagnostic or negative chest CT with high suspicion of PE, or contraindications to or difficulty completing imaging for PE (see PE-specific testing section).
    - **Serial testing** can improve the diagnostic yield of compression ultrasound. If a patient with a clinically suspected lower extremity DVT has a negative initial noninvasive test and no satisfactory alternative explanation, one can withhold anticoagulant therapy and repeat testing at least once 3-14 days later.
    - **Ultrasound is recommended to exclude DVT in the setting of superficial venous thrombosis** (*Ann Intern Med 2010;152:218*).
- **PE-specific testing**
    - **Contrast-enhanced spiral (helical) chest CT**
        - PE protocol chest CT requires IV administration of iodinated contrast.
        - Contraindications to spiral CT include renal dysfunction and dye allergy.
        - Used according to standardized protocols in conjunction with expert interpretation, spiral CT has good accuracy for detection of large (proximal) PEs, but it has lower sensitivity for detecting small (distal) emboli (*N Engl J Med 2006;354:2317*).
        - The sensitivity of CT for PE improves by combining the CT pulmonary angiography results with objective grading of clinical suspicion.
        - **Clinical suspicion discordant with the objective test finding** (e.g., high suspicion with a negative CT scan or low suspicion with a positive CT scan) **should lead to further testing**.

- Advantages of CT scan over V/Q scan includes more diagnostic information (positive or negative) with fewer indeterminate or inadequate studies and the detection of alternative or concomitant diagnoses, such as dissecting aortic aneurysm, pneumonia, and malignancy (*JAMA 2007;298:2743*).

- **V/Q scan**
  - V/Q scans require administration of radioactive material (via inhaled and IV routes).
  - V/Q scans may be classified as normal, nondiagnostic (i.e., very low probability, low probability, intermediate probability), or high probability for PE.
  - V/Q scans are most useful in a patient with a normal CXR, because nondiagnostic V/Q scans commonly occur in the setting of an abnormal CXR.
  - Use of clinical suspicion improves the accuracy of V/Q scanning. In patients with normal or high-probability V/Q scans and matching pretest clinical suspicion, the testing has a PPV of 96% (*JAMA 1990;263:2753*).
- **Pulmonary angiography**
  - Angiography requires placement of a pulmonary artery catheter, infusion of IV contrast, and exposure to radiation.
  - Contraindications to angiography include renal dysfunction and dye allergy.
  - Less invasive tests (i.e., CT angiography) have mostly replaced pulmonary angiography.

- **Electrocardiogram, troponin and brain natriuretic peptide (BNP) levels, arterial blood gas, CXR, and echocardiogram** may to help assess clinical probability of PE, cardiopulmonary reserve, and potential benefit of thrombolysis (see thrombolytic therapy in Medications section).
- **Studies do not support extensive screening for an associated occult malignancy** in patients with a first, unprovoked VTE (*N Engl J Med 2015;373:697-704*). However, such patients should undergo a comprehensive history and physical examination, routine blood work, age- and gender-appropriate cancer screening (e.g., colonoscopy, mammography, Papanicolaou smear, prostate-specific antigen), and specific cancer screening tests indicated for distinct populations (e.g., chest CT to search for lung cancer in smokers of advanced age).

TREATMENT

- **VTE therapy** should aim to prevent recurrent VTE, consequences of VTE (i.e., postphlebitic syndrome [i.e., pain, edema, and ulceration], pulmonary arterial hypertension, and death), and complications of therapy (e.g., bleeding and HIT/HITT).
- Clinicians should perform standard laboratory tests (i.e., CBC, PT/INR, and aPTT) and assess bleeding risk before starting anticoagulants.
- Unless contraindications exist, **initial treatment of VTE should consist of anticoagulation** with IV or SC UFH, SC LMWH, SC pentasaccharide (fondaparinux), or a rapidonset targeted oral anticoagulant (see Medications).

Medications

- **Anticoagulants, oral**
  - **Warfarin**, **an oral anticoagulant**, inhibits reduction of vitamin K to its active form and leads to depletion of the vitamin K-dependent clotting factors II, VII, IX, and X, and proteins C, S, and Z.
    - The initial INR rise primarily reflects warfarin-related depletion of factor VII; the depletion of factor II takes several days due to its relatively long half-life.

- Because of the rapid depletion of the anticoagulant protein C and a slower depletion of factor II, patients might develop increased hypercoagulability during the first few days of warfarin therapy if warfarin is not combined with a parenteral anticoagulant (*Thromb Haemost 1997;78:785*).
- The **starting dose** of warfarin depends on many factors and ranges from 2-4 mg in older or petite patients to 10 mg in young, robust patients (*www.warfarindosing.org*). Patients with polymorphisms in genes for cytochrome P450 2C9 or vitamin K epoxide reductase (*VKORC1*) may benefit from lower dose warfarin initiation. Use the INR to adjust dosing.
- **Treatment of DVT/PE with warfarin requires overlap therapy with a parenteral anticoagulant** (UFH, LMWH, or pentasaccharide) for at least 4-5 days and until the INR reaches at least 2.0.

  For most indications, **target INR** is 2.5 with a therapeutic range of 2-3.

  Patients with **mechanical mitral valves** require a higher level of anticoagulation (INR target range 2.5-3.5) and typically benefit from concomitant low-dose ASA.
- **INR monitoring should occur frequently during the first month of warfarin therapy (e.g., twice weekly for 1-2 weeks, then weekly for 2 weeks, then less frequently).**

  Patients receiving a stable warfarin dose should have INR monitoring performed approximately monthly, although patients with labile INRs should have more frequent monitoring (e.g., weekly). Typical dose adjustments after the first couple of weeks of therapy change the weekly dose by 10-25%.

  The addition or discontinuation of medications, especially amiodarone, certain antibiotics (e.g., rifampin, sulfamethoxazole), or antifungal drugs (e.g., fluconazole), should trigger more frequent INR monitoring and may require dose adjustments >25%.

  In eligible patients, home INR monitoring may improve INR control and patient satisfaction (*N Engl J Med 2010;363:1608*).

  Compliant patients who have unacceptable INR lability likely benefit from a targetspecific oral anticoagulant other than warfarin.

- **Target-specific oral anticoagulants** (Table 20-5): These currently include two categories, **DTI** (dabigatran) and **direct Xa inhibitors** (rivaroxaban, apixaban, and edoxaban)
  - As compared to warfarin, these oral anticoagulants have a more rapid onset, shorter half-life, wider therapeutic window, and more predictable pharmacokinetics. These features allow for sole oral therapy without the need for an overlapping parenteral agent (with the exception of edoxaban for VTE), no need for titration or dose adjustments in patients with normal renal function, and no need for routine monitoring.
  - Compared to warfarin, the target-specific anticoagulants have a lower risk of intracranial hemorrhage (*J Thromb Haemost 2014;12:320*).
  - Issues of concern include the lack of antidotes, risk of thrombosis due to missed doses, and drug level effects based on renal function.
  - In the United States, currently available oral direct Xa inhibitors include rivaroxaban, apixaban, and edoxaban.

- **Anticoagulants, parenteral**
  - **UFH** inactivates thrombin and factor Xa via AT.
    - At usual doses, UFH prolongs aPTT and thrombin time, although it has variable effect on the PT.
    - Because the anticoagulant effects of UFH normalize within hours of discontinuation and **protamine sulfate** reverses it even faster, UFH is the anticoagulant of choice during initial therapy for patients with a high risk of bleeding.

- Abnormal renal function does not typically affect UFH dosing.
- For **DVT prophylaxis**, the typical dosage is 5000 units SC q8-12h, and aPTT monitoring is not necessary.
- For **therapeutic anticoagulation**, UFH is usually administered IV with a bolus (e.g., 80 units/kg) followed by continuous infusion (e.g., 18 units/kg/h) that has a dose titration based on standard protocols (i.e., heparin nomogram), usually to a goal aPTT of 2- to 2.5-fold of normal range (see Table 20-5).

- **LMWHs**, produced by chemical or enzymatic cleavage of UFH, indirectly inactivate thrombin and factor Xa via AT.
  - Because LMWH inactivates factor Xa to a greater extent than it does thrombin (IIa), LMWH minimally prolongs the aPTT.
  - Factor Xa monitoring is not needed, except in special circumstances: renal dysfunction, morbid obesity, or pregnancy. For therapeutic anticoagulation, peak factor Xa levels, measured 4 hours after an SC dose, should be 0.6-1.0 IU/mL for q12h dosing and 1-2 IU/mL for q24h dosing (*Blood 2002;99:3102*).
  - Different LMWH preparations have different dosing recommendations (see Table 20-5).
  - Given the renal clearance of LMWHs, they are generally contraindicated in patients with creatinine clearance (**CrCl**) <10 mL/min, and patients with a CrCl of 10-30 mL/min require dose adjustments (e.g., enoxaparin 1 mg/kg daily).
  - **LMWH** is the first choice in **pregnant** women (without artificial heart valves) with thrombosis. Warfarin is teratogenic, at least during the first trimester.
- **Fondaparinux**, a synthetic pentasaccharide structurally similar to the region of the heparin molecule that binds AT, functions as a selective indirect factor Xa inhibitor.
  - Because fondaparinux inhibits factor Xa and does not inhibit thrombin, it does not prolong the aPTT.

TABLE 20-5 Anticoagulant Dosing for Treatment of Venous Thromboembolism

Anticoagulant	Mechanism of Action	Initial Treatment Dose(s)	Subsequent Dose	Contraindications[a]
Warfarin	Vitamin K antagonist	2-10 mg; overlapped for 4-5 d with a faster-acting anticoagulant; goal INR 2-3 (see *www.warfarindosing.org*)	Adjusted per INR	Pregnancy
Apixaban	Direct FXa inhibitor	10 mg PO bid × 7 d	5 mg PO bid	
Edoxaban	Direct FXa inhibitor	Initially treat with parenteral anticoagulant for 5-10 d	60 mg PO daily, *or* 30 mg PO daily (if CrCl 30-50 mL/min, body weight	

			≤60 kg, or using strong P-gp inhibitor)	
Rivaroxaban	Direct FXa inhibitor	15 mg PO bid × 21 d	20 mg PO daily	CrCl <30 mL/min
Dabigatran	Direct thrombin (FIIa) inhibitor	Initially treat with parenteral anticoagulant for 5-10 d	150 mg bid (CrCl >30 mL/min)	CrCl <15 mL/min
Dalteparin	FXa > FIIa inhibition	200 IU/kg SC daily	Transition to oral agent *or*, for cancer patients, after 30 d of initial therapy, reduce dose to 150 IU/kg SC daily	HIT; hypersensitivity to pork
Enoxaparin	FXa > FIIa inhibition	1 mg/kg SC q12h *or* 1.5 mg/kg SC q24h; lower dose if CrCl <30 mL/min	Transition to long-term oral agent[b]	HIT; hypersensitivity to pork
Fondaparinux	Binds to antithrombin, primarily inhibiting FXa	Weight <50 kg: 5 mg SC daily Weight 50-100 kg: 7.5 mg SC daily Weight >100 kg: 10 mg SC daily	Transition to long-term oral agent[b]	CrCl <30 mL/min
Tinzaparin	FXa > FIIa inhibition	175 IU/kg SC daily	Transition to long-term oral agent[b]	HIT
Unfractionated heparin	Binds to antithrombin	Continuous IV: Goal aPTT 2.0-2.5× normal range	Transition to long-term oral agent[b]	HIT; hypersensitivity to pork

aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; FIIa, factor IIa; FXa, factor Xa; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; P-gp, P-glycoprotein.

[a]Invasive procedures (e.g., neuraxial anesthesia), bleeding, and bleeding diathesis (e.g., liver disease, thrombocytopenia) are contraindications to all anticoagulants.

[b]For venous thromboembolism (VTE) treatment, overlap therapy of warfarin and parenteral agent should be at least 5 days, until the INR is at least 2. Low-molecular-weight heparin can be prescribed long term for VTE (e.g., in setting of cancer).

- Dosing of fondaparinux is weight based (see Table 20-5; *Ann Intern Med 2004; 140:867*).
- Similar to the LMWHs, factor Xa monitoring is not routinely used.
- Fondaparinux is not recommended for patients with CrCl <30 mL/min.

- **Argatroban** is a synthetic DTI used for **HIT** therapy.
  - Argatroban has a half-life of <1 hour, and a reversal agent is not available.
  - Argatroban is infused IV at an initial rate of ≤2 µg/kg/min. Special patient populations require lower initial infusion rates: patients with recent cardiac surgery, heart failure, hepatic dysfunction, or anasarca (*Chest 2012;141:e495S*).
  - aPTT monitoring should occur 2 hours after beginning the infusion, and the infusion rate should undergo adjustment to achieve a therapeutic aPTT (1.5-3.0 times the patient's baseline aPTT).
  - Overlap argatroban therapy with warfarin therapy for at least 5 days and until warfarin leads to a therapeutic INR. During warfarin coadministration, argatroban should be discontinued for an INR >4, and the INR should be measured again within 4-6 hours.
- **Bivalirudin** is a DTI with an indication for treatment of **HIT** in the setting of percutaneous coronary intervention in patients receiving ASA.
  - Bivalirudin has a half-life of 25 minutes in patients with normal renal function.
  - Because of its renal clearance, bivalirudin requires dose adjustment of the infusion rate in patients with renal insufficiency.
  - Bivalirudin dosing for HIT should start at a rate of 0.15-0.20 mg/kg/h IV with titration to a target aPTT 1.5-2.5 times baseline. An initial bolus dose is not recommended (*Chest 2012;141:e495s*; *Pharmacotherapy 2008;28:1115*). Lower rates should be initiated for patients with renal insufficiency (*Ann Pharmacother 2011;45:1185*).
  - aPTT monitoring during bivalirudin therapy should occur 2 hours after a dose change.
  - The interpretation of the INRs in patients receiving warfarin must take into account the increased PT/INR caused by bivalirudin.

- **Thrombolytic therapy**
  - Thrombolytic therapy (e.g., alteplase or recombinant tissue plasminogen activator as a 100-mg IV infusion over 2 hours) is indicated for patients with **PE** and systemic hypotension who do not have a high risk of bleeding (*Chest 2012;141:e419S*).
  - Thrombolytic therapy also should be considered in normotensive patients who have PE associated with right ventricular dysfunction and elevated troponin (*Eur Heart J 2014;35:3033*). Despite the prevention of hemodynamic decompensation and a possible mortality benefit, use of thrombolysis in this situation remains controversial because of an increased risk of major bleeding (especially hemorrhagic stroke in the elderly) in comparison to heparin therapy alone (*N Engl J Med 2014;370:1402*; *JAMA 2014;311:2414*).
  - Thrombolytic therapy has been used in selected cases of DVT. The main indication is DVT leading to venous congestion that compromises the arterial supply to the limb. The **CaVenT trial** showed that

thrombolysis in patients with massive iliofemoral DVT reduced postthrombotic syndrome but increased bleeding (*Lancet 2012;379:31*).

- **Duration of anticoagulation for DVT or PE**
  - **Duration of anticoagulation** should be individualized and based on risk of recurrent VTE, risk of hemorrhage, and patient preference (*Chest 2012;141:e419S*).
  - Patients with a **first episode of VTE due to reversible risk factors** (e.g., surgery, major trauma, estrogen therapy) have a low risk of recurrence (≤2% per year), and 3 months of anticoagulation are recommended (*Blood 2014;123:1794*; *Chest 2012;141:e419S*). Provoked distal DVTs can be treated with 6 weeks (*BMJ 2011;342:d3036*) to 3 months of anticoagulation.
  - Guidelines recommend at least 3 months of anticoagulant therapy for patients with a **first episode of VTE** associated with less compelling and transient risk factors, such as prolonged travel, oral contraceptive pills/hormone replacement therapy, or minor injury (*Chest 2012;141:e419S*).

  - For **unprovoked PE**, many experts anticoagulate for >3 months in patients with low to moderate risk of bleeding. Some experts recommend long-term anticoagulation for men with low to moderate risk of bleeding and an unprovoked PE (*Ann Intern Med 2015;162:27*).
  - Patients with **cancer and VTE** should continue anticoagulation until cancer resolution or development of a contraindication. LMWH is the treatment of choice in cancerassociated VTE due to superior efficacy over warfarin (*Lancet Oncol 2008;9:577*).
  - For patients with a **first VTE and one inherited hypercoagulable risk factor**, consider an extended anticoagulation duration, depending on the type of thrombophilia.
    - Heterozygous factor V Leiden or heterozygous prothrombin 20210A modestly increases the odds of recurrence (relative risk, 1.6 and 1.4, respectively); prolonged anticoagulation is not recommended. Deficiency of protein S, protein C, or AT carries a significant risk of recurrence (*JAMA 2009;301:2472*); long-term anticoagulation is recommended.
    - For patients with a **first VTE and APS or two inherited risk factors**, indefinite anticoagulation should be considered.
  - Patients with **recurrent idiopathic VTE** should receive extended-duration anticoagulation, unless a contraindication develops or patient preferences or high bleeding risk dictate otherwise (*Chest 2012;141:e419S*).
  - Patients with a history of VTE, especially those with risk factors, should possibly receive prophylactic anticoagulation (e.g., low-dose LMWH SC) during **periods of increased VTE risk**.

Other Nonpharmacologic Therapies

- **Leg elevation** is useful for the treatment of edema associated with DVT.
- **Ambulation** is encouraged for patients with DVT, especially after improvement of pain and edema, although strenuous lower extremity activity should initially be avoided.
- **Fitted below-the-knee graduated compression stockings** can reduce swelling after DVT, but does not prevent DVT recurrence, and the reduction of postthrombotic syndrome is controversial (*Lancet 2013;383:880*).
- In patients with **congenital AT deficiency**, infusion of **AT concentrate** can be used for an acute thrombosis (*Br J Haematol 1982;50:531*).
- **Inferior vena cava (IVC) filters** are mainly indicated for acute DVTs when there are **absolute contraindications to anticoagulation** (e.g., bleeding). They may also be used when a recurrent VTE has occurred despite therapeutic anticoagulation.

- Prophylactic IVC filters in patients with acute DVT/PE halve the risk of recurrent PE; however, they do not decrease mortality, and they increase DVT recurrence (*Circulation 2005;112:416*).
- Several types of **temporary/retrievable IVC filters** exist and provide a physical barrier against emboli from the lower extremities. To reduce the risks from retrievable IVC filters, they should be removed when they are no longer indicated. However, if an IVC filter placed for VTE is left in place after a bleeding contraindication has resolved, guidelines recommend a full course of anticoagulation (*Chest 2012;141:e419S*).

- **Catheter embolectomy, often combined with local thrombolytic therapy,** can treat large, proximal, acute PE and DVT. This approach is primarily considered for patients with PE and hypotension who have failed systemic thrombolytic therapy or who have contraindications to it (*Chest 2012;141:e419S*).

Surgical Management

Surgical embolectomy should be considered in patients with life-threatening massive PE who have contraindications to or have failed thrombolytic therapy (*Chest 2012;141:e419S*). Predictors of life-threatening massive PE include signs of cardiovascular dysfunction (e.g., elevated plasma BNP, tachycardia, hypotension, right ventricular strain on echocardiogram, and right ventricular enlargement on chest CT) (*Circulation 2004;110:3276*).

SPECIAL CONSIDERATIONS

Anticoagulant Bridging

- **Perioperative management of anticoagulation** requires close coordination with the surgical service (see Perioperative Medicine in Chapter 1) to address timing of interventions and therapeutic changes with the aim of VTE prevention and avoidance of bleeding.
- **Invasive procedures** usually require discontinuation of anticoagulation.
  - For patients receiving warfarin, to achieve a preoperative INR ≤1.4, stop the warfarin therapy 4-5 days before the invasive procedure.
  - If an INR around 1.7 is acceptable for the procedure, the warfarin dose can be halved for 4 days preoperatively (*Clin Lab Haematol 2003;25:127*).
  - In situations where a clinician aims to minimize the patient's time off therapeutic anticoagulation, parenteral anticoagulation should be initiated when the INR becomes subtherapeutic (approximately 3 days after the last warfarin dose) but should be stopped 6-48 hours prior to the procedure (depending on the half-life of the parenteral drug).
  - In some instances, IV UFH is the preferred bridging therapy (e.g., pregnant woman with a mechanical heart valve).
  - After the procedure, resume warfarin and/or parenteral anticoagulation as soon as hemostasis and bleeding risk reach an acceptable level, typically within 24 hours (*J Thromb Haemost 2014;12:1254*).
- Studies are needed to address the risks and benefits of anticoagulation for **isolated subsegmental PE**.
- **Upper extremity acute DVT** (*N Engl J Med 2011;364:861*) that involves axillary or more proximal vein(s) should receive standard-duration (e.g., 3 months) anticoagulation. If the DVT is associated with a functioning central venous catheter, it does not need to be removed, but anticoagulation should be continued as long as the catheter is in place (*Chest 2012;141:e419S*).
- **Isolated calf acute DVT** without severe symptoms or risk factors for extension may undergo serial imaging in 1-2 weeks instead of anticoagulation. Clot extension should lead to full-dose anticoagulation. Alternatively, treat with 6-12 weeks of anticoagulation in patients at low risk of bleeding.
- **Superficial vein thrombophlebitis (SVT)**

- **Small SVTs (<5 cm in length)** and SVT associated with IV infusion therapy do not require anticoagulation; treatment consists of oral NSAIDs and warm compresses.
- Treatment of **extensive SVT (e.g., >5 cm in length)** with a short course of prophylactic doses of fondaparinux (2.5 mg SC daily for 6 weeks) (*N Engl J Med 2010;363:1222*) or LMWH (e.g., enoxaparin 40 mg SC daily for 10 days) (*Arch Intern Med 2003;163:1657*) decreases the incidence of SVT recurrence, SVT extension, and VTE (*Chest 2012;141:e419S*) but increases the risk of bleeding.
- **Recurrent SVT** may be treated with anticoagulation or vein stripping (*Br J Haematol 1982;50:531*).

- **Chronic PE** occurs in 2-4% of patients with PE (*N Engl J Med 2011;364:351*), and patients with this disorder should undergo evaluation for chronic thromboembolic pulmonary hypertension (CTPH). Those with CTPH should undergo extended-duration anticoagulation, consideration of IVC filter placement, consideration of riociguat therapy (*N Engl J Med 2013;369:330*), and evaluation by an experienced team for possible pulmonary thromboendarterectomy.

COMPLICATIONS

- **Bleeding** is the major complication of anticoagulation.
  - Up to 2% of patients who receive short-term anticoagulation for VTE therapy experience major bleeding.

  - For patients receiving chronic oral therapy, the annual incidence of major bleeding is approximately 1-3% per year.
  - Concomitant use of **antiplatelet agents** increases the risk of bleeding.
  - Major bleeding in a patient with an acute VTE should lead to the discontinuation of anticoagulation and consideration of a temporary IVC filter. Reinitiation of anticoagulation should occur after the bleeding events have resolved, and the IVC filter can be removed at that time.
- **INR elevation** on warfarin
  - Asymptomatic minor INR elevations <5 should be managed by holding or reducing warfarin dose until the INR returns to the appropriate range and then resuming warfarin at a lower dose.
  - Moderate elevation (INR ≥5 but <9) of the INR in asymptomatic patients should be treated by holding one or more warfarin doses. Treatment with oral vitamin K_1 1-5 mg does not reduce the risk of hemorrhage in this setting as compared to warfarin cessation alone and is not routinely recommended (*Ann Intern Med 2009;150:293*).
  - Severe elevation (INR ≥9) should be treated with vitamin K (e.g., oral vitamin K_1 2-10 mg) (*Thromb Res 2004;113:205*) unless the INR is likely to be spurious.
- **Bleeding with warfarin**
  - **Vitamin K replacement** should be given PO or IV. Vitamin K has variable absorption when administered SC, especially in edematous patients. IV vitamin K carries the risk of anaphylactoid reactions. With adequate replacement therapy, the INR should begin to normalize within 12 hours and normalize completely in 24-48 hours (*Ann Intern Med 2002;137:251*). Serious hemorrhages should be treated with vitamin K (10 mg) by slow IV infusion and four-factor PCC. When four-factor PCC is not available, threefactor PCC and/or FFP (two or three units) can be used. Because of the long half-life of warfarin (approximately 36 hours), vitamin K should be repeated every 8-12 hours to prevent INR rebound.
  - Although expensive and potentially thrombogenic (*N Engl J Med 2010;363:1791*), **rFVIIa** may stop life-threatening bleeding (*Br J Haematol 2002;116:178*).
- **Bleeding with UFH, LMWH, and pentasaccharide**

- Discontinuation usually sufficiently restores normal hemostasis.
- With moderate to severe bleeding, FFP may reduce bleeding.
- For patients receiving **UFH** who develop major bleeding, heparin can be completely reversed by infusion of **protamine sulfate** in situations where the potential benefits outweigh the risks (e.g., intracranial bleed, epidural hematoma, retinal bleed).
- Approximately 1 mg of protamine sulfate IV neutralizes 100 units of heparin, up to a maximum dose of 250 mg. The dose can be given as a loading dose of 25-50 mg by slow IV injection over 10 minutes, with the rest of the dose over 12 hours.
- Heparin serum concentrations decline rapidly due to a short half-life after IV administration, and the amount of protamine required decreases based on time since heparin treatment.
- For major bleeding associated with **LMWH**, protamine sulfate neutralizes only approximately 60% of LMWH (*Reg Anesth Pain Med 2003;28:172*). Protamine does not reverse **pentasaccharide** (e.g., **fondaparinux**).
- For patients with serious bleeding on fondaparinux, concentrated factor VIIa may be used.

- **Bleeding with target-specific oral anticoagulants**
  - No antidotes are FDA approved at this time. FFP rarely adequately addresses bleeding associated with direct oral anticoagulants.
  - **Bleeding with apixaban, edoxaban, rivaroxaban:** Four-factor PCC can reverse direct factor Xa inhibitors, but evidence is limited to animal studies or case reports (*Circulation 2011;124(14):1573*). aPCC or factor VII concentrate may decrease bleeding. The high degree of albumin binding in plasma does not allow dialysis to significantly lower these drug concentrations.

  - **Bleeding with dabigatran:** Neither factor VII concentrate nor PCC adequately reverse dabigatran (*Circulation 2011;124(14):1573*), although they have been used in the clinical setting. Because the majority of dabigatran remains unbound to plasma proteins, **hemodialysis** will decrease the drug concentration and lower the thrombin clotting time. In a prospective cohort study, idarucizumab (5 g IV), a monoclonal antibody that binds to free and thrombin-bound dabigatran and neutralizes its activity, completely reversed the anticoagulation effect of dabigatran in minutes (*N Engl J Med 2015;373:511*). Idarucizumab currently does not have FDA approval.
- **Occult gastrointestinal or genitourinary bleeding** is a relative and not absolute contraindication to anticoagulation, although its presence prior to or during anticoagulation warrants an investigation for underlying disease.
- **Warfarin-induced skin necrosis**, associated with rapid depletion of protein C, may occur during initiation of warfarin therapy.
  - Necrosis occurs most often in areas with a high percentage of adipose tissue, such as breast tissue, and it can be life threatening.
  - Therapeutic anticoagulation with an immediate-acting anticoagulant (e.g., UFH, LMWH) and/or avoiding “loading doses” of warfarin prevents warfarin-induced skin necrosis.
- **Warfarin is absolutely contraindicated in early** (i.e., first-trimester) **pregnancy** because of the **risk of teratogenicity**, and it is often avoided during the entire **pregnancy** because of the **risk of fetal bleeding**, although it is safe for infants of nursing mothers.
- **Osteoporosis** may occur with long-term heparin or warfarin use (*Arch Intern Med 2006;166:241*).

MONITORING/FOLLOW-UP

- For a suspicious clinical presentation, **testing for intrinsic hypercoagulable risk factors** ideally should wait until

the patient is in stable health and off anticoagulation therapy for at least 2 weeks (e.g., at the end of a standard course of treatment) **to avoid false-positive results** for nongenetic testing.

  - Although uncommon, if reasons exist to screen for hypercoagulable risk factors around the time of diagnosis, collect blood for **factor V Leiden and prothrombin gene mutations and LA**.
  - If done, blood collection for **protein C, protein S, and AT activity and antigen level** testing should occur while patients are not on anticoagulation and should be avoided in the setting of acute thrombosis. If testing occurs near the time of the acute VTE, normal protein C, protein S, and AT tests rule out congenital deficiencies, and abnormally low results require confirmation through repeat testing (or screening first-degree relatives) to rule out a temporary deficiency related to the acute thrombosis.

- Although **testing for PE in patients with DVT and testing for DVT in patients with PE** will produce many positive findings, such testing rarely affects therapy.
- **Outpatient therapy** is appropriate for most DVTs and for selected (low-risk) PEs (*Lancet 2011;378:41*).
- Decisions regarding the **prolongation of anticoagulation duration** remain controversial in patients with residual thrombosis on compression ultrasonography at the end of standard-duration anticoagulation for proximal DVT (*Ann Intern Med 2009;150:577*) or in those with a positive D-dimer weeks after completing a standard duration of therapy for VTE (*N Engl J Med 2006;355:1780*). Prolonged-duration anticoagulation reduces VTE recurrence but increases bleeding.
- After completion of anticoagulation for an unprovoked VTE, **low-dose ASA** reduces the risk of arterial and venous thrombosis (*N Engl J Med 2012;366:1959*; *N Engl J Med 2012;367:1979*).

21
Hematologic Disorders and Transfusion Therapy

Amy Zhou
Tom Regenbogen
Ronald Jackups
Morey Blinder

ANEMIA

Anemia Introduction

GENERAL PRINCIPLES

Definition

Anemia is defined as a decrease in circulating red blood cell (RBC) mass; the usual criteria in adults being hemoglobin (Hgb) <12 g/dL or hematocrit (Hct) <36% for nonpregnant women and Hgb <13 g/dL or Hct <39% in men.

Classification

Anemia can be broadly classified into three etiologic groups: **blood loss (acute or chronic), decreased RBC production, and increased RBC destruction (hemolysis)**. It is also described morphologically as microcytic, normocytic, or macrocytic.

DIAGNOSIS

Anemia is always caused by an underlying disorder; thus, a careful evaluation to determine the etiology is required in each case.

Clinical Presentation

Based on the history, one can often discern timeline (acute, subacute, or chronic), severity, and the underlying etiology.

- Acute anemia: Patients with abrupt onset of anemia tolerate diminished red cell mass poorly. Patients may have symptoms of fatigue, malaise, dizziness, syncope, or angina.
- Chronic anemia: In contrast to acute anemia, patients with stable chronic anemia are occasionally asymptomatic or minimally symptomatic. However, patients usually have symptoms when Hgb <7 g/dL.
- The following history will aid in the evaluation and management of anemia:
  - Gastrointestinal (GI) hemorrhage
  - Obstetric and menstrual history
  - Comorbidities associated with anemia such as GI resection or malabsorption, renal disease, rheumatologic disease, or other chronic inflammatory conditions
  - Comorbid conditions that may be exacerbated by anemia, such as cardiovascular disease
  - Family history of anemia
  - Prescribed and over-the-counter medicines including herbal supplements, alcohol consumption, diet,

ethnic background, and religious beliefs pertaining to blood transfusions
- Symptoms suggestive of other cytopenias (such as bruising thrombocytopenia) or infections (neutropenia)

Physical Examination

Common signs and symptoms of anemia include pallor, tachycardia, hypotension, dizziness, tinnitus, headaches, loss of concentration, fatigue, and weakness. Atrophic glossitis, angular cheilosis, koilonychias (spoon nails), and brittle nails are more common in severe long-standing anemia. Patients may also experience reduced exercise tolerance, dyspnea on exertion, and heart failure. High-output heart failure and shock may be seen in the most severe cases.

Diagnostic Testing

Laboratories

- The complete blood count (CBC) and reticulocyte count will guide further laboratory testing because they provide a morphologic classification and assessment of RBC production.
- The Hgb level is a measure of the concentration of Hgb in blood as expressed in grams per deciliter (g/dL), whereas the Hct is the percentage of RBC in blood. Hgb and Hct are unreliable indicators of red cell mass in the setting of rapid shifts of intravascular volume (i.e., an acute bleed).
- The most useful red cell indices are:
  - Mean corpuscular volume (MCV): mean volume of the red cells. Normal range: 80-100 fL.
    - **Microcytic: MCV <80 fL**
    - **Normocytic: MCV of 80-100 fL**
    - **Macrocytic: MCV >100 fL**
  - Red cell distribution width (RDW): A reflection of the variability in the size of the red cells and is proportional to the standard deviation of the MCV. **An elevated RDW indicates an increased variability in RBC size.**
  - Mean cellular hemoglobin (MCH): Describes the concentration of Hgb in each cell, and an elevated level is often indicative of spherocytes or a hemoglobinopathy.
- **The relative reticulocyte count** measures the percentage of immature red cells in the blood and reflects production of RBCs in the bone marrow (BM).
  - A normal RBC has a life span of approximately 120 days, and the reticulocytes circulate for about 1 day; therefore, the normal reticulocyte count is 1-2%.
  - In the setting of anemia from blood loss, the BM should increase its production of RBCs in proportion to loss of RBCs, and thus a 1% reticulocyte count in the setting of anemia is inappropriate.
  - **The reticulocyte index** (RI) is a determination of the BM's ability to respond to anemia and is calculated by % reticulocytes/maturation correction × actual Hct/normal Hct (normally 45). The maturation correction factor is 1.0 for Hct >30%, 1.5 for 24-30%, 2.0 for 20-24%, and 2.5 for <20%.
  - **RI <2 with anemia indicates decreased production of RBCs (hypoproliferative anemia)**. **RI >2 with anemia may indicate hemolysis or bleeding**, leading to increased compensatory production of reticulocytes (hyperproliferative anemia).
- The **peripheral smear** is reviewed to assess the morphologic characteristics of RBC including the shape, size, presence of inclusions, and orientation of cells in relation to each other. RBCs can appear in many abnormal forms, such as acanthocytes, schistocytes, spherocytes, or teardrop cells, and abnormal

orientation such as agglutination or Rouleaux formation. Each is associated with several specific disease processes.

Diagnostic Procedures

A **BM biopsy** may be indicated in cases of unexplained normocytic anemias with a low reticulocyte count or with anemias associated with other cytopenias. The biopsy may

confirm a myelophthisic process (i.e., presence of teardrop or fragmented cells, nucleated RBCs, or immature white blood cells [WBCs] on peripheral blood smear) in the setting of pancytopenia.

ANEMIAS ASSOCIATED WITH DECREASED RED BLOOD CELL PRODUCTION

Iron Deficiency Anemia

GENERAL PRINCIPLES

- **Iron deficiency** is the most common cause of anemia in the ambulatory setting and is usually microcytic.
- The most common causes of iron deficiency are blood loss (e.g., menses, GI blood loss), decreased absorption (e.g., achlorhydria, celiac disease, bariatric surgery, *Helicobacter pylori* infection), and increased iron requirement (e.g., pregnancy).
- It is important to determine the cause of iron deficiency, and in the absence of menstrual bleeding, evaluation of the GI tract should be performed to identify a source and exclude occult malignancy.

DIAGNOSIS

Clinical Presentation

- Patients often present with fatigue or malaise that is typically worsened with activity, as well as pica (consumption of substances such as ice, starch, or clay). Iron deficiency is also associated with restless leg syndrome.
- Pallor is a common physical finding in patients with anemia. Rarely, splenomegaly, koilonychia (“spoon nail”), and glossitis (i.e., Plummer-Vinson syndrome) can be seen with severe iron deficiency.

Diagnostic Testing

Peripheral blood smear may show hypochromia (increased central pallor of RBCs), microcytosis, and pencil-shaped cells.

Laboratories

- **Ferritin** is the primary storage form for iron in the liver and BM and is the best surrogate marker of iron stores.
  - A ferritin level of <10 ng/mL in women or <20 ng/mL in men is a specific marker of low iron stores.
  - Ferritin is an acute-phase reactant, so normal levels may be seen in inflammatory states despite low iron stores. **A serum ferritin level of >200 ng/mL generally excludes an iron deficiency**; however, in renal dialysis patients, a functional iron deficiency may be seen with a ferritin up to 500 ng/mL.
  - **Iron, total iron binding capacity (TIBC), and transferrin saturation** are often used in combination with ferritin to diagnose iron deficiency anemia. Serum iron level alone is often unreliable given its

significant fluctuation based on patients' diets.

- **Reticulocyte count is often normal or decreased in iron deficiency anemia.**

TABLE 21-1 Oral Iron Preparations

Preparation	Common Dosing Regimen	Elemental Iron (mg per dose)
Ferrous sulfate	325 mg tid	65
Ferrous gluconate	300 mg tid	36
Ferrous fumarate	100 mg tid	33
Iron polysaccharide complex	150 mg bid	150
Carbonyl iron	50 mg bid-tid	50

Diagnostic Procedures

A **BM biopsy** that shows absent staining for iron is the definitive test to diagnose iron deficiency anemia and is helpful when the serum tests do not clearly demonstrate the diagnosis.

TREATMENT

- **Oral iron therapy.** Given in stable patients with mild symptoms. Several different preparations are available (Table 21-1).
  - Iron is best absorbed on an empty stomach, and 3-10 mg of elemental iron can be absorbed daily.
  - Oral iron ingestion may induce a number of GI side effects, including epigastric distress, bloating, and constipation. As a result, nonadherence is a common problem. These side effects can be decreased by initially administering the drug with meals or once per day and increasing the dosage as tolerated. Concomitant treatment with a stool softener can also alleviate these symptoms.
  - Ferrous sulfate is the most commonly prescribed formulation. If there are unacceptable side effects, consider using a lower dose or an alternative formulation such as ferrous gluconate or ferrous fumarate, which contain lower amounts of elemental iron and may be better tolerated.
  - Administration of vitamin C along with iron improves absorption by maintaining the iron in the reduced state. Certain medications (e.g., H2 blockers, proton pump inhibitors) and foods (e.g., coffee, tea, phosphate-containing carbonated beverages) may decrease iron absorption, and patients should be made aware of these effects when prescribed oral iron therapy.
  - The total iron deficit may be calculated using the patient's baseline Hgb and body weight (*http://www.globalrph.com/irondeficit.htm*).

- In general, patients responding to oral iron therapy should see an increase in reticulocyte count within 1 week of therapy followed by an increase in Hgb in 2-4 weeks. Treatment should be continued until the total iron deficit is replete.

- **Parenteral iron therapy** (Table 21-2). There are several formulations of IV iron, and indications for parenteral iron over oral iron include:
  - Poor absorption (e.g., inflammatory bowel disease, malabsorption).
  - Very high iron requirements that cannot be met with oral supplementation (e.g., ongoing bleeding)
  - Intolerance to oral preparations
  - Relative iron deficiency in chronic kidney disease (CKD)

Specific Considerations

- IV iron infusion **should not be given** in patients with an active infection (i.e., fever) due to concern for increased adverse reactions.

TABLE 21-2 IV Iron Preparations

Preparation	IV Administration	Caution
Iron dextran (INFeD, Dexferrum)	The entire dose may be diluted and infused in one setting; 1000 mg can be given over 1 h.	A 0.5-mL test dose should be given; observe patient for at least 1 h prior to full dose.
Iron sucrose (Venofer)	Administered undiluted as slow IV injection or infusion in diluted solution: Injection: 100 mg over 2-5 min 200 mg over 2-5 min Infusion: 100 mg/100 mL over 15 min 300 mg/250 mL over 1.5 h 400 mg/250 mL over 2.5 h >500 mg/250 mL over 3.5 h	
Ferric gluconate (Ferrlecit)	Injection: 125 mg over 10 min Infusion: 125 mg/100 mL over 1 h	
Ferumoxytol (Feraheme)	510 mg over 20 min; given as 2 doses 7 d apart	Observe patient for at least 30 min after administration. Serious hypersensitivity reactions have been observed with rapid IV injection (<1 min).

Ferric carboxymaltose (Injectafer)	750 mg over 15-30 min; given as 2 doses 7 d apart	

- **Iron dextran** (INFeD, Dexferrum) **may be the least expensive and allows for highdose repletion in a single dose**; however, infusion can be complicated by serious side effects including **anaphylaxis**.
  - An IV **test dose** of 0.5 mL should be administered over 5-10 minutes at 30-60 minutes prior to the full dose. Methylprednisolone, diphenhydramine, and 1:1000 epinephrine 1-mg ampule (for SC administration) should be immediately available at all times during the infusion.
  - A dose of 1000 mg can be administered over 1 hour (*Am J Hematol 2011;86(10):860*).
  - Delayed reactions to IV iron, such as arthralgia, myalgia, fever, pruritus, and lymphadenopathy, may be seen within 3 days of therapy and usually resolve spontaneously or with NSAIDs.
- **Second-generation irons** include **ferric gluconate** (Ferrlecit) and **iron sucrose** (Venofer) and can be given at a faster infusion rate than iron dextran. Anaphylaxis is rare, and a test dose is often not needed; however, a single infusion cannot be used to replenish the entire iron deficit. Higher doses of iron sucrose (i.e., >400 mg/250 mL doses) are associated with a higher adverse event rate.
- **Third-generation irons** include **ferumoxytol** (Feraheme) and **ferric carboxymaltose** (Injectafer) and allow for administration of a high dose with a rapid infusion. A rare complication is severe hypotension, which can be related to the rapidity of the injection. Of note, ferumoxytol is also available as an MRI contrast agent, and radiology should be made aware if a patient received ferumoxytol within 3 months of a scheduled MRI study.

Thalassemia

GENERAL PRINCIPLES

Definition

The **thalassemia syndromes** are inherited disorders characterized by reduced Hgb synthesis associated with mutations in either the α- or β-gene of the molecule (Table 21-3).

Etiology

- **β-Thalassemia** results in a decreased production of β-globin and a resultant excess of α-globin, forming insoluble α-tetramers and leading to ineffective erythropoiesis.
  - **β-Thalassemia minor (trait)** occurs with one gene abnormality with underproduction of β-chain globin. Patients are asymptomatic and present with microcytic, hypochromic RBCs and Hgb levels >10 g/dL.
  - **β-Thalassemia intermedia** occurs with dysfunction in both β-globin genes so that anemia is more severe (Hgb, 7-10 g/dL).
  - **β-Thalassemia major** (Cooley anemia) is caused by severe abnormalities of both genes that produce no β-globin and generally requires lifelong transfusion support.
- **α-Thalassemia** occurs with a deletion of one or more of the four β-globin genes, leading to a β-globin excess.

- Mild microcytosis and mild hypochromic anemia (Hgb >10 g/dL) are seen with the loss of one or two α-globin genes (silent carrier and α-thal trait), whereas Hgb H disease (deletion of three α-globin genes) results in splenomegaly and hemolytic anemia.
- In patients with Hgb H disease, transfusion or splenectomy is often not necessary until after the second or third decades of life. In addition, oxidant drugs similar to those that

exacerbate glucose-6-phosphate dehydrogenase (G6PD) deficiency should be avoided because increased hemolysis may occur.

TABLE 21-3 Thalassemias

	Genotype	Hemoglobin (g/dL)	Mean Corpuscular Volume (fL)	Transfusion Dependent
α-Thalassemia				
Silent carrier	αα/α-	Normal	None	No
Trait	α-/α- or αα/--	>10	<80	No
Hemoglobin H	α-/--	7-10	<70	+/-
Hydrops fetalis	α-/--	Incompatible with life		
β-Thalassemia (Thal)				
Silent carrier	β/β^1	>10	<80	No
β-Thal minor (trait)	β/β^0	>10	<80	No
β-Thal intermedia	β^1/β^1	7-10	65-75	+/-
β-Thal major	β^1/β^0 or β^0/β^0	<7	<70	Yes

β^+, β-thalassemia genes produce some β-globin chains but with impaired synthesis; β^0, β-thalassemia genes produce no β-globin chains.

- Hydrops fetalis occurs with the loss of all four α-globin genes and is incompatible with life.

DIAGNOSIS

Diagnostic Testing

- Peripheral smear may show microcytic hypochromic RBCs, along with poikilocytosis and nucleated RBCs.
- Hgb electrophoresis is diagnostic for β-thalassemia showing an increased percentage of Hgb A2 (α2δ2) and Hgb F (α2γ2).
- Silent carriers with a single α-chain loss have an essentially normal electrophoresis. Those with Hgb H disease have increased Hgb H (β-tetramers). The diagnosis of β-thalassemia is made by α-globin gene analysis.

TREATMENT

- Patients with thalassemia trait require no specific treatment.
- In patients with more severe forms of the disease, RBC transfusions to maintain an Hgb level of 9-10 g/dL are needed to prevent the skeletal deformities that result from accelerated erythropoiesis.
- In severe forms of thalassemia, repeated transfusions result in tissue iron overload, which may cause congestive heart failure (CHF), hepatic dysfunction, glucose intolerance, and secondary hypogonadism. **Iron chelation therapy** delays or prevents these complications. Once clinical organ deterioration has begun, it may not be reversible.
- **Chelation therapy** is indicated for transfusion-associated iron overload from any cause. It is indicated in patients with iron infusion burden of >20 units of packed RBCs and ferritin consistently >1000 ng/mL.
  - Deferoxamine, 40 mg/kg SC or IV over 8-12 hours continuous infusion (*N Engl J Med 2011;364(2):146*).
  - Deferasirox 20-40 mg/kg/d (as Exjade) is an effective oral agent. Side effects of deferasirox include moderate to severe GI disturbances and skin rash. A recently available formulation of deferasirox (Jadenu) is dosed at 70% of Exjade and seems to be better tolerated. Dose can be titrated every 3-6 months based on ferritin level. Efficacy is similar to that of deferoxamine.
  - Chelation therapy should be continued until ferritin levels of <1000 mg/L are maintained.
- Hydroxyurea (15-35 mg/kg/d) to increase Hgb F may reduce transfusion requirements in some patients with β-thalassemia.
- Stem cell transplantation (SCT) is the only curative therapy and should be considered in young patients with thalassemia major who have HLA-identical donors. Gene therapy is the subject of ongoing research and holds promise (*Blood 2011;118(13):3479*).

Surgical Management

Splenectomy should be considered in patients with accelerated (more than two units/month) transfusion requirements. To decrease the risk of postsplenectomy sepsis, immunization against *Pneumococcus*, *Haemophilus influenzae*, and *Neisseria meningitidis* should be administered at least 2 weeks before surgery if not previously vaccinated (see Appendix A, Immunizations and Postexposure Therapies). Splenectomy is not recommended if the patient is younger than 5-6 years because of the risk of sepsis.

Sideroblastic Anemias

GENERAL PRINCIPLES

Definition

Sideroblastic anemias are hereditary or acquired RBC disorders characterized by abnormal iron metabolism associated with the presence of ring sideroblasts in the BM aspirate and normal cytogenetics.

Etiology

- Acquired
  - Primary sideroblastic anemia (myelodysplastic syndrome [MDS])
  - Sideroblastic anemia secondary to drugs (i.e., chloramphenicol, cycloserine, ethanol, isoniazid, pyrazinamide), lead or zinc toxicity, chronic ethanol use, or copper deficiency
- Hereditary
  - X-linked
  - Autosomal
  - Mitochondrial

DIAGNOSIS

A BM examination including cytogenetics is needed to evaluate for the presence of ring sideroblasts or other abnormal marrow forms.

TREATMENT

- Remove any possible offending agent.
- Pyridoxine 50-200 mg daily may be used to treat hereditary sideroblastic anemias.

Macrocytic/Megaloblastic Anemia

GENERAL PRINCIPLES

Definition

Megaloblastic anemia is a term used to describe disorders of impaired DNA synthesis in hematopoietic cells but that affect all proliferating cells.

Etiology

- Almost all cases are due to folic acid or vitamin B_{12} deficiency.
- **Folate deficiency** results from a negative folate balance arising from malnutrition, malabsorption, or increased requirement (pregnancy, hemolytic anemia).

- Patients on slimming diets, alcoholics, the elderly, and psychiatric patients are particularly at risk for nutritional folate deficiency.
- **Pregnancy and lactation** require three- to fourfold increased daily folate needs and are commonly associated with megaloblastic changes in maternal hematopoietic cells, leading to a dimorphic (combined folate and iron deficiency) anemia.
- Folate malabsorption can also be seen in celiac disease.
- Drugs that can interfere with folate absorption include ethanol, trimethoprim, pyrimethamine, diphenylhydantoin, barbiturates, and sulfasalazine.
- Dialysis-dependent patients require more folate intake because of increased folate losses.

- Patients with hemolytic anemia, such as sickle cell anemia, require increased folate for accelerated erythropoiesis and can present with aplastic crisis (rapidly falling RBC counts) with folate deficiency.

- **Vitamin B_{12} deficiency** occurs insidiously over 3 or more years because daily vitamin B_{12} requirements are low (6-9 µg/d), whereas total body stores are 2-5 mg.
  - Because multivitamins, bread, and cereals are enriched in folic acid, the hematologic manifestations of vitamin B_{12} deficiency may be obscured, and neurologic symptoms may be the sole presenting features.
  - Vitamin B_{12} deficiency occurs in up to 20% of untreated patients within 8 years of partial gastrectomy and in almost all patients with total gastrectomy or pernicious anemia (PA). Older patients with gastric atrophy may develop a food-bound vitamin B12 deficiency in which vitamin B12 absorption is impaired. In nonvegan adults, vitamin B12 deficiency is almost always due to malabsorption.
  - PA usually occurs in individuals who are older than 40 years (mean age of onset, 60 years). Up to 30% of patients have a positive family history. PA is associated with other autoimmune disorders (Graves disease 30%, Hashimoto thyroiditis 11%, and Addison disease 5-10%). Of patients with PA, 90% have antiparietal cell immunoglobulin (IgG) antibodies, and 60% have anti-intrinsic factor antibodies.
  - Other etiologies include pancreatic insufficiency, bacterial overgrowth, and intestinal parasites (*Diphyllobothrium latum*).

DIAGNOSIS

Clinical Presentation

- Folate-deficient patients may present with sleep deprivation, fatigue, and manifestations of depression, irritability, or forgetfulness.
- In addition to symptoms of anemia, vitamin B_{12} deficiency may demonstrate neurologic symptoms, such as peripheral neuropathy, paresthesias, lethargy, hypotonia, and seizures.
- Important physical findings include signs of poor nutrition, pigmentation of skin creases and nail beds, or glossitis. Jaundice or splenomegaly may indicate ineffective and extramedullary hematopoiesis. Vitamin B12 deficiency may cause decreased vibratory and positional sense, ataxia, paresthesias, confusion, and dementia. Neurologic complications may occur even in the absence of anemia and may not fully resolve despite adequate treatment. **Folic acid deficiency does not result in neurologic disease.**

Diagnostic Testing

Laboratories

- Macrocytic anemia is usually present unless there is also a coincident cause of microcytic anemia present, and leukopenia and thrombocytopenia may occur.
- The peripheral smear may show anisocytosis, poikilocytosis, and macro-ovalocytes; hypersegmented neutrophils (containing more than six nuclear lobes) are common.
- Lactate dehydrogenase (LDH) and indirect bilirubin are typically elevated, reflecting ineffective erythropoiesis and premature destruction of RBCs (intramedullary hemolysis).
- Serum vitamin B_{12} and folate levels should be measured.
- RBC folate is a more accurate indicator of body folate stores than serum folate, particularly if measured after folate therapy or improved nutrition has been initiated.
- **Serum methylmalonic acid (MMA) and homocysteine (HC)** may be useful when the vitamin B_{12} is between 100-400 pg/mL (or borderline low per the laboratory reference range). MMA and HC are elevated in vitamin B_{12} deficiency; only HC is elevated in folate deficiency.
- Detecting **antibodies to intrinsic factor** is specific for the diagnosis of PA.

Diagnostic Procedures

BM biopsy may be necessary to rule out MDS or acute leukemia because these disorders may present with findings similar to those of megaloblastic anemia.

TREATMENT

- Potassium supplementation may be necessary when treatment is initiated to avoid potentially serious arrhythmias due to transient hypokalemia induced by enhanced hematopoiesis.
- Reticulocytosis should begin within 1 week of therapy, followed by a rising of Hgb over 6-8 weeks.
- Coexisting iron deficiency is present in one-third of patients and is a common cause for an incomplete response to therapy.
- Folic acid 1 mg daily is given until the deficiency is corrected. High doses of folic acid (5 mg daily) may be needed in patients with malabsorption syndromes.
- Vitamin B_{12} deficiency is corrected by administering cyanocobalamin. Initial treatment (1 mg/d intramuscular cyanocobalamin) is typically administered in the setting of severe anemia, neurologic dysfunction, or chronic malabsorption. After 1 week of daily therapy, a commonly employed regimen is 1 mg/wk given for 4 weeks and then 1 mg/month for life.
- High-dose enteral therapy (1000-2000 µg/d PO) may be considered in those without neurologic involvement who refuse parenteral therapy (*Blood 2008;112:2214*).
- After the initial repletion, patients who decline or cannot take parenteral therapy may be prescribed oral cyanocobalamin tablets or syrup 1000 µg/d as maintenance.

Anemia of Chronic Renal Insufficiency

GENERAL PRINCIPLES

Anemia of chronic renal insufficiency is attributed primarily to decreased endogenous erythropoietin (EPO)

production and may occur as the creatinine clearance declines to below 50 mL/min. Other causes including iron deficiency may contribute to the etiology (see the previous description).

DIAGNOSIS

- Laboratory evaluation typically reveals a normal MCV.
- Peripheral smear: The RBCs are often hypochromic, with the occasional presence of echinocytes (burr cells).
- If the patient's creatinine level is >1.8 mg/dL, the primary cause of the anemia can be assumed to be EPO deficiency and/or iron deficiency, and an EPO level is unnecessary.
- Iron status should be evaluated in patients who are undergoing dialysis by obtaining levels of ferritin and transferrin saturation. Oral iron supplementation is not effective in CKD; therefore, parenteral iron to maintain a ferritin level of >500 ng/mL is recommended (*Kidney Int 2005;68:2846*).

TREATMENT

- Treatment has been revolutionized by erythropoiesis-stimulating agents (ESAs) including epoetin alfa and darbepoetin alfa (Table 21-4).
- Therapy is initiated in predialysis patients who are symptomatic.
- Objective benefits of reversing anemia include enhanced exercise capacity, improved cognitive function, elimination of RBC transfusions, and reduction of iron overload.

Subjective benefits include increased energy, enhanced appetite, better sleep patterns, and improved sexual activity.

TABLE 21-4 Erythropoietin Dosing

	Agent and Initial Dose (SC or IV)	
Indication	Erythropoietin[a]	Darbepoetin[b]
Chemotherapy-induced anemia from nonmyeloid malignancy, multiple myeloma, lymphoma; anemia secondary to malignancy or myelodysplastic syndrome	40,000 units/wk or 150 units/kg 3 times a week	2.25 µg/kg/wk or 100 µg/wk or 200 µg/2 wk or 500 µg/3 wk
Anemia associated with renal failure	50-150 units/kg 3 times a week	0.45 25 µ/kg/wk
Anemia associated with HIV infection	100-200 units/kg 3 times a week	Not approved
Anemia of chronic disease	150-300 units/kg	Not approved

	3 times a week	
Anemia in patients unwilling or unable to receive RBCs; anemic patients undergoing major surgery	600 units/kg/wk × 3 300 units/kg/d × 1-2 wk	Not recommended

RBC, red blood cell.

[a]Dose increase after 48 weeks up to 900 units/kg/wk or 60,000 units/wk; discontinue if hematocrit (Hct) is >40%; resume when Hct is <36% at 75% of previous dose.

[b]Dose increase after 6 weeks up to 4.5 mg/kg/wk or 150 mg/wk or 300 mg/2 wk; hold dose if Hct is >36%, then resume when Hct is <36% at 75% of previous dose.

- Administration of ESAs can be IV (hemodialysis patients) or SC (predialysis or peritoneal dialysis patients). In dialysis and predialysis patients with CKD, **the target Hgb should be between 11-12 g/dL and should not exceed 12 g/dL**. Hgb and Hct should be measured at least monthly while receiving an ESA. Dose adjustments should be made to maintain the target Hgb. The US Food and Drug Administration (FDA) requires ESA prescribers to be certified by a risk evaluation and mitigation strategy (REMS).
- Side effects of ESAs: Targeting higher Hgb levels and/or exposure to high doses of ESAs is associated with a greater risk of cardiovascular complications and mortality. In addition, a higher Hct level from ESAs increases the risk of stroke, heart failure, hypertension, and deep vein thrombosis (*N Engl J Med 2006;355:2085*).
- **Suboptimal responses to ESA therapy** are most often due to iron deficiency, inflammation, bleeding, infection, malignancy, malnutrition, and aluminum toxicity.
  - Because anemia is a powerful determinant of life expectancy in patients on chronic dialysis, IV iron administration has become first-line therapy for individuals with transferrin saturation <20% and/or ferritin <500 ng/mL. It has also been shown to reduce the ESA dosage required to correct anemia.
  - A ferritin level and transferrin saturation should be tested at least monthly during the initiation of ESA therapy with a goal ferritin level of >200 ng/mL and a transferrin saturation of >20% in dialysis-dependent patients and a ferritin level of >100 ng/mL and a transferrin saturation of >20% in predialysis or peritoneal dialysis patients.
  - Iron therapy is unlikely to be useful if the ferritin level is >500 ng/mL.
  - Secondary hyperparathyroidism that causes BM fibrosis and relative ESA resistance may also occur.

Anemia of Chronic Disease

GENERAL PRINCIPLES

- Anemia of chronic disease (ACD) often develops in patients with long-standing inflammatory diseases, malignancy, autoimmune disorders, and chronic infection.

- Etiology is multifactorial, including defective iron mobilization during erythropoiesis, inflammatory cytokine-mediated suppression of erythropoiesis, and impaired EPO response to anemia. Hepcidin is a critical regulator of iron homeostasis and is normally low when iron is deficient, allowing for increased iron absorption and utilization. Chronic inflammation increases hepcidin levels and causes a functional iron deficiency due to impaired iron recycling and utilization. Hepcidin is renally cleared, suggesting a role in anemia of chronic renal disease (*Biochim Biophys Acta 2012; 1823(9):1434*).

DIAGNOSIS

- Anemia is normocytic in 75% of cases and microcytic in the remainder of cases.
- The soluble transferrin receptor level is helpful in differentiating ACD (normal) and iron deficiency (elevated) when the ferritin is indeterminate. Measurement of serum hepcidin may become part of the standard evaluation of anemia when the assay becomes widely available.
- Iron studies may show low serum iron and TIBC.
- Ferritin level below 30 ng/mL suggests coexisting iron deficiency and should be treated with supplemental iron. Clinical responses to IV iron therapy may occur in patients with ferritin levels up to 100 ng/mL.

TREATMENT

- Therapy for ACD is directed toward the underlying disease and eliminating exacerbating factors such as nutritional deficiencies and marrow-suppressive drugs.
- Note that IV iron should not be administered in the setting of active infection. Enteral iron is typically ineffective in ACD due to reduced intestinal absorption of iron.
- ESA therapy should be considered if the patient is transfusion dependent or has symptomatic anemia. ESA therapy is discontinued when the Hgb is >11 g/dL to reduce risk of cardiovascular adverse events. Suboptimal (<1 g/dL) increase in Hgb 2 weeks after ESA dose prompts a reevaluation of iron stores.
  - Effective doses of ESA are higher than those reported in anemia from renal insufficiency.
  - If no responses have been observed at 900 units/kg/wk, further dose escalation is unlikely to be effective.

Anemia in Cancer Patients

Although ESA therapy has been shown to reduce transfusion requirements in chemotherapyrelated anemia, their use remains controversial due to evidence of increased mortality risk in cancer patients (*Cochrane Database Syst Rev 2012;12:CD003407*). In addition, ESAs are ineffective in patients who are not receiving chemotherapy and have not been shown to increase quality of life (*J Clin Oncol 2005;23:5960*). They confer an elevated risk of thrombosis likely regardless of baseline Hgb level. Current guidelines recommend ESA therapy should only be considered in transfusion-dependent patients with Hgb level <10 g/dL

who are receiving chemotherapy with palliative intent and do not have high risks for thromboembolism. As of 2010, the FDA requires prescribers to enroll in a REMS program termed APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs), which provides written documentation that adequate patient counseling of the risks has been performed.

Anemia Associated with HIV Disease

- Anemia is the most common cytopenia in patients with HIV; the prevalence increases as the disease progresses and the CD4 count drops (*Am J Med 2004;116(suppl 7A):27S*).
- *Mycobacterium avium* complex infections are frequently associated with severe anemia. Diagnosis is established on BM examination or culture. Treatment of *M. avium* complex is described in Chapter 16, Sexually Transmitted Infections, Human Immunodeficiency Virus, and Acquired Immunodeficiency Syndrome.
- Parvovirus B19 should be considered in HIV-infected patients with transfusiondependent anemia and a low reticulocyte count.
  - Laboratory studies: Parvovirus by polymerase chain reaction from serum or BM.
  - Treatment with IV immunoglobulin (IVIG) 0.4 g/kg daily for 5-10 days results in erythropoietic recovery. Relapses have occurred between 2-6 months and can be successfully managed with maintenance IVIG at a dose of 0.4 g/kg IV every 4 weeks (*Ann Intern Med 1990;113(12):926*).

Aplastic Anemia

GENERAL PRINCIPLES

- Aplastic anemia (AA) is a disorder of hematopoietic stem cells that usually presents with pancytopenia.
- Most cases are acquired and idiopathic, but AA can also arise from an inherited BM failure syndrome such as Fanconi anemia. Approximately 20% of cases may be associated with drug or chemical exposure (Table 21-5).
- 10% of cases are associated with viral illnesses (e.g., viral hepatitis, Epstein-Barr virus, cytomegalovirus [CMV]).

DIAGNOSIS

Diagnostic Criteria

AA is a diagnosis of exclusion, and other causes of pancytopenia should be ruled out. Prognosis in AA is dependent on disease severity and patient age (*Br J Haematol 2009; 147(1):43*):

- Moderate or nonsevere AA
  - BM cellularity <30%
  - Absence of criteria for severe AA
  - At least two of three blood lines are lower than normal
- Severe AA
  - BM cellularity <25% with normal cytogenetics, OR
  - BM cellularity <50% with normal cytogenetics, and <30% residual hematopoietic cells, AND two of three peripheral blood criteria:
    - Absolute neutrophil count (ANC) <500/µL
    - Platelet count <20,000/µL
    - Absolute reticulocyte count <20,000/µL
  - No other hematologic disease

TABLE 21-5 Commonly Used Drugs That Can Induce Red Blood Cell Disorders

Sideroblastic Anemia	Aplastic Anemia[a]	G6PD Deficiency	Immune Hemolytic Anemia
Chloramphenicol	Acetazolamide	Dapsone	Cephalosporins (cefotetan, ceftriaxone)
Cycloserine	Antineoplastic drugs	Doxorubicin	Penicillins (piperacillin)
Ethanol	Carbamazepine	Methylene blue	Purine nucleoside analogues (fludarabine, cladribine)
Isoniazid	Chloramphenicol	Nalidixic acid	NSAIDs (diclofenac, ibuprofen)
Pyrazinamide	Gold salts	Nitrofurantoin	Quinidine
	Hydantoins	Phenazopyridine	Quinine
	Penicillamine	Primaquine	Rifampin
	Sulfonamides	Sulfacetamide	Sulfonamides (trimethoprim/sulfamethoxazole)
	Phenylbutazone	Sulfamethoxazole	
	Quinacrine	Sulfanilamide	
		Sulfapyridine	

G6PD, glucose-6-phosphate dehydrogenase.

[a]Drugs with .30 cases reported; many other drugs rarely are associated with aplastic anemia and are considered low risk.

Data compiled from multiple sources. Agents listed are available in the United States.

- Very severe AA
  - The criteria of severe AA are met, AND
  - ANC <200/μL

Diagnostic Testing

BM biopsy is required for diagnosis. Morphology of BM may be difficult to distinguish from hypocellular MDS and paroxysmal nocturnal hemoglobinuria (PNH). Evidence of dysplasia or abnormal cytogenetics is suggestive of MDS. PNH clones can be detected by flow cytometry of the blood or BM.

TREATMENT

- Suspected offending drugs should be discontinued and exacerbating factors corrected. Rarely, spontaneous recovery of normal hematopoiesis can occur, usually within 1-2 months of discontinuing the offending drug.
- Once the diagnosis is established, care should be provided in a center experienced with AA.
- Therapy is optional in moderate AA unless there is transfusion dependence; however, severe or very severe AA requires urgent treatment given the high risk of infectious and hemorrhagic complications.
- AA typically does not respond to EPO. Granulocyte colony-stimulating factor may be effective in some patients and can be used while awaiting definitive therapy; however, there is no clear evidence of survival benefit with the use of these agents.

- Immunosuppressive treatment with cyclosporine and antithymocyte globulin (ATG) should be considered in patients with severe AA who do not undergo an SCT (*Blood 2012;120(6):1185-96*). Overall response rate at 3 months is between 60-80%, and most responses occur by 6 months.

- Corticosteroids have not been shown to be effective and can increase the risk of infections and **should not** be used in the treatment of AA.
- **SCT.** Early referral to a center that is experienced in managing AA is recommended. When feasible, SCT from an HLA-identical sibling is generally recommended and has achieved a long-term survival rate of 60-70%.
- **Transfusions in AA.** Transfusions with RBCs should be kept to a minimum. Prophylactic platelet transfusions are generally recommended if the platelet count is <10,000/μL. Transfusion of irradiated, leukocyte-depleted blood products is preferred to decrease the risk of alloimmunization.
- **Eltrombopag**, 50-150 mg/d, a thrombopoietin agonist, has been shown to be effective in some patients who do not respond to cyclosporine and ATG and may be an option for patients with refractory severe AA (*Blood 2014;123(12):1818-25*).

ANEMIAS ASSOCIATED WITH INCREASED RED BLOOD CELL DESTRUCTION

Anemias Associated with Increased Erythropoiesis

GENERAL PRINCIPLES

Definition

Anemias associated with increased erythropoiesis (i.e., an elevated reticulocyte count) are caused by bleeding or destruction of RBCs (hemolysis) and may exceed the capacity of normal BM to correct the Hgb. Bleeding is much more common than hemolysis.

Etiology

- **Blood loss.** If no obvious source, suspect occult loss into GI tract, retroperitoneum, thorax, or deep compartments of thigh depending on history (recent instrumentation, trauma, hip fracture, coagulopathy).
- **Hemolysis** can be categorized into two broad groups based on the cause of destruction: intrinsic (caused by deficits inherit to the RBC) and extrinsic (caused by factors external to the RBC).
  - In general, intrinsic causes are inherited, whereas extrinsic causes tend to be acquired. Intrinsic disorders are a result of defects of the red cell membrane (i.e., hereditary spherocytosis), Hgb composition (i.e., sickle cell disease), or enzyme deficiency (i.e., G6PD deficiency).
  - Extrinsic disorders can result from antibodies (i.e., cold or warm reactive immunoglobulin), infectious agents (i.e., malaria), trauma, chemical agents (i.e., venom), or liver disease.
  - Hemolytic disorders are also commonly categorized by the location of RBC destruction: intravascular (within the circulation) or extravascular (within the macrophagemonocyte system typically in the liver or spleen).

DIAGNOSIS

Laboratory assessment of patients with suspected hemolysis should include:

- **Decreased Hgb** and **Hct**.
- **Elevated reticulocyte count** (occurs within 3-5 days of onset).
- **Elevated LDH** and **indirect hyperbilirubinemia** reflect increased RBC turnover.
- **Decreased haptoglobin** due to binding of intravascular Hgb.
- The **direct Coombs test** (direct antiglobulin testing [DAT]) is an indicator of the presence of antibodies or complement bound to RBC.

- The **indirect Coombs test** indicates the presence of antibody in the plasma.
- A peripheral blood smear is essential and can aid in determining the etiology of hemolysis. Intravascular hemolysis may reveal red cell fragmentation (i.e., schistocytes, helmet cells), whereas spherocytes indicate extravascular hemolysis. Polychromasia and nucleated RBCs are indicators of increased erythropoiesis.

Sickle Cell Disease

GENERAL PRINCIPLES

- Sickle cell disease (SCD) is a group of hereditary Hgb disorders in which Hgb undergoes a sickle shape transformation under conditions of deoxygenation.
- The most common are homozygous sickle cell anemia (Hgb SS) or other doubleheterozygous conditions (Hgb SC, Hgb S-β°, or Hgb S-β+ thalassemia).
- Newborn screening programs for hemoglobinopathies identify most patients in infancy.
- In the United States, the incidence of SCD is approximately 1 in 625 births.
- **Sickle cell trait** is present in 8-10% of African Americans (*N Engl J Med 1973;288:31*). It is generally considered to be a benign hereditary condition, but high-altitude hypoxia is associated with splenic infarction, whereas intense physical exertion has been associated with sudden death.
- Sickle cell trait has been associated with an increased risk of CKD; thus, minimizing other risk factors for kidney disease is likely to benefit these patients (*JAMA 2014;312(20):2115-25*).

DIAGNOSIS

Diagnostic Testing

- Hgb analysis by high-pressure liquid chromatography is most commonly used in the diagnosis of hemoglobinopathies.
- Laboratory abnormalities include anemia (mean Hgb in SCD, 8 g/dL), reticulocytosis (3-15%), indirect hyperbilirubinemia, elevated LDH, and decreased or absent haptoglobin. Leukocytosis (10,000-20,000/μL) and thrombocytosis (>450,000/μL) are common, due to enhanced stimulation of the marrow compartment and autosplenectomy.
- Peripheral smear shows sickle-shaped RBCs, target cells (particularly in Hgb SC and Hgb S-β thalassemia), and Howell-Jolly bodies, indicative of functional asplenism.

Clinical Presentation

- Clinical presentation of SCD is heterogeneous and is dependent on type and degree of hemoglobinopathy. The most common clinical manifestations of SCD result from hemolysis and/or

vascular occlusions.

- Vascular occlusions include pain crises, avascular necrosis, priapism, and acute chest syndrome, whereas hemolytic complications include pulmonary hypertension, cholelithiasis, and leg ulcers. Strokes and renal medullary infarctions are complications of both.
- **Vaso-occlusive complications (VOCs)** result from polymerization of deoxygenated Hgb S. These polymerized RBCs assume the classic sickle shape and develop a marked loss of deformability, leading to vaso-occlusion.
  - **Acute painful episodes ("sickle cell pain crisis")**
    - Sickle cell pain crisis is the most common VOC and manifestation of SCD.
    - Pain is typically in the long bones, back, chest, and abdomen.
    - Precipitating factors can include stress, infection, dehydration, alcohol, and weather. However, a majority of cases have no identifiable trigger.

    - Typical duration of the episode is 2-6 days.
    - Higher levels of fetal Hgb (Hgb F) seem to be protective against VOC.
  - **Acute chest syndrome** is a life-threatening emergency that occurs when decreased oxygen saturation (<90%) leads to increased intravascular sickling and irreversible occlusion of the microvasculature in the pulmonary circulation. It is diagnosed based on a pulmonary infiltrate involving at least one complete segment and one of the following: fever, hypoxemia, tachypnea, respiratory failure, chest pain, or wheezing. ACS precipitated by infection tends to be less severe than pulmonary embolism or fat emboli as the inciting events.
  - **Priapism** often presents in adolescence and may result in impotence.
  - **Retinopathy** is caused by chronic vaso-occlusion of the retina, which causes proliferative retinopathy and may lead to complications including vitreous hemorrhage and retinal detachment.
  - **Functional asplenia** results from recurrent splenic infarcts due to sickling and eventually results in the loss of splenic function. The majority of cases occur before the age of 1 year. Functional asplenia places patients at higher risk of infection, especially with encapsulated organisms.
  - **Avascular necrosis (AVN)** is the result of infarction of bone trabeculae and occurs most commonly in the femoral and humeral heads. Up to 50% of adults affected by SCD can manifest AVN, which is a leading cause of pain and disability.
- **Hemolytic complications**
  - **Cholelithiasis** is present in >80% of patients and is primarily due to bilirubin stones. It may lead to acute cholecystitis or biliary colic.
  - **Leg ulceration** occurring at the ankle is often chronic and recurring.
  - **Pulmonary hypertension** has been linked to several hemolytic disorders and can occur in up to 60% of patients with SCD (*N Engl J Med 2004;350:857*). The pathophysiology is unclear but may be the result of nitric oxide depletion.
- **Renal medulla infarction** is the result of repeated occlusion of renal medullary capillaries, resulting in CKD in many patients. This can lead to isosthenuria (inability to concentrate urine) and hematuria, predisposing patients to dehydration and thus increasing the risk of VOC.
- **Neurologic complications** occur in up to 25% of patients with SCD by the age of 45 years (*Am J Med 1978;65:461*) and include cerebrovascular accidents (transient ischemic attacks, infarction, cerebral

hemorrhage), seizure, and sensory hearing loss. Ischemic stroke is felt to result from recurrent endothelial injury from hemolysis and vaso-occlusion, resulting in intimal hyperplasia with large-artery vasculopathy (*Stroke 2011;42:227*). High cerebral flow rate (>200 cm/s) detected by transcranial Doppler has been associated with increased risk of stroke in children. This risk is greatly reduced by routine transfusion or exchange therapy (*N Engl J Med 1998;339:5*). Current recommendations for adults include evaluation for known additional stroke risk factors with management accordingly (*Circulation 2006;113:e873*).

- **Infections** typically occur in tissues susceptible to vaso-occlusive infarcts (i.e., lungs, bone, kidney). The most common infectious organisms include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Salmonella* spp., *Mycoplasma pneumoniae*, or *H. influenzae*. Vaccinations are a key mechanism in prevention.
- **Aplastic "crisis"** occurs when there is a transient halt of erythropoiesis due to an inciting event causing a sudden decrease in Hgb. The most common etiology in children with SCD is parvovirus B19 infection. Folate deficiency should also be suspected because of the chronic increased requirements for erythropoiesis.
- **Pregnancy** in a patient with sickle cell anemia should be considered high risk and is associated with increased spontaneous abortions or premature delivery, along with increased occurrence of vaso-occlusive crises.

TREATMENT

- Evidence-based management of SCD has been recently updated and is available online at *http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines*.
- **Acute painful episodes.** Management of **acute painful episodes** consists of rehydration (3-4 L/d), evaluation for and management of infections, analgesia, and if needed, antipyretic and empiric antibiotic therapy.
  - **Opioids** (see Chapter 1, Inpatient Care in Internal Medicine, see the section on opioids in the Medication section, under Pain) are typically used and are effectively administered by a **patient-controlled analgesia pump**, allowing the patient to self-administer medication within a set limit of infusions (lockout interval) and basal rate. Morphine (2 mg/h basal rate with boluses of 2-10 mg every 6-10 minutes) is the drug of choice for moderate or severe pain. If patient-controlled analgesia is not used, morphine (0.1-0.2 mg/kg IV q2-3h) or hydromorphone (0.02-0.04 mg/kg IV q2-3h) is recommended.
  - Transfusion therapy has no role in the treatment of uncomplicated vaso-occlusive crises.
  - Supplemental oxygen does not benefit acute pain crisis unless hypoxia is present.
- **Acute chest syndrome.** Multimodal treatment includes adequate analgesia, volume resuscitation, supplemental oxygen and incentive spirometry, and blood transfusion. It is unclear whether exchange transfusion is superior to simple RBC transfusion; however, it is standard practice to perform exchange transfusion for moderate to severe cases, whereas simple transfusion to >10 g/dL for mild cases may be sufficient. The presentation of acute chest syndrome is clinically indistinguishable from pneumonia; thus, empiric broad-spectrum antibiotics should also be administered.
- **Priapism** is initially treated with hydration and analgesia. Persistent erections for more than 24 hours may require transfusion therapy or surgical drainage.

- **AVN** management consists of local heat, analgesics, and avoidance of weight bearing. Hip and shoulder arthroplasty are often effective at decreasing symptoms and improving function.
- **Cholelithiasis.** Induced acute cholecystitis should be treated medically with antibiotics followed by cholecystectomy when the attack subsides. Elective cholecystectomy for asymptomatic gallstones is controversial.
- **Leg ulcers** should be treated with rest, leg elevation, and intensive local care. Wet to dry dressings should be applied three to four times per day. A zinc oxide-impregnated bandage (Unna boot), changed weekly for 3-4 weeks, can be used for nonhealing or more extensive ulcers.
- There is no standard therapy for treatment of **pulmonary hypertension** in SCD, with clinical trials of sildenafil showing conflicting results (*Br J Haematol 2005;130:445*; *Blood 2001;118:855*); thus, patients should be referred to a clinical specialist.
- **Acute cerebrovascular accident** should be managed based on current standards. Longterm transfusions to maintain the Hgb S concentration to <50% for at least 5 years significantly reduce the incidence of recurrence.
- Patients with suspected **aplastic crisis** require hospitalization. Therapy includes folic acid, 5 mg/d, as well as supportive RBC transfusions.
- **Iron chelation therapy** can be used to prevent or treat iron overload in patients with high transfusion requirements.

Risk Modification

- **Dehydration and hypoxia** should be avoided because they may precipitate or exacerbate irreversible sickling.
- **Folic acid** (1 mg PO daily) is administered to patients with SCD because of chronic hemolysis.
- **Hydroxyurea** (15-35 mg/kg PO daily) has been shown to increase levels of Hgb F and significantly decreases the frequency of VOC and acute chest syndrome in adults with

SCD (*N Engl J Med 1995;332:1317*). In practice, the dose is increased until the ANCs are between 2000-4000/µL.
- **Antimicrobial prophylaxis** with penicillin VK, 125 mg PO bid to age 3 years and then 250 mg PO bid until age 5 years, is effective at reducing risk of infection (*N Engl J Med 1986;314:1593*). Patients who are allergic to penicillin should receive erythromycin 10 mg/kg PO bid. Prophylaxis should be stopped at age 5 years to avoid development of resistant organisms (*J Pediatr 1995;127:685*).
- **Immunizations** against the usual childhood illnesses should be given to children with SCD, including hepatitis B vaccine. After 2 years of age, a polyvalent pneumococcal vaccine should be administered. Yearly influenza vaccine is recommended.
- **Ophthalmologic examinations** are recommended yearly in adults because of the high incidence of proliferative retinopathy.
- Local and regional anesthesia can be used without special precautions. Care should be taken to avoid volume depletion, hypoxia, and hypernatremia. For surgery with general anesthesia, RBC transfusions to increase the Hgb to 10 g/dL is as effective as more aggressive thresholds to decrease postoperative complications (*N Engl J Med 1995;333:206*).

Glucose-6-Phosphate Dehydrogenase Deficiency

GENERAL PRINCIPLES

G6PD deficiency represents the most common disorder of RBC metabolism worldwide. Deficiency of G6PD renders RBCs more susceptible to oxidative damage through decreased glutathione reduction, leading to chronic or acute episodic hemolysis in the presence of oxidative stress.

Classification

More than 400 variants of G6PD are recognized. The severity of hemolysis depends on the degree of deficiency present (*Blood Rev 2007;21:267*).

- Milder forms, such as those seen in men of African heritage in the United States, result in self-limiting acute hemolytic episodes (G6PD A^-).
- More severe forms, such as the Mediterranean variant, can result in severe hemolysis.
- The most severe type causes a chronic, hereditary, nonspherocytic hemolytic anemia in the absence of an inciting cause.

Epidemiology

- X-linked inheritance; thus degree of involvement in females is dependent on lyonization.
- In the United States, 10% of African American males are affected by a mild form.
- G6PD is felt to be protective against malaria, thus accounting for its prevalence in malaria-stricken areas.
- Hemolysis is triggered by exposure to mediators of oxidative stress (i.e., drugs [see Table 21-5]), infections, and fava beans.

DIAGNOSIS

- Examination of a peripheral blood smear reveals presence of “bite cells” and **Heinz bodies** (represents precipitated Hgb within RBCs).
- Diagnosis is determined by showing deficient amounts of reduced nicotinamide adenine dinucleotide phosphate (NADPH) generated from NADP using quantitative spectrophotometric analysis or rapid fluorescent screening test.
- False-negative results may occur in patients with high levels of reticulocytes or in patients recently transfused because these cells have innately higher levels of G6PD.

TREATMENT

- Hemolytic episodes tend to be self-limiting; the mainstay of treatment is supportive.
- The underlying cause of oxidative stress should be addressed (i.e., treatment of infection, removal of drug).

Autoimmune Hemolytic Anemia

GENERAL PRINCIPLES

Definition

Autoimmune hemolytic anemia (AIHA) results from autoantibodies targeted to antigens on the patient's own RBCs, resulting in extravascular hemolysis (removal of RBC by tissue macrophages in the liver or spleen).

Classification

There are two main causes of AIHA: warm and cold AIHA. Warm AIHA antibodies interact best with RBCs at 37°C, whereas cold AIHA antibodies are most active at temperatures below 37°C and almost always fix complement.

Etiology

- Warm antibody AIHA is usually caused by an IgG autoantibody. It may be idiopathic or secondary to an additional process (i.e., lymphoma, chronic lymphocytic leukemia [CLL], collagen vascular disorder, or drugs [see Table 21-5]).
- Cold antibody AIHA is typically caused by an IgM autoantibody (in cold agglutinin disease).
  - The acute form is often secondary to an infection (*Mycoplasma*, Epstein-Barr virus).
  - The chronic form is usually due to a paraprotein associated with lymphoma, CLL, or Waldenström macroglobulinemia (WM) in approximately one-half of cases and is usually idiopathic in the others.

DIAGNOSIS

Diagnostic Testing

- Laboratory data usually identify hemolysis with anemia, reticulocytosis, elevated LDH, decreased haptoglobin, and indirect hyperbilirubinemia.
- Peripheral blood smear may show spherocytes, occasional fragmented RBCs, polychromasia, and nucleated RBCs.
- The hallmark of diagnosis is by a positive **DAT (also known as a direct Coombs test)**. The DAT detects the presence of IgG or complement bound to the RBC surface and may be falsely negative in cases of IgM-mediated hemolysis.
  - Warm AIHA: IgG+ and/or C3+
  - Cold AIHA: IgG- and C3+
- The indirect antiglobulin test (indirect Coombs) detects the presence of autoantibodies in the serum but also detects alloantibodies in the serum from alternate causes including from transfusion or maternal-fetal incompatibility.
- An elevated cold agglutinin titer is seen with cold AIHA.
- If secondary AIHA is suspected, a workup for the underlying cause should be performed.

TREATMENT

- Initial therapy should be aimed at correcting complications from the hemolytic anemia. Definitive therapy should include identification and treatment of any underlying cause.

- **RBC transfusions may exacerbate hemolysis** with hemolysis of transfused cells. Autoantibodies may confound plasma antibody screens and conventional cross-matches, and therefore, alloantibodies may go undetected. **In life-threatening circumstances, transfusion of universal donor (O negative) blood is appropriate.**
- **Warm AIHA**
  - First-line treatment involves **glucocorticoids**, such as prednisone 1 mg/kg/d, which is effective in 70-80% of patients. They decrease macrophage clearance of antibodycoated RBCs. Response is typically seen in 7-10 days. When hemolysis has abated, glucocorticoids can be tapered over 2-3 months. Rapid steroid taper can result in relapse.
  - Second-line treatments include **splenectomy**, which should be considered for steroidresistant AIHA, and **rituximab**, a monoclonal antibody directed against CD20 antigen expressed on B cells. Rituximab 375 mg/m^2 weekly for four doses has been shown to be effective in 80-90% of cases, and responses to treatment are observed with monotherapy or in combination with corticosteroids (*Haematologica 2014;99(10):1547*). Low-dose rituximab, 100 mg weekly for four doses, has also demonstrated efficacy in AIHA (*Haematologica 2007;92:1695*).
  - Additional immunosuppressive therapies have also been used such as azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil.
  - Treatment for relapsed/refractory cases includes IVIG, danazol, plasma exchange, alemtuzumab, and high-dose cyclophosphamide.
- **Idiopathic cold AIHA**
  - Avoidance of cold exposure can minimize exacerbations. RBC transfusions at 37°C and keeping the room warm can prevent exacerbation of hemolysis.
  - Glucocorticoids and splenectomy have low efficacy in treatment.
  - Plasma exchange removes approximately 80% of IgM, thus offering effective control of the disease.
  - Rituximab has shown to be effective in some cases (*Blood 2004;103(8):2925*).

Drug-Induced Hemolytic Anemia

GENERAL PRINCIPLES

- **Drug-induced hemolytic anemia** is anemia resulting from exposure to a medication. Table 21-5 lists common offending medications.
- Hemolysis occurs by several mechanisms such as drug-induced antibodies, hapten formation, and immune complexes. The most commonly implicated agents are cephalosporins, penicillins, NSAIDs, and quinine or quinidines.

TREATMENT

The initial treatment may be similar to treatment of warm AIHA with corticosteroids if the etiology is unclear, but if drug-induced hemolytic anemia is suspected, the most important treatment is discontinuation of the offending agent.

Microangiopathic Hemolytic Anemia

GENERAL PRINCIPLES

Definition

Microangiopathic hemolytic anemia (MAHA) is a syndrome of traumatic intravascular hemolysis causing fragmentation of the RBCs that are seen on peripheral blood smear (schistocytes). It is not a specific diagnosis but suggests a limited differential diagnosis.

Etiology

Possible causes of MAHA include **mechanical heart valve**, **malignant hypertension**, **vasculitis**, **adenocarcinoma**, **preeclampsia/eclampsia**, **disseminated intravascular coagulation (DIC)**, **thrombotic thrombocytopenic purpura (TTP)**, and **hemolytic-uremic syndrome (HUS)/atypical HUS** (see Chapter 20, Disorders of Hemostasis and Thrombosis, for a discussion of DIC, TTP, and HUS/atypical HUS).

DIAGNOSIS

MAHA is established by confirming the presence of hemolysis with laboratory data and identifying RBC fragments (schistocytes) on peripheral blood smear.

TREATMENT

The treatment depends on the underlying etiology of microangiopathy.

WHITE BLOOD CELL DISORDERS

Leukocytosis and Leukopenia

GENERAL PRINCIPLES

Definition

- Leukocytosis is an elevation in the absolute WBC count (>10,000 cells/μL).
- Leukopenia is a reduction in the WBC count (<3500 cells/μL).

Etiology

- **Leukocytosis**
  - An elevated WBC can be the normal response of BM to an infectious or inflammatory process, steroid, β-agonist or lithium therapy, splenectomy, or stress, and is usually associated with an **absolute neutrophilia**.
  - Occasionally, leukocytosis is due to a primary BM disorder in WBC production, maturation, or death (apoptosis). This may occur in the setting of leukemia or myeloproliferative disorders and can affect any cell in the leukocyte lineage.
  - A "**leukemoid reaction**" is defined as an excessive WBC response usually reserved for neutrophilia (>50,000/μL) due to a reactive cause.

- Lymphocytosis is less commonly encountered and is typically associated with atypical infections (i.e., viral), medication use, or leukemia/lymphoma.

- **Leukopenia**
  - Leukopenia can occur in response to infection (i.e., HIV), inflammation, primary BM disorders (i.e., malignancy), medications, environmental exposure (i.e., heavy metals or radiation), and vitamin deficiencies.
  - Many cases are medication induced (i.e., chemotherapeutic or immunosuppressive drugs).
  - Idiopathic chronic benign neutropenia is often caused by an antineutrophil antibody or an inherited disorder.

DIAGNOSIS

Diagnostic Testing

Laboratories

- Review of the peripheral smear is very helpful in the evaluation of WBC disorders. The presence of blasts is concerning for acute leukemia and warrants emergent evaluation.

- Flow cytometry of the blood may help determine if there is an underlying clonal process in lymphocytosis (i.e., CLL).
- A BCR-ABL molecular study may be warranted in cases of unexplained neutrophilia to diagnose chronic myeloid leukemia (CML), especially if there is associated eosinophilia or basophilia.
- Additional laboratory abnormalities are related to the underlying disorder and may include elevation in LDH and uric acid from high cell turnover in acute leukemia.
- An infectious workup should be performed as indicated, including assessment for HIV.
- Prothrombin time, international normalized ratio, partial thromboplastin time, and fibrinogen should also be considered, especially if acute promyelocytic leukemia is suspected because this can be associated with DIC.

Diagnostic Procedures

A BM biopsy with ancillary studies such as cytogenetics, special stains, and flow cytometry may be required to establish the diagnosis.

TREATMENT

- The primary goal of therapy is treatment of the underlying cause.
- See Chapter 22, Cancer, for the treatment of acute and chronic leukemia.
- If symptoms of **leukostasis** are present (neurologic symptoms, dyspnea, hypoxia, or fever), emergent leukopheresis should be done to decrease WBC burden and relieve symptoms.
- Growth factor support should be considered in patients with chronic neutropenia and ongoing infections until the neutropenia resolves (see Oncologic Emergencies in Chapter 22, Cancer).

PLATELET DISORDERS

Discussed in Chapter 20, Disorders of Hemostasis and Thrombosis.

BONE MARROW DISORDERS

Myelodysplastic Syndrome

Discussed in Chapter 22, Cancer.

Myeloproliferative Disorders

GENERAL PRINCIPLES

Myeloproliferative disorders (MPDs) are a group of disorders characterized by clonal expansion of a hematopoietic stem cell resulting in overproduction of mature, largely functional cells. The 2008 World Health Organization (WHO) designated seven conditions as MPDs, including polycythemia vera (PV), essential thrombocytosis (ET) (discussed in Chapter 22, Cancer), CML (discussed in Chapter 22, Cancer), primary myelofibrosis (PMF), chronic neutrophilic leukemia, chronic eosinophilic leukemia, and mast cell disease (*Cancer 2009;17:3842*). The most common MPDs include PV, ET, CML, and PMF. This section will focus on PV and PMF.

TABLE 21-6 Diagnostic Criteria for Polycythemia Vera

Presence of *JAK2* Mutation	**Absence of *JAK2* Mutation**	
	Four Major **or** Three Major + Two Minor	
	Major Criteria	**Minor Criteria**
Hct >52% in males	Hct >60% in males	Platelets >450,000/μL
Hct >48% in females	Hct >56% in females	Neutrophils >10,000/μL
	Palpable splenomegaly No secondary erythrocytosis Presence of genetic mutations (excludes *JAK2*)	Radiographic splenomegaly Low serum erythropoietin

Hct, hematocrit.

DIAGNOSIS

Diagnostic Criteria

- **PV**

  Criteria for the diagnosis of PV have been updated and include Hct >52% in males or >48% in females in

addition to presence of *JAK2* mutation. In the absence of *JAK2* mutation, four major criteria or three major and two minor criteria need to be met for diagnosis (*N Engl J Med 2006;355:2452*) (Table 21-6).

- **PMF**

  The WHO diagnostic criteria for PMF are listed in Table 21-7 (*Blood 2007;110:1092*). All three major criteria and at least two minor criteria need to be met for the diagnosis.

TABLE 21-7 Diagnostic Criteria for Primary Myelofibrosis

Major Criteria
Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis Not meeting WHO criteria for PV, CML, MDS, or other myeloid neoplasm Presence of *JAK2* or other clonal marker, or no evidence of bone marrow fibrosis due to underlying inflammatory or neoplastic diseases in the absence of a clonal marker
Minor Criteria
Leukoerythroblastosis Increase in serum LDH level Anemia Palpable splenomegaly

CML, chronic myelogenous leukemia; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PV, polycythemia vera; WHO, World Health Organization.

Diagnostic Testing

Laboratories

- Patients with PV typically present with an elevated Hct and platelet count (>400,000/μL), the presence of *JAK2* mutation (>95%), and decreased EPO level.
- Patients with PMF may present with leukocytosis or cytopenias and may have mutations in *JAK2* (50%), *MPL* (10%), or calreticulin (*CALR*) (40%).

Diagnostic Procedures

A BM biopsy should be included in the diagnostic workup of PMF, but not necessarily in PV. Cytogenetic studies should be performed for PMF because they have a significant impact on prognosis (*J Clin Oncol 2011;29(4):392*).

TREATMENT

- **PV:** The main goal of treatment is to decrease the risk of thrombotic complications. Treatment includes

serial phlebotomy along with aspirin 81 mg/d. Hydroxyurea may be added depending on the risk for thrombosis.

- In patients with low risk for thrombosis (age <60 years, no history of thrombosis): serial phlebotomy to keep goal Hct <45% in men and <42% in women.
- Patients with high risk for thrombosis (age >60 years, prior thrombosis) should be treated with serial phlebotomy and hydroxyurea.
- Ruxolitinib 10 mg twice a day, a JAK inhibitor first approved for treatment of myelofibrosis, was recently approved by the FDA for the treatment of PV in patients who fail hydroxyurea therapy. It improves the Hct and improves pruritus (*N Engl J Med 2015;372(5):426*).

- **PMF:** Patients are risk stratified based on several prognostic scoring systems and treatment depends on risk category. Treatment may not be needed for low-risk patients.
  - Low-dose aspirin should be started to decrease the risk of thrombosis in the absence of significant thrombocytopenia.
  - Cytoreductive agents such as hydroxyurea have been used historically to improve leukocytosis but do not significantly improve constitutional symptoms or splenomegaly and can cause myelosuppression.
  - Allogeneic hematopoietic SCT is the only curative therapy and should be considered for high-risk patients.
  - Ruxolitinib is useful for the treatment of patients with intermediate-1 and -2 risk myelofibrosis. It is effective in improving constitutional symptoms and splenomegaly. The main side effect is myelosuppression, and initial dosing is dependent on the platelet count.
  - Splenectomy may be considered for painful splenomegaly in patients intolerant to or not responsive to the JAK inhibitor.
  - Involved-field radiotherapy may also offer symptomatic relief for drug-refractory splenomegaly or sites of extramedullary hematopoiesis; however, the effects are usually transient.

MONOCLONAL GAMMOPATHIES

Monoclonal Gammopathy of Unknown Significance

GENERAL PRINCIPLES

Definition

Monoclonal gammopathy of unknown significance (MGUS) is a commonly occurring premalignant condition characterized by the presence of a small (<10%) population of

neoplastic, clonal plasma cells in the BM that occurs in the absence of any end-organ damage. Progression to a more serious disorder including multiple myeloma, WM, or primary amyloidosis occurs at a rate of approximately 1% per year.

DIAGNOSIS

- Patients with MGUS are asymptomatic and diagnosed when a monoclonal protein is detected on serum protein electrophoresis (SPEP) during workup of an elevated protein or other unrelated clinical finding. Most of the gammopathies are identified as IgG, but gammopathies in all immunoglobulin classes occur.

- Serum free light chain assay is used in both prognosis of MGUS and in the diagnosis of multiple myeloma.
- The Multiple Myeloma International Working Group identified diagnostic criteria for MGUS in 2003. All three criteria are required:
  - Presence of a serum monoclonal protein (M protein) IgG, IgA, or IgM <3 g/dL
  - Presence of clonal BM plasma cells comprising <10% of the marrow
  - Absence of end-organ damage attributed to the underlying plasma cell disorder, such as hypercalcemia, renal insufficiency, anemia, or lytic bone lesions

TREATMENT

There is currently no treatment recommended for MGUS. The vast majority of patients will not progress to a malignant disease. Generally, it is accepted practice to follow these patients annually with an evaluation that includes SPEP, urine protein electrophoresis (UPEP), CBC, serum creatinine, and calcium. If patients develop symptoms concerning for a malignant plasma cell disease, they should undergo an extensive evaluation.

PROGNOSIS

MGUS can evolve into a malignant lymphoproliferative disorder. Factors for higher risk of progression include an M protein >1.5 g/dL, non-IgG monoclonal gammopathy, and abnormal serum free light chain ratio (<0.26 or >1.65).

Multiple Myeloma

Discussed in Chapter 22, Cancer.

Waldenström Macroglobulinemia

WM is an uncommon IgM monoclonal disorder also known as lymphoplasmacytic lymphoma, characterized by mild hematologic abnormalities, and accompanied by tissue infiltration including lymphadenopathy, splenomegaly, or hepatomegaly. Because of its high molecular weight and concentration, IgM gammopathy can lead to hyperviscosity (central nervous system, visual, cardiac) manifestations. In these cases, emergent plasmapheresis to decrease IgM concentration is indicated. Asymptomatic patients may be observed initially, whereas durable responses have been observed in those requiring chemotherapy (*Blood 2014;124(9):1404-11*). The Bruton tyrosine kinase inhibitor ibrutinib received FDA approval in January 2015 based on an overall response rate of 62% in a study of 63 patients with WM (*N Engl J Med 2015;372:1430*).

Amyloidosis

GENERAL PRINCIPLES

Primary (AL) amyloidosis is an infiltrative disorder due to monoclonal, light chain deposition in various tissues most often involving the kidney (renal failure, nephrotic syndrome), heart (nonischemic cardiomyopathy), peripheral nervous system (neuropathy), and GI tract/liver (macroglossia, diarrhea, nausea, vomiting). Unexplained findings in any of these organ systems should prompt evaluation for amyloidosis.

DIAGNOSIS

- SPEP, UPEP, and serum free light chains may detect an M protein that is found in >90% of patients with AL amyloidosis. Congo red staining for amyloid in tissue or marrow establishes the diagnosis, and additional staining may identify the subtype of amyloid.
- Secondary (AA) amyloidosis is caused by chronic inflammation but occasionally may be idiopathic. In the absence of a measurable M protein, consider secondary amyloidosis or transthyretin-related hereditary amyloidosis because these are nonclonal disorders.
- Several effective chemotherapy regimens have been developed during the last decade (*Oncology 2012;26(2):152*). However, treatment of amyloidosis is difficult, and progressive organ failure is frequent. Cardiac involvement generally portends the worst prognosis. Transthyretin-related hereditary amyloidosis may be cured by liver transplantation.

Transfusion Medicine

GENERAL PRINCIPLES

Transfusion is a commonly used therapy for a variety of hematologic and hemostatic disturbances. The benefits and risks must be carefully weighed in each situation because blood products are a limited resource with potentially life-threatening side effects.

TREATMENT

- **Packed RBCs (pRBCs)**. RBC transfusion is indicated to increase the oxygen-carrying capacity of blood in anemic or bleeding patients.
  - Hgb threshold for transfusion (*Ann Intern Med 2012;157:49*):
    - Stable patient, no cardiac risk: 7 g/dL (*N Engl J Med 1999;340:409*).
    - Cardiac risk factors: 8 g/dL (*N Engl J Med 2011;365:2453*).
    - Active acute coronary syndrome: Thresholds have not been established; higher thresholds (8-10 g/dL) may be considered.
  - One unit of pRBCs increases the Hgb level by approximately 1 g/dL or Hct by 3% in the average adult.
  - If the cause of anemia is easily treatable (e.g., iron or folic acid deficiency) and no cerebrovascular or cardiopulmonary compromise is present, it is preferable to avoid transfusion.
- **Fresh frozen plasma (FFP):** Plasma transfusion is used to replace certain plasma proteins, usually coagulation factors, to treat bleeding or as bleeding prophylaxis for patients undergoing invasive procedures.
  - Common indications include:
    - Acquired coagulopathy in a patient with serious or massive bleeding
    - Warfarin overdose with life-threatening bleeding: consider using four-factor (II, VII, IX, X) prothrombin complex concentrates instead
    - Factor deficiencies for which specific factor concentrates are unavailable

  - The usual dose is 10 to 20 mL/kg. One unit of FFP contains approximately 250 mL of plasma and 250 units of factor activity for each factor.

- Plasma should not be used as a volume expander and is usually not indicated in patients who are not currently bleeding, even those with an abnormal PT or activated PTT. In the case of warfarin overdose with a very prolonged PT but no bleeding, vitamin K should be used instead.

- **Platelets:** Platelet transfusion is indicated to prevent or treat bleeding in a thrombocytopenic patient or patients with dysfunctional platelets (e.g., due to aspirin).
  - Platelet count threshold for transfusion (*Ann Intern Med 2015;162:205*):
    - Nonbleeding, stable inpatients: 10×10^9/L (*N Engl J Med 2013;368:1771*).
    - Nonbleeding, stable outpatients: 20×10^9/L.
    - Central line placement in a stable patient: 20×10^9/L.
    - Major invasive procedures or bleeding: 50×10^9/L.
    - High-risk surgery (e.g., neurosurgery) or life-threatening bleeding may require higher thresholds.
  - Most platelet infusions are from a single donor collected by platelet pheresis rather than pooled platelets from a number of individuals
  - One unit of single donor platelets increases the platelet count by 30-50 $\times 10^9$/L.
  - Platelets have a short shelf life (<5 days) and are stored at room temperature; they must never be placed on ice or refrigerated, which can cause platelet activation.
  - **Platelet refractoriness** (poor platelet recovery after transfusion) may be due to immunologic causes (anti-ABO, anti-HLA, or antiplatelet antibodies) or nonimmunologic causes (e.g., sepsis, DIC, fever, active bleeding, splenic sequestration, certain drugs). Immunologic causes are likely if a 10- to 60-minute posttransfusion platelet count shows little increment and may be prevented in future transfusions by the use of ABOand/or HLA-compatible platelets (*Br J Haematol 2008;142:348*).

- **Cryoprecipitate**
  - Cryoprecipitate contains the cold-precipitated portion of plasma and is enriched in the following factors:
    - Fibrinogen
    - von Willebrand factor (vWF)
    - Factor VIII
    - Factor XIII
  - It is most commonly indicated to replace **fibrinogen** in patients with hypofibrinogenemia or DIC, and should not be used to replace vWF or factor VIII, for which specific products exist.
  - One unit increases fibrinogen concentration by approximately 7-8 mg/dL. Doses are frequently ordered in pools of 5 or 10 units.

SPECIAL CONSIDERATIONS

- **Pretransfusion testing**
  - The **type and screen** procedure tests the recipient's RBCs for the A, B, and D (Rh) antigens and also screens the recipient's serum for antibodies against other RBC antigens.
  - The **cross-match** tests the recipient's serum for antibodies against antigens on a specific donor's RBCs and is performed for each unit of blood that is dispensed for a patient.

- **Modifications of blood products**
  - **Leukoreduction** is performed by the use of filters to eliminate WBC contamination before storage or at the bedside. Indicated for all patients to reduce the risk of the following transfusion complications:
    - Nonhemolytic febrile transfusion reactions
    - Transfusion-transmitted CMV infection
    - Formation of HLA alloantibodies

  - **CMV-seronegative** blood products may be indicated for immunocompromised patients who are CMV seronegative to reduce the risk of CMV transmission. However, prestorage leuko-reduced products are considered equivalently "CMV reduced risk" and can be used in place of CMV-seronegative products.
  - **Irradiation** eliminates immunologically competent lymphocytes in order to prevent transfusion-associated graft-versus-host disease and is indicated for certain immunocompromised patients, BM transplant recipients, or patients who receive directed donations from HLA-matched donors or relatives.
  - **Washing** of blood products is rarely indicated but should be considered for patients in whom plasma proteins may cause a serious reaction (e.g., recipients with IgA deficiency or a history of anaphylactic reactions).
- **Blood administration**
  - Patient and blood product identification procedures must be carefully followed to avoid any transfusion-related errors including ABO-incompatible transfusion.
  - The IV catheter should be at least 18 gauge to allow adequate flow.
  - All blood products should be administered through a 170- to 260-μm "standard" filter to prevent infusion of macroaggregates, fibrin, and debris.
  - Patients should be observed with vital signs for the first 10-15 minutes of each transfusion for adverse effects and at regular intervals thereafter.
  - RBC infusion is typically administered over 1-2 hours, with a maximum of 4 hours.
- **Emergency transfusion** may be considered in situations in which massive blood loss has resulted in cardiovascular compromise.
  - Before the patient's ABO type can be confirmed, "emergency release" blood may be used, consisting of uncross-matched group O pRBCs and group AB or A plasma.
  - If **massive transfusion** (replacement of ≥10 units of pRBCs in <24 hours) is indicated, hemostatic components (plasma, platelets, and cryoprecipitate) should be included to correct the loss and dilution of hemostatic factors. In addition, care must be taken to manage the potential iatrogenic complications of massive transfusion, such as hypothermia, hypocalcemia (due to the citrated preservative solution), and hyperkalemia.

COMPLICATIONS

- **Transfusion-transmitted infections**
  - Donors and blood products are screened for HIV-1/2, human T-lymphotropic virus 1/2 (HTLV-1/2), hepatitis B, hepatitis C, West Nile virus, syphilis, *Trypanosoma cruzi* (Chagas), and bacteremia

(platelets only).

- Viral transmission may occur when donors are in the “window period” (i.e., undetectable to testing).
  - The risk of hepatitis B transmission is approximately 1 in 1,000,000; other tested viruses have a transmission risk of <1 in 1,000,000.
  - CMV transmission risk may be reduced in immunocompromised patients by the use of CMV-seronegative or prestorage leuko-reduced products.
- Bacterial transmission may occur from either a donor infection or a contaminant at the time of collection or processing.
  - Platelet transfusions are more likely than RBCs to have bacterial contamination because they are stored at room temperature.
  - The most common organisms identified are *Yersinia enterocolitica* in RBCs and *Staphylococcus* spp. in platelets.

- **Noninfectious hazards of transfusion**
  - **Acute hemolytic transfusion reactions** are usually caused by **preformed antibodies** in the recipient and are characterized by intravascular hemolysis of the transfused RBCs soon after the administration of ABO-incompatible blood.

    - **Fever, chills, back pain, chest pain, nausea, vomiting, anxiety, and hypotension** may develop. Acute renal failure with hemoglobinuria may occur. In the unconscious patient, hypotension or hemoglobinuria may be the only manifestation.
    - If a hemolytic transfusion reaction is suspected, **the transfusion should be stopped immediately and all IV tubing should be replaced**. Samples of the patient's blood should be delivered to the blood bank along with the remainder of the suspected unit for repeat of the cross-match. Direct and indirect Coombs tests should be performed, and the plasma and freshly voided urine should be examined for free Hgb.
    - Management includes preservation of intravascular volume and protection of renal function. Urine output should be maintained at ≥100 mL/h with the use of IV fluids and diuretics or mannitol, if necessary. The excretion of free Hgb can be aided by alkalinization of the urine. Sodium bicarbonate can be added to IV fluids to increase the urinary pH to ≥7.5.
  - **Delayed hemolytic transfusion reactions** typically occur 3-10 days after transfusion and are caused by either a primary or an anamnestic antibody response to specific RBC antigens on donor RBCs.
    - Hgb and Hct levels may fall.
    - The DAT is usually positive, depending on when follow-up testing is conducted.
    - Reactions may at times be severe; these cases should be treated similarly to acute hemolytic reactions.
  - **Nonhemolytic febrile transfusion reactions** are characterized by fevers and chills.
    - Cytokines released from white cells are thought to be the cause.
    - Treatment and future prophylaxis may include acetaminophen and prestorage leukoreduced blood products.
  - **Allergic reactions** are characterized by urticaria and, in severe cases, bronchospasm and hypotension.

- The reactions are due to plasma proteins that elicit an IgE-mediated response. The reaction may be specific to the plasma proteins of a particular donor and therefore may occur infrequently or never again.
- Treatment and future prophylaxis may include antihistamines such as diphenhydramine or corticosteroids.
- **Anaphylactic reactions** may require the addition of corticosteroids and washed or plasma-reduced products. Additionally, check serum immunoglobulins, because patients with IgA deficiency who receive IgA-containing blood products may experience anaphylaxis with small exposure to donor plasma.

- **Transfusion-associated circulatory overload** (TACO) is a relatively common yet under-recognized complication of blood transfusion. Volume overload with pulmonary edema and signs of CHF may be seen when patients with cardiovascular compromise are transfused. The clinical and radiographic features may be difficult to distinguish from that of transfusion-related acute lung injury (TRALI) (*Crit Care Med 2006;34(5 suppl):S109*). Slowing the rate of transfusion and judicious use of diuretics help prevent this complication, as well as avoidance of unnecessary transfusion.
- **TRALI** is indistinguishable from acute respiratory distress syndrome and occurs within 6 hours of a transfusion.
  - Symptoms include dyspnea, hypoxemia, and possibly fever.
  - New or worsening pulmonary edema is typically seen on CXR, as with TACO.
  - Anti-HLA or antineutrophil antibodies in the donor's serum directed against the recipient's WBCs are thought to cause the disorder.
  - On recognition, transfusions must be stopped and the blood bank notified so that other products from the donor(s) in question may be quarantined.
  - Hypoxemia resolves rapidly, typically in about 24 hours, but ventilatory assistance may be required during that time.

  - Despite clinical or radiographic findings that suggest pulmonary edema, data indicate that diuretics have no role and may be detrimental (*Blood 2005;105(6):2266*).
- **Transfusion-associated graft-versus-host disease** is a rare but serious complication usually seen in immunocompromised patients (and immunocompetent patients receiving blood from a relative) and is thought to result from the infusion of immunocompetent donor T lymphocytes.
  - Symptoms include rash, elevated liver function tests, and severe pancytopenia.
  - Mortality is >80%.
  - **Irradiation** of blood products for at-risk patients prevents this disease.
- **Posttransfusion purpura** is a rare syndrome of severe thrombocytopenia and purpura or bleeding that starts 7-10 days after exposure to blood products. This disorder is described in Chapter 20, Disorders of Hemostasis and Thrombosis, in the Platelet Disorders section.

22
Cancer

Siddhartha Devarakonda

Daniel Morgensztern

Ramaswamy Govindan

Cancer is the leading cause of mortality in developed countries and the second leading cause of death in developing countries. It is estimated that nearly 589,430 people will die from cancer in the United States in 2015 (*CA Cancer J Clin 2015;65:5*). The most common malignancies in the United States are lung cancer, prostate cancer, breast cancer, and colon cancer (Table 22-1). However, cancer death rates have declined over the past decade due to advances in drug development and availability of better supportive care. Improved understanding of the molecular pathways operative in cancer cells has led to the development of targeted agents and personalized treatment approaches that continue to demonstrate meaningful clinical benefit. This chapter provides an overview of cancer therapy.

Approach to the Cancer Patient

GENERAL PRINCIPLES

- The median age at diagnosis for all cancers in the United States is 67 years (*CA Cancer J Clin 2008;58:71*).
- The lifetime probability of being diagnosed with cancer is 43% in males and 38% in females.
- Tobacco use is the most common cause of cancer death and is associated with lung, head and neck, esophageal, gastric, pancreatic, kidney, and bladder cancers.
- Diet, obesity, inactivity, and height have also been shown to be associated with increased risk of developing selected cancers.
- Chronic inflammatory states such as ulcerative colitis and infections such as HIV, hepatitis, Epstein-Barr virus (EBV), human papillomavirus (HPV), and *Helicobacter pylori* are also associated with increased cancer risk.
- Several familial cancer syndromes have been described to date, which have important implications for cancer screening (Table 22-2).
- Prior exposure to cytotoxic chemotherapy or radiation therapy is associated with an increased risk of developing secondary cancers. For instance, exposure to alkylating agents or topoisomerase II inhibitors increases the risk of developing treatment-related leukemia, and exposure to radiation therapy increases risk for developing cancers such as breast cancer, angiosarcoma, and osteosarcoma.

DIAGNOSIS

- Obtaining tissue is crucial for facilitating a definitive tissue diagnosis, examining molecular features, and treatment planning.
- **Cytology** specimens often consist of only a few malignant cells that are obtained either invasively through biopsy (fine-needle or core biopsies), brushings (Pap smear or endoscopic), or aspiration of body fluids (blood, cerebrospinal fluid [CSF], pleural, pericardial, or peritoneal) or noninvasively though collection of fluids such as sputum and urine. Although these approaches are relatively less invasive compared to surgical approaches and easier to pursue, cytologic samples are often inadequate for

molecular testing. Furthermore, the loss of tissue architecture also makes it challenging to diagnose certain malignancies such as lymphomas.

TABLE 22-1 Most Common Cancer Diagnoses and Rates of Death in the United States for 2015

Sites	New Cases			Deaths
	Both Sexes	Male	Female	Total
Lung	221,200	115,610	105,590	158,040
Prostate	220,800	220,800		27,540
Breast	234,190	2,350	231,840	40,730
Colon	93,090	45,890	47,200	49,700

- **Histology** specimens are obtained through large-core needle biopsies, excisional biopsies, or surgical resection. These specimens are ideal for diagnosing most malignancies and provide enough tissue for molecular testing. However, these procedures are more invasive and not feasible in all patients.

STAGING

- Once a tissue diagnosis is obtained, most cancer patients will require additional imaging, procedures, and laboratory testing for determining the disease burden and stage. This workup is cancer and patient specific, and also varies by local and institutional patterns of practice. Organizations such as the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Society of Medical Oncology (ESMO) review available evidence and issue periodic recommendations to guide appropriate staging workup and management.
- Cancer stage provides an assessment of the extent of tumor dissemination, which is crucial for treatment.
  - Most malignancies are staged according to the tumor, lymph node, and metastasis (TNM) system from stages I to IV. The T classification is based on the size and extent of local invasion. The N classification describes the extent of lymph node involvement, and the M classification is based on the presence or absence of distant metastasis.
  - Performance status provides a quantitative measure of a patient's generalized well-being and quality of life. It has important implications for treatment planning (Table 22-3).

TREATMENT

Surgical Management

- Surgical resection is often performed with curative intent, although selected patients may benefit from palliative surgery that is performed for debulking large tumor masses (e.g., ovarian cancer), increasing

the efficacy of immunotherapy (e.g., renal cell carcinoma), or relieving symptoms (e.g., mastectomy for local control in a patient with metastatic disease).

- Surgery can facilitate staging and guide subsequent therapeutic decisions (adjuvant treatment), including chemotherapy or radiation therapy.
- Surgical resection of isolated metastatic sites in selected patients can improve survival. Examples include solitary brain metastases, pulmonary metastases from sarcomas, and liver metastases from colorectal cancer.

TABLE 22-2 List of Selected Familial Cancer Syndromes with High Penetrance

Syndrome	Defect	Associated Cancer Type
Ataxia-telangiectasia	*ATM*	Multiple; predominantly leukemia and lymphoma
Birt-Hogg-Dube	*BHD*	Chromophobe RCC
Bloom syndrome	*BLM*	Multiple
Cowden syndrome	*PTEN*	Multiple; predominantly breast, thyroid, RCC, endometrial
Familial adenomatous polyposis	*APC*	Colorectal, desmoid
Fanconi anemia	*DNA* repair complex	Multiple; predominantly MDS and AML
Hereditary breast-ovarian cancer	*BRCA1* and *BRCA2*	Multiple; predominantly breast, ovarian
Hereditary diffuse gastric cancer	*CDH1*	Gastric, lobular breast cancer
Hereditary leiomyomatosis and RCC	*FH*	Papillary RCC
Lynch syndrome (HNPCC)	Mismatch repair	Multiple; predominantly colorectal
Hereditary papillary RCC	*MET*	Papillary RCC
Juvenile polyposis syndrome	*MADH4 (SMAD4), BMPR1A*	Digestive tract and pancreas
Li-Fraumeni syndrome	*TP53*	Multiple

MEN type 1	*MEN1*	Islet cell tumors
MEN type 2	*RET*	Medullary thyroid cancer
Neurofibromatosis type 1	*NF1*	MPNST, glioma
Neurofibromatosis type 2	*NF2*	Meningioma, glioma, schwannoma
Nijmegen breakage syndrome	*NBS1*	Predominantly lymphoma
Peutz-Jeghers syndrome	*LKB1 (STK11)*	Multiple; predominantly breast, GI, pancreas
Retinoblastoma, hereditary	*RB*	Retinoblastoma, primitive neuroectodermal tumor
Rothmund-Thomson syndrome	*RECQL4*	Osteosarcoma
Tuberous sclerosis (TS)	*TSC1, TSC2*	RCC, giant cell astrocytoma
von Hippel-Lindau	*VHL*	Clear cell RCC
Xeroderma pigmentosum	Nucleotide excision repair	Multiple, cutaneous

AML, acute myeloid leukemia; GI, gastrointestinal; HNPCC, hereditary nonpolyposis colorectal cancer; MDS, myelodysplastic syndrome; MEN, multiple endocrine neoplasia; MPNST, malignant peripheral nerve sheath tumor; RCC, renal cell carcinoma.

TABLE 22-3 Eastern Cooperative Oncology Group (ECOG) and Karnofsky Score

ECOG	Karnofsky Score Correlate	Description
0	100	Fully active, able to carry on all predisease performance without restriction.
1	80-90	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office

		work).
2	60-70	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	40-50	Capable of only limited self-care, confined to bed or chair >50% of waking hours.
4	20-30	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	0	Dead.

From Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649.

Principles of Radiation

- Radiation is used for treatment of benign and malignant diseases. Commonly used forms of radiation include external-beam photons and electrons. Photons are usually x-rays or γ-rays. With the exception of stereotactic radiation to the brain, γ-rays are rarely used today. Protons and neutrons are other forms of external-beam radiation. Electrons are mostly useful for treating skin and superficial tumors.
- Brachytherapy is an alternative method of radiation therapy, where radioactive sources are placed close to or in contact with their target tissue. This ensures a higher dose delivery to the targeted tissue over a short duration of time. Brachytherapy sources can be temporary (e.g., iridium-192 in cervical cancer) or permanent (e.g., iodine-125 in prostate cancer).
- Radioactive substances can also be administered systemically. For instance, iodine-131 is administered orally for treating thyroid cancer, yttrium-90 microspheres are injected into the liver vasculature in hepatocellular cancer, and radium-223 is dosed intravenously in patients with prostate cancer and skeletal metastases.
- Radiation planning is designed to deliver a precise dose of radiation to a tumor while sparing surrounding tissues.
- **Curative** intent radiotherapy is used in several settings.
  - **Neoadjuvant:** Preoperative therapy intended to reduce both the extent of surgery and the risk of local relapse. Radiation in this setting is almost always administered in combination with chemotherapy.
  - **Adjuvant:** Postoperative therapy intended to reduce the risk of local relapse.
  - **Definitive:** High dose with curative intent.
  - **Concurrent chemoradiation:** Chemotherapy with definitive radiation is associated with increased efficacy but at a cost of increased toxicity compared to either chemotherapy or radiation alone.
- **Palliative** radiotherapy is used in lower dosing to reduce symptoms, including bone pain, obstruction, bleeding, and neurologic symptoms.

- The total dose of radiation administered is usually spread out over time (fractionated). This allows time for normal tissue repair and increases the probability of delivering radiation to tumor cells in a

radiosensitive phase of cell cycle. Radiation treatments are usually delivered either through conventional fractionation, hypofractionation, hyperfractionation, or accelerated fractionation schedules.

- **Conventional fractionation** consists of daily fractions typically of 1.8-2.0 Gy, usually delivered 5 days per week.
- **Hypofractionation** refers to delivery of larger fraction sizes once daily and a lower total dose.
- **Hyperfractionation** refers to the delivery of smaller doses per fraction and a higher total dose.
- **Accelerated fractionation** refers to the delivery of smaller fraction sizes, more frequently, and over a shorter duration of time, while keeping the total dose administered the same or slightly lower.

Principles of Chemotherapy

- Cytotoxic chemotherapy targets all dividing cells and has broad toxicities.
- In patients with resectable disease, chemotherapy may be used prior to the surgery (neoadjuvant) or following complete resection (adjuvant).
- Chemotherapy is typically given in 2-, 3-, or 4-week cycles. In most regimens, IV treatment is given on the first few days of the cycle, with no further treatment until the next cycle. In other regimens, treatments are administered weekly for 2-3 weeks, with 1 week off between cycles.
- **Curative** intent chemotherapy includes neoadjuvant, adjuvant, and chemoradiation protocols in solid tumors. Chemotherapy alone is curative in many lymphomas, leukemias, and germ cell tumors.
- **Palliative** chemotherapy is used in advanced solid tumors and relapsed hematologic malignancies, with a focus on prolonging survival and improving the quality of life.
- Most agents have a very narrow therapeutic index, and dosing is based on body surface area (mg/m^2). Chemotherapy toxicities are widely variable and can be life threatening.

Principles of Targeted Therapy

- The advent of molecularly targeted agents has led to marked advances in the treatment of selected malignancies.
- The most common classes of drugs are monoclonal antibodies and receptor tyrosine kinase inhibitors (TKIs). Monoclonal antibodies are administered IV and by standard nomenclature have names that end with the stem -mab. Substems indicate the source and target of the antibody. The most common source substems in oncology include -xi- indicating a chimeric antibody (e.g., cetuximab), -zu- indicating humanized antibody (e.g., bevacizumab), and -u- indicating fully human antibodies (e.g., ipilimumab). The most common target substems include -ci- indicating circulatory system (e.g., bevacizumab), -tu- indicating tumor (e.g., cetuximab), and -li- indicating immune system (e.g., ipilimumab).
- TKIs are administered orally and have names that end with -ib. The most common substems include -ti- indicating tyrosine kinase inhibition (e.g., imatinib) and -zom- indicating proteasome inhibition (e.g., bortezomib).
- Most antibodies are used in combination with chemotherapy or radiation, whereas most TKIs are used as single agents.
- Toxicities of targeted therapies are unique to each agent, although specific classes of drugs can be associated with characteristic side effects.
  - Inhibitors of the epidermal growth factor receptor (EGFR) frequently cause an acnelike rash on the face and upper chest, which can be severe. Treatment is typically with topical corticosteroids or oral minocycline.

TABLE 22-4 Summary of Selected Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria

Measurable lesions	Tumor: >10 mm in longest diameter (LD) on axial CT or MRI
	Lymph node: >15 mm in short axis on CT
Method	Sum of longest diameter (SLD) of the lesions in axial plane. Up to five target lesions (two per organ).
Response	
Complete response (CR)	Disappearance of all nonnodal target lesions. All target lymph nodes must be <10 mm in short axis.
Partial response (PR)	At least 30% decrease in the SLD of target lesions, with baseline sum of diameters as reference.
Progressive disease (PD)	New lesions or SLD increased by ≥20%.
Stable disease (SD)	Neither PR nor PD.

- Inhibitors of human epidermal growth factor receptor 2 (HER2) are associated with a reversible decline in cardiac systolic function, which should be monitored in these patients periodically.
- Inhibitors of angiogenesis are associated with endothelial toxicity, leading to hypertension, proteinuria, delayed wound healing, mild cardiac toxicity, increased risk of bleeding, thromboembolism, and gastrointestinal (GI) perforation/fistula. All antiangiogenics should be held in the perioperative period.

Assessing Response to Therapy

Objective assessment of changes in tumor burden, i.e., tumor shrinkage or progression, is crucial for planning cancer treatment and evaluating the efficacy of experimental interventions. Criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) are commonly used for this purpose (Table 22-4).

Lung Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Lung cancer is the most common cause of cancer death in the United States, with an estimated 158,040 deaths in 2015. Smoking is the greatest risk factor for lung cancer, with over 90% of cases being tobacco related. The risk of smoking-related lung cancer persists for 20-30 years after quitting smoking. Other environmental risks include exposure to asbestos and radon.

Pathology

Non-small-cell lung cancer (NSCLC) accounts for over 85% of cases. The most common histologic subtypes are adenocarcinoma and squamous cell carcinoma. Small-cell lung cancer (SCLC) is associated with a rapid tumor growth and early development of metastases compared to NSCLC.

Screening

- In 2011, the National Lung Screening Trial (NLST) research team showed a 20% relative reduction in lung cancer mortality and a 6.7% relative reduction in all-cause mortality (*N Engl J Med 2011;365:395*). The NLST included more than 50,000 asymptomatic current and former smokers at high risk for developing lung cancer. Participants were randomly assigned to screening with baseline low-dose chest CT (LDCT) or CXR, followed by annual scans at years 1 and 2.
- The number needed to screen to prevent one lung cancer death was 320 in the NLST.
- Based on these data, the US Preventive Services Task Force (USPSTF) currently recommends annual screening for lung cancer with LDCT in current smokers or former smokers who quit within the past 15 years, are between 55-80 years old, and have a 30-pack-year smoking history.

DIAGNOSIS

Clinical Presentation

- Symptoms in patients with lung cancer can be related to local disease (cough, dyspnea, wheezing, hemoptysis), intrathoracic extension (hoarseness from recurrent laryngeal nerve involvement, dysphagia, chest wall pain, Horner syndrome, symptoms related to brachial plexus involvement, superior vena cava syndrome), systemic metastases (fever, jaundice, bone pain, headaches, back pain), or paraneoplastic syndromes.
- Paraneoplastic syndromes in lung cancer typically include hypercalcemia,, hyponatremia from syndrome of inappropriate antidiuretic hormone secretion, and hypertrophic pulmonary osteoarthropathy.

Diagnostic Testing

- Any patient with a smoking history and concerning pulmonary symptoms should undergo a chest CT scan. A normal CXR does not exclude lung cancer. Diagnosis can be made from pleural fluid cytology, bronchoscopy with biopsy, brushings or washings, or ultrasound/CT-guided needle biopsy. Core needle biopsy is preferable to fine-needle aspiration (FNA).
- Staging evaluation in all patients should include a CT scan of the chest and abdomen. Additional imaging depends on the initial findings. In potentially curable patients, evaluation may also include brain MRI, positron emission tomography (PET)/CT scan, and mediastinoscopy.

TREATMENT

- **NSCLC**
  - Stages I and II: Surgery is the preferred therapy. Radiation therapy is an option for those who are not candidates for surgical resection. Postoperative platinum doublet chemotherapy improves overall survival in patients with surgically resected stage II and III NSCLC.
  - Stage III: The standard therapy is concurrent radiation and chemotherapy. Surgery is indicated for

selected patients.

- Stage IV: The standard treatment is with chemotherapy.
  - Frontline platinum-based doublet chemotherapy provides modest improvement in survival compared to best supportive care, and there is no difference in outcomes among the multiple regimens (*N Engl J Med 2002;346:92*).
  - EGFR TKIs, such as erlotinib or afatinib, should be considered as frontline therapy in patients whose tumors harbor activating mutations in *EGFR* (*J Thorac Oncol 2015;10:S1*).

  - Crizotinib and ceritinib are TKIs effective in patients with tumors harboring the *EML4-ALK* fusion gene (*J Clin Oncol 2013;31:1105*). Crizotinib is also associated with marked clinical activity in tumors harboring *ROS1* rearrangements (*N Engl J Med 2014;371:1963*).
  - Nivolumab, which targets the programmed death-1 (PD-1) receptor, has been approved for patients with previously treated metastatic squamous cell lung cancer.

- **SCLC**
  - Limited stage (stages I to III): The standard therapy is concurrent radiation therapy and chemotherapy with a platinum agent (carboplatin or cisplatin) plus etoposide.
  - Extensive stage (stage IV): The treatment of choice is with chemotherapy, usually with a platinum agent (cisplatin or carboplatin) plus etoposide.
  - Prophylactic cranial irradiation is recommended for all patients with limited stage and selected patients with extensive stage after completion of initial therapy.

Breast Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Breast cancer is the most common cancer in women in developed countries and is expected to account for 29% of new cancers in women in 2015. Nearly 231,840 patients develop breast cancer per year in the United States, and less than 1% of cases are reported in men. *BRCA1* and *BRCA2* mutations are associated with a 57% and 49% cumulative risk of breast cancer by age 70, respectively (*J Clin Oncol 2007;25:1329*). However, less than 10% of all breast cancers are attributable to mutations involving susceptibility genes. Alcohol consumption, early menarche, late menopause, nulliparity, postmenopausal obesity, hormone replacement therapy, and delayed first pregnancy are all risk factors for breast cancer. Women receiving mantle field radiation for Hodgkin disease also carry a higher lifetime risk.

Pathology

- Noninvasive: Ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).
- Invasive: Ductal carcinoma is more common than lobular carcinoma.
- Estrogen receptor (ER) is expressed in nearly 75% of all cases. ER positivity (ER+) is associated with good prognosis and responsiveness to endocrine therapies.
- Progesterone receptor expression (PR+) usually correlates with ER expression.
- Approximately 20% of tumors are HER2 positive (HER2+) by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). HER2 positivity is associated with higher grade cancers, but HER2+ breast cancers have

a very good outcome when treated with HER2-directed targeted therapies (e.g., trastuzumab).

Screening and Prevention

- The American Cancer Society (ACS) recommends a clinical breast exam every 3 years between 20-39 years of age and annually thereafter. The role of self-breast examination is controversial and should only be performed as an adjunct to clinical exam and mammography.
- The ideal age to begin screening mammography and optimal screening intervals are unknown, and recommendations vary among organizations and clinicians.
- The ACS recommends annual mammography from age 40, for as long as the person does not have serious illnesses that shorten life expectancy. MRI along with mammography is indicated in select individuals with a strong family history of breast cancer.

- Prophylactic mastectomy and oophorectomy are recommended for carriers of *BRCA1* or *BRCA2* mutations.
- Chemoprevention with tamoxifen and raloxifene is an option in women who are at high risk for developing breast cancer (family history and LCIS).

DIAGNOSIS

Clinical Presentation

Most breast cancers are identified by screening tests, but patients can present with a painless, palpable mass in the breast or axilla. Some patients may have nipple discharge, pain, and skin changes associated with the mass and nipple retraction. Patients with inflammatory breast cancer can complain of a “warm” breast and erythema. Inflammatory breast cancer is rare, but patients with these symptoms should be promptly evaluated by a clinician experienced with this diagnosis.

Diagnostic Testing

- Patients with palpable breast masses require diagnostic mammograms and ultrasonography. Patients with axillary mass and no detectable breast mass by routine imaging and examination should receive an MRI to identify occult cancer. Any clinically concerning mass needs to be biopsied irrespective of its radiographic appearance.
- CXR is routinely obtained. Bone scan and CT imaging are indicated in patients with stage III or higher disease, localizing symptoms, and abnormal laboratory values that suggest liver or skeletal involvement. CT scans can be considered in patients with stage II disease with node involvement.

TREATMENT

Surgery

- Lumpectomy (breast conservation therapy) with adjuvant radiation is equivalent to mastectomy (*N Engl J Med 1995;332:907*).
- Sentinel lymph node biopsy is the most common procedure for evaluation of regional lymph nodes.
- Whole-breast radiation therapy with radiotherapy boost to the tumor bed is recommended for patients following breast conservation surgery (BCS). Postmastectomy radiation is recommended in selected patients.

Endocrine Therapies

- Tamoxifen is an estrogen antagonist used in ER+ breast cancer. Fulvestrant is an ER antagonist that is approved for use in postmenopausal women.
- Luteinizing hormone-releasing hormone (LHRH) agonists (goserelin, leuprolide) can be used for ovarian suppression in premenopausal women, as an alternative to oophorectomy.
- Aromatase inhibitors (AIs) are the most commonly used endocrine drugs in postmenopausal patients and work by blocking androgen to estrogen conversion in peripheral tissues. These agents (letrozole, anastrozole, exemestane) can be used in conjunction with ovarian suppression in premenopausal women.

Treatment by Stage

- **DCIS and LCIS (stage 0)**

  Mastectomy or lumpectomy with negative margins followed by adjuvant radiation. Repeat resections for positive margins may be necessary. Tamoxifen is typically used if the tumor is ER+.

- **Resectable breast cancer (stages I-III)**
  - Surgical approach depends on the size of the tumor, patient preference, and the presence or absence of contraindications to BCS. Contraindications for BCS include multicentric disease, extensive microcalcifications, and previous irradiation. Neoadjuvant (preoperative) chemotherapy or hormonal therapy can be used to shrink larger tumors to facilitate BCS.
  - For ER+ and/or PR+ cancers, adjuvant endocrine therapy with tamoxifen or a combination of AI and ovarian suppression is recommended in premenopausal women (*N Engl J Med 2014;371:107*). For postmenopausal women, an AI is standard of care. Treatment duration is 5-10 years.
  - Adjuvant chemotherapy is generally recommended based on node involvement, tumor size, and ER, PR, and HER2 status.
  - Adjuvant treatment with the HER2 inhibitor trastuzumab dramatically reduces rate of relapse and improves survival in HER2+ breast cancer (*N Engl J Med 2005; 353:1673*).
  - Pertuzumab is another HER2 inhibitor that has recently been approved for the treatment of HER2+ cancer in the neoadjuvant and metastatic settings (*N Engl J Med 2012;366:109*).
- **Treatment of metastatic breast cancer**
  - Radiation therapy is urgently needed for brain metastases and can be used for symptomatic bone metastases.
  - Endocrine therapy is usually preferred in ER+/PR+ patients. Upfront use of chemotherapy can be considered in ER+/PR+ patients with visceral metastases. ER-/PR-metastatic breast cancer requires chemotherapy.
  - HER2+ metastatic breast cancer requires HER2-directed targeted drugs, such as trastuzumab, pertuzumab, T-DM1, or lapatinib, and these are typically combined with chemotherapy.
  - Bone-strengthening agents, such as bisphosphonates or denosumab (an anti-RANKL antibody), are recommended for patients with bone metastases to reduce risks of fracture or other bone complications.

Head and Neck Cancer

GENERAL PRINCIPLES

Head and neck squamous cell cancer (HNSCC) includes carcinoma of the lip, oral cavity, pharynx, nasopharynx, and larynx. It is estimated that nearly 59,000 patients will be diagnosed with HNSCC in the year 2015. Tobacco use and alcohol consumption are associated with increased risk of developing HNSCC. HPV infection is implicated in oropharyngeal squamous cell carcinomas, and the incidence of HPV-associated HNSCC has quadrupled since the 1980s. EBV infection is associated with nasopharyngeal cancers.

- **Field cancerization** is an important concept in HNSCC. Given the diffuse nature of mucosal exposure to tobacco smoke, the primary cancer site is often surrounded by areas of premalignant lesions (carcinoma in situ and dysplasia). For this reason, patients with tobacco-associated HNSCC are at increased risk for developing secondary cancers.
- **Leukoplakia and erythroleukoplakia** are premalignant lesions of the oral mucosa. Leukoplakia refers to a white mucosal patch that cannot be scraped off, whereas erythroleukoplakia appears red and velvety. Erythroleukoplakias are associated with a higher risk of malignant transformation.

DIAGNOSIS

Clinical Presentation

Patients with HNSCC can present with a variety of symptoms depending on the primary tumor site: oral mass, nonhealing ulcers, trismus from invasion of pterygoid muscles, dysphagia, odynophagia, otitis media from eustachian tube blockage, hoarseness, neck mass, weight loss, and cranial nerve palsies. Nasopharyngeal tumors can invade the cavernous sinus and frequently affect the abducens and trigeminal nerves. Salivary gland tumors, which can have nonsquamous pathology, can invade the facial nerve and cause facial nerverelated symptoms.

Diagnostic Testing

- Comprehensive ear, nose, and throat (ENT) evaluation with fiberoptic endoscopy or mirror exam is required. Particular attention should be paid to assess dentition. Functional evaluation that includes assessment of swallowing, biting, chewing, and speech should be performed.
- Examination under anesthesia is a critical component of staging. Imaging should include a panorex to evaluate dentition and mandibular bony involvement. A CT of the neck and chest should be obtained to evaluate lymph node involvement and rule out pulmonary metastases, respectively. Whole-body PET can be considered in select patients.
- p16 positivity on IHC is used as a surrogate for HPV infection and is an independent favorable prognostic factor for survival (*N Engl J Med 2010;363:24*).
- **Stage classification:** Stage I to II disease does not show lymph node involvement. Stage III tumors are larger (defined as >4 cm for most sites) or have isolated lymph node involvement. Stage IVA/B tumors are locally advanced tumors or show bilateral or bulky cervical lymph node involvement. Stage IVC tumors are associated with distant metastasis.

TREATMENT

- Early stage (I-II): Either surgery or definitive radiation.
- Locally advanced (stage III-IVA/B): Treatment approaches include:
  - Definitive surgical resection followed by adjuvant radiation with or without chemotherapy

- Concurrent chemotherapy with radiation
- Induction chemotherapy followed by concurrent chemotherapy with radiation or radiation alone

- Metastatic (stage IVC): Palliative chemotherapy.
- **Chemotherapy:** Cisplatin is the chemotherapy agent commonly used in combination with radiation for definitive treatment. Induction regimens usually involve a platinum combination with drugs such as 5-fluorouracil (5FU) and a taxane (paclitaxel or docetaxel).
- **Targeted therapy:** Cetuximab, a monoclonal antibody against EGFR, can be used in combination with definitive radiation in patients who cannot tolerate traditional chemotherapeutic regimens or in combination with cisplatin and 5FU for the treatment of metastatic disease (*N Engl J Med 2008;359:1116*).
- **Surgery:** Nodal neck dissection is an important part of surgical management. Radical neck dissection refers to surgical removal of lymph nodes from all five neck stations unilaterally, along with excision of the internal jugular vein, spinal accessory nerve, and sternocleidomastoid. Modified neck dissections spare some of these structures.
- **Organ sparing:** Chemoradiation or induction chemotherapy followed by radiation can potentially spare patients from undergoing a total laryngectomy and improve quality of life.

- **Supportive care:** Dental evaluation is indicated prior to radiation. Patients undergoing definitive radiation or adjuvant radiation may develop severe mucositis requiring the placement of gastric feeding tube for nutrition. Surgery may lead to loss of speech, swallowing dysfunction, permanent tracheostomy, and disfigurement. Swallowing impairment can lead to aspiration. Radiation can result in severe xerostomia.

Sarcoma

GENERAL PRINCIPLES

Epidemiology and Etiology

In the United States, approximately 14,000 patients will be diagnosed with sarcomas in the year 2015. Risk increases with age. Predisposing factors include prior radiation, chemical and chemotherapy exposure, genetic syndromes, Paget disease of the bone, HIV/human herpesvirus 8 (HHV8) infection (Kaposi sarcoma), and chronic lymphedema (lymphangiosarcoma, also known as Stewart-Treves syndrome).

Pathology

Soft tissue sarcomas consist of at least 50 different types of histologies. Review by a pathologist who has expertise in the diagnosis of sarcoma is recommended.

DIAGNOSIS

Clinical Presentation

Symptoms depend on the site of disease. Sarcomas arising in extremities can present as a painless soft tissue mass. Visceral sarcomas can be associated with GI bleeding, early satiety, dysphagia, dyspepsia, or vaginal bleeding. Retroperitoneal tumors can result in early satiety, nausea, paresthesias, or abdominal mass and pain.

Diagnostic Testing

Initial imaging studies include MRI for sarcomas involving the extremities or pelvis and CT for retroperitoneal and visceral sarcomas. PET/CT maybe helpful in high-grade sarcomas. Chest imaging with radiography and CT is important because the majority of sarcomas first metastasize to the lungs.

Treatment

Early stage (stages I-III)

- Surgical excision is the mainstay of therapy. Adjuvant radiotherapy is often indicated in patients with large (>5 cm) tumors and positive or equivocal margins when re-excision is not feasible.
- Although the role of neoadjuvant and adjuvant chemotherapy is controversial, patients should be seen in conjunction with a center that has extensive experience in the treatment of sarcoma.

Metastatic disease

- Palliative chemotherapy is the primary mode of treatment. Doxorubicin, ifosfamide, gemcitabine, docetaxel, dacarbazine, and pazopanib are commonly used.
- Metastasectomy can be considered in patients with oligometastatic disease to the lungs.
- **GI stromal tumor (GIST):** The most common site is stomach, followed by small bowel. Surgery should be performed if feasible. Most GISTs overexpress KIT and are highly responsive to imatinib. Adjuvant and/or neoadjuvant imatinib can be considered in select patients.

- **Ewing sarcoma:** This tumor is usually responsive to chemotherapy. Metastatic disease can be potentially cured with chemotherapy in a few cases.

GASTROINTESTINAL MALIGNANCIES

Esophageal Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Esophageal cancer is estimated to account for nearly 15,590 deaths in the United States in 2015. Esophageal cancer is three to four times more common in men than in women. Risk factors include tobacco, alcohol, obesity, gastroesophageal reflux disease, Barrett esophagus, achalasia, and caustic injury.

Pathology

Adenocarcinomas are most common in the lower third of the esophagus and at the gastroesophageal junction and have had a sharp increase in incidence over the last few decades in the United States. Squamous cell carcinomas are more common in the upper and middle esophagus.

DIAGNOSIS

Clinical Presentation

Patients usually present with progressive dysphagia and weight loss. Other symptoms include odynophagia, cough, regurgitation, and hoarseness.

Diagnostic Testing

- The diagnosis is usually established through upper endoscopy with biopsy.

- Staging workup includes CT of the chest and abdomen (with or without PET) to determine the presence of distant metastases. For patients without distant metastases, endoscopic ultrasonography (EUS) is required for the definition of tumor depth and lymph node status.
- Tumors located above the carina increase the risk of tracheoesophageal (TE) fistula formation and should be evaluated with bronchoscopy. Patients with TE fistulas often present with postprandial cough and aspiration pneumonias.

TREATMENT

- **Resectable disease:** Patients with resectable disease are candidates for esophagectomy with or without preoperative chemotherapy and radiation (*N Engl J Med 2012;366:2074*), depending on the extent of disease.
- **Unresectable primary disease:** Patients diagnosed with locally advanced disease are usually managed by concurrent chemoradiation.
- **Metastatic disease** is treated with palliative chemotherapy, usually with regimens including 5FU, platinum, and a taxane or anthracycline agent. Ramucirumab, an antibody against vascular endothelial growth factor receptor-2 (VEGFR-2), is approved for use in the second-line setting in combination with paclitaxel or as a single agent (*Lancet 2014;383:31*).
- **Trastuzumab** can be used in combination with chemotherapy in patients with *HER2*-amplified esophageal or gastroesophageal junction metastatic adenocarcinomas.

Gastric Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

The highest incidence rates for gastric cancer are in eastern Asia, eastern Europe, and South America, whereas the lowest incidence is in North America and Africa. Gastric cancer will account for an estimated 10,720 deaths in 2015 in the United States. Risk factors include *H. pylori* infection, previous partial gastrectomy for benign ulcer, achlorhydria associated with pernicious anemia, cigarette smoking, and blood group A. Hereditary diffuse gastric cancer is an inherited type of gastric cancer in families with germline *CDH1* (E-cadherin) mutations.

Pathology

More than 90% are adenocarcinomas. Tumors may be subdivided according to the Lauren classification into intestinal or diffuse types. Intestinal type is more common in older patients and has a better prognosis. Diffuse type, the most common subtype in the United States, is more prevalent in younger patients and is associated with a worse prognosis. Linitis plastica (leather bottle stomach) refers to a diffusely infiltrating type of gastric adenocarcinoma. Nearly 15-20% of patients with gastric cancer have *HER2* amplification or overexpression.

DIAGNOSIS

Clinical Presentation

The most common symptoms are weight loss, decreased appetite, and abdominal discomfort. Dysphagia may occur with gastroesophageal junction tumors, and persistent vomiting may occur if there is pyloric obstruction. Physical exam may show metastases to the left supraclavicular node (Virchow node) or

periumbilical node (Sister Mary Joseph node).

Diagnostic Testing

Diagnosis is established by upper endoscopy. CT of the chest and abdomen should be obtained in all patients, and CT of the pelvis should be performed in women to exclude ovarian involvement (Krukenberg tumor). Other tests include *H. pylori* testing, EUS, and PET scan. Staging laparoscopy may be indicated prior to surgery in select patients for assessing peritoneal involvement.

TREATMENT

- Medically fit patients with resectable disease should undergo surgery. Chemotherapy or chemoradiation is commonly used, either before or after the resection, except in patients with very early stage disease.
- Patients with unresectable disease are treated with palliative chemotherapy. Trastuzumab can be used in combination with chemotherapy in patients with HER2-positive gastric cancers. Trastuzumab and anthracyclines should not be administered concurrently due to increased cardiotoxicity.
- Prophylactic total gastrectomy is recommended in carriers of *CDH1* germline mutations.

Colorectal Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Colorectal cancer is the third most common malignancy worldwide. The incidence is higher in Western industrialized countries, with 93,090 cases estimated to be diagnosed

in the United States in 2015. Although the incidence of colorectal cancer in adults age 50 years or older is declining, largely due to screening colonoscopy, the incidence among young adults (age 20-49 years) has increased over the last few decades. Risk factors include age >50 years, physical inactivity, obesity, diet with increased red meat and decreased fiber, personal history of polyps or colorectal cancer, inflammatory bowel disease, and hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis (FAP).

DIAGNOSIS

Clinical Presentation

The most common symptoms include lower GI bleeding, abdominal pain, change in bowel habits, and obstruction. Patients can also rarely present with perforation, peritonitis, and fever. Any unexplained iron deficiency anemia should be evaluated with upper and lower endoscopy to evaluate for a GI malignancy. Colorectal carcinomas are also identified through screening colonoscopies.

Diagnostic Testing

- A thorough family history must be obtained to rule out a hereditary cancer syndrome, especially in younger (<50 years) patients.
- Diagnosis is typically made through colonoscopy with biopsy.
- Imaging studies include CT scan of the chest, abdomen, and pelvis. PET scan is not routinely indicated but is useful in patients being considered for definitive resection of oligometastatic disease.
- Additional studies include serum carcinoembryonic antigen (CEA) levels.

TREATMENT

- **Localized disease** should be treated with surgical resection. Adjuvant chemotherapy is indicated in patients with stage III disease and may also be beneficial in selected patients with stage II disease. The preferred regimen in the adjuvant setting includes 5FU (or capecitabine), leucovorin, and oxaliplatin (FOLFOX).
- **Unresectable metastatic disease** is treated with combination palliative chemotherapy, usually including 5FU plus leucovorin, capecitabine, and oxaliplatin (FOLFOX or XELOX), or irinotecan (FOLFIRI). The combination of bevacizumab, a vascular endothelial growth factor (VEGF) monoclonal antibody, and chemotherapy improves survival compared with chemotherapy alone. EGFR antibodies, cetuximab and panitumumab, are associated with improved outcomes when combined with chemotherapy in tumors lacking *KRAS* and *NRAS* gene mutations (*N Engl J Med 2013;369:1023*).
- **Surgical resection of metastatic disease**, with a curative intent, can be attempted in patients with a limited number of liver or lung metastases. Aggressive chemotherapy can be employed in selected patients initially presenting with unresectable liver metastases to achieve maximal response and make them eligible for resection.

Treatment of Rectal Cancer

Patients without metastatic disease should undergo endorectal ultrasound or pelvic MRI for the evaluation of tumor depth and lymph node status.

- **Early stage disease:** The treatment of choice is resection. Low anterior resection (LAR) is suitable for tumors located in the middle and upper third of the rectum, whereas abdominoperineal resection (APR) might be warranted in low-lying cancers. Preoperative radiation can be considered in low-lying cancers with an attempt to convert APR to a sphincter-preserving LAR.

- **Locally advanced disease:** These patients are usually treated with 5FU (or capecitabine)-based neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy (FOLFOX).
- **Metastatic disease:** The standard of care is palliative chemotherapy with the same drugs used in colon cancer.

Pancreatic Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Pancreatic cancer is the fourth most common cause of cancer-related death in the United States, estimated to result in 40,560 deaths in 2015. Incidence increases with age, with median age at diagnosis between 60 and 80 years. Risk factors include cigarette smoking, obesity, inactivity, diabetes, chronic nonhereditary and hereditary pancreatitis, and inherited syndromes such as ataxia telangiectasia and hereditary intestinal polyposis syndrome (Peutz-Jeghers).

Pathology

Pancreatic adenocarcinoma is the most common subtype. Pancreatic neuroendocrine tumors are less common, associated with a better prognosis, and managed differently.

DIAGNOSIS

Clinical Presentation

Common symptoms include painless jaundice, anorexia, weight loss, and abdominal pain. Pancreatic cancer should be suspected when diabetes mellitus develops suddenly in patients older than 50 years.

Diagnostic Testing

Diagnosis is usually suspected by the presence of a pancreatic mass or dilated biliary duct on CT scan or ultrasound. Those without metastatic disease will require endoscopic retrograde cholangiopancreatography or EUS-guided FNA. Pancreatic protocol CT (triple-phase, contrastenhanced, helical CT) with thin slices is often recommended to evaluate tumor resectability.

- Resectability is defined based on the extent of vascular involvement and often involves the absence of distant metastases, superior mesenteric artery encasement (more than half of vessel circumference), and direct involvement of celiac artery, hepatic arteries, and inferior vena cava.
- In case of metastatic disease, biopsy of the metastatic lesion is preferred.
- CA19-9 is not a reliable diagnostic marker because it can be elevated in patients with benign biliary obstruction and falsely low in 10% of patients who are Lewis-negative phenotypes.

STAGING

Based on imaging, pancreatic cancer is classified as resectable, borderline resectable, locally advanced, or metastatic disease. The definition of borderline resectability can be variable but usually involves focal abutment of vasculature by the pancreatic tumor.

TREATMENT

- **Resectable disease:** Surgical resection is the only potentially curative therapy, which is typically a pancreaticoduodenectomy (Whipple procedure). At presentation, only 15%

of patients present with resectable disease. Patients who have adequately recovered from surgery may benefit from adjuvant chemotherapy (usually including gemcitabine) and radiation because nearly 70% of patients will experience a distant relapse.
- **Borderline resectable and locally advanced disease:** For borderline resectable disease, induction chemotherapy and chemoradiotherapy are often used to induce response, which may increase the probability of resection with negative margins. For unresectable locally advanced disease, palliative chemotherapy with or without radiation is used for disease control.
- **Metastatic disease** is treated with palliative chemotherapy.
- FOLFIRINOX, a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, 5FU, and leucovorin, is an option for use in patients with good performance status (*N Engl J Med 2011;364:1817*). The combination of gemcitabine with albumin-bound paclitaxel (nab-paclitaxel) can also be used in patients with good performance status. Patients who are unable to tolerate these regimens can be treated with single-agent gemcitabine.

Hepatocellular Carcinoma

GENERAL PRINCIPLES

Epidemiology and Etiology

An estimated 35,660 patients are estimated to be diagnosed with liver and intrahepatic bile duct tumors in 2015 in the United States. Risk factors include chronic viral hepatitis B or C, autoimmune hepatitis, nonalcoholic steatohepatitis (NASH), hemochromatosis, and cirrhosis (primary biliary or from other causes such as aflatoxin, alcohol, etc.). Most patients with hepatocellular carcinoma (HCC) have cirrhosis.

SCREENING

Patients with chronic hepatitis B (Asian males >40 years, Asian females >50 years, African or African American ethnicity, or family history of HCC) and all patients with cirrhosis irrespective of etiology are candidates for screening. Ultrasonography every 6-12 months is the preferred screening modality.

DIAGNOSIS

Clinical Presentation

Common symptoms include abdominal pain, anorexia with weight loss, jaundice, and vomiting. Invasion of the hepatic veins may cause Budd-Chiari syndrome, characterized by tender hepatomegaly and tense ascites. HCC should be suspected in patients with stable cirrhosis who decompensate rapidly. Most common paraneoplastic syndromes include hypoglycemia, hypercalcemia, dysfibrinogenemia, and erythrocytosis.

Diagnostic Testing

- The classic feature of HCC in CT is rapid enhancement during the arterial phase of contrast administration, followed by “washout” during the later venous phases. Lesions <1 cm have low probability of being HCC and should be followed with repeated imaging to detect growth suspicious of malignancy.
- Tumors that do not show the radiologic hallmarks for HCC may need biopsy for diagnosis.
- It is important to assess liver function in patients with HCC through scoring systems such as the Child-Pugh classification.

Treatment

- **Surgery** is the only curative option. Liver transplant should be considered in patients ineligible for surgery. To be deemed eligible for transplantation, patients are required to fulfill the Milan criteria, which include single tumor ≤5 cm or up to three tumors <3 cm, absence of macrovascular invasion, and absence of extrahepatic disease.
- **Other local therapies** such as percutaneous ethanol injection, radiofrequency ablation, cryoablation, transarterial chemoembolization, and radiation can be considered in select patients for palliation or to control tumor growth.
- **Chemotherapy** has minimal efficacy in HCC. Sorafenib is well tolerated and improves survival modestly compared to best supportive care (*N Engl J Med 2008;359:378*).

GENITOURINARY MALIGNANCIES

Renal Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Renal cell carcinoma (RCC) is estimated to result in approximately 14,080 deaths in the United States in 2015. It is more commonly diagnosed in men, and the risk increases with age. Other risk factors include tobacco smoking, obesity, and hypertension.

Pathology

RCC is a malignancy of the renal parenchyma. Clear cell RCC is the most common subtype (80-85%), followed by papillary (15%) and chromophobe (5%) RCCs. Transitional cell (urothelial) carcinoma of the renal pelvis is treated as bladder cancer.

DIAGNOSIS

Clinical Presentation

Most patients in the United States are diagnosed by incidental findings on CT scan. The most common symptoms are anemia, hematuria, cachexia, and fever. The classic triad of flank pain, hematuria, and a palpable mass is uncommonly seen. Hypercalcemia is the most common paraneoplastic manifestation of RCC. Although erythrocytosis from erythropoietin production can be seen in RCC, anemia is more common. Stauffer syndrome refers to a paraneoplastic syndrome characterized by nonmetastatic hepatic dysfunction seen in RCC.

Diagnostic Testing

CT is usually sufficient for staging. MRI and magnetic resonance angiography (MRA) may be useful for further evaluation of the collecting system and inferior vena cava for involvement. The role of PET imaging is limited because normal renal tissue excretes fluorodeoxyglucose in the urine and has a high background activity. RCC often spreads to brain and bone, and thus, symptomatic patients should undergo additional imaging with CT, MRI, or bone scan to look for sites of metastasis. In patients without metastatic disease, resection can be both diagnostic and therapeutic.

TREATMENT

- **Localized disease:** The treatment of choice is surgery. A nephron-sparing approach (partial nephrectomy) can be considered if feasible.

- **Locally advanced disease:** The treatment of choice is radical nephrectomy, which involves removal of the Gerots fascia, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. There is no role for adjuvant therapy
- **Metastatic disease**
  - Surgery is an option in patients with oligometastatic disease. Cytoreductive nephrectomy followed by immunotherapy with interferon-α (IFN-α) can be considered in patients with resectable primary tumors and good performance status. Emerging data also suggest a benefit of cytoreductive surgery in patients treated with VEGF-targeted therapies, and randomized trials addressing this are ongoing.
  - Targeted agents approved for metastatic RCC include the VEGF inhibitors sunitinib, sorafenib, pazopanib, and axitinib, and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. The choice of therapy depends on the histology, patient risk category, and adverse effect profile of targeted therapies.

- **Immunotherapy** with high-dose interleukin (IL)-2 and IFN-α were predominantly used before the advent of targeted therapies. However, high-dose IL-2 should be considered in select patients with good performance status given the potential for durable cures in a small subset (approximately 5-15%) of patients. The role of newer immunotherapies targeting PD-1 and PD-L1 is actively being investigated (*N Engl J Med 2012;366:2443*).

Bladder Cancer

GENERAL PRINCIPLES

Bladder cancer is one of the more commonly diagnosed malignancies in the United States, with 74,000 estimated cases in 2015. Transitional cell or urothelial carcinoma is the most common histology. Tobacco smoking, chronic cystitis from long-term indwelling catheters, previous pelvic radiation or prolonged cyclophosphamide use, and exposure to benzene and other industrial chemicals are all risk factors. Bladder cancer is three times more common in men than in women, with a median age at diagnosis of 65. *Schistosoma haematobium* infection is linked to squamous cell bladder cancer.

DIAGNOSIS

Clinical Presentation

Most patients present with hematuria (microscopic or macroscopic). Lower urinary tract symptoms such as increased frequency, urgency, and dysuria can be seen in patients with bladder neck tumors.

Diagnostic Testing

The presence of >3 red blood cells per high-power field (HPF) is considered significant hematuria. Hematuria should be evaluated with urine cytology, upper tract imaging (IV pyelogram or CT), and cystoscopy with transurethral resection of bladder tumor (TURBT).

STAGING

Bladder cancers are broadly divided into non-muscle-invasive, muscle-invasive, and metastatic cancers. Cystoscopy with biopsies or TURBT determines the depth of invasion; imaging is not reliable to distinguish noninvasive from muscle-invasive disease in the majority of cases.

TREATMENT

The following describes treatment options by stage.

- **Superficial tumors** (no muscle invasion, stages 0-I) are treated with TURBT. Intravesicular bacille Calmette-Guérin (BCG) vaccine instillation reduces recurrence, and both induction and maintenance courses can be used. Intravesicular chemotherapy (typically mitomycin C) can be used in cases of BCG failure.
- **Muscle-invasive disease** is defined by the invasion of muscle or adjacent tissue (stages II and III). The treatment of choice is radical cystectomy with urinary diversion by creating an ileal conduit. Neoadjuvant chemotherapy has been shown to provide a survival benefit and should be considered in appropriate patients. For patients who cannot get neoadjuvant treatment, adjuvant chemotherapy can help reduce recurrences. Radiation, often with concurrent chemotherapy, is an alternative to surgery if resection cannot be performed.

- **Metastatic disease**, including node-positive or distant disease, is managed with chemotherapy, most commonly the combination of gemcitabine and cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC).

Prostate Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Prostate cancer is the most common cancer in men in the United States, with an estimated 220,800 new cases and 27,540 deaths in 2015. African American ethnicity, family history, and a high-fat/low-vegetable diet are a few predisposing risk factors.

Screening

The absolute risk reduction in mortality from annual prostate-specific antigen (PSA) is modest and should be discussed with patients older than 50 years of age with known risk factors. The USPSTF currently does not recommend annual PSA-based screening, although there are conflicting data from American and European trials looking at the benefit of prostate cancer screening.

DIAGNOSIS

Clinical Presentation

The most common presentation in the United States is asymptomatic elevation in PSA. Digital rectal examination (DRE) findings of asymmetric induration or nodules are suggestive, and any palpable nodule should be biopsied. Less common symptoms are obstructive symptoms, new-onset erectile dysfunction, hematuria, or hematospermia. Bone is the most common site of metastatic involvement, and patients with skeletal metastases can present with pain, fractures, and nerve root compression.

Diagnostic Testing

DRE supplemented by transrectal ultrasound helps in assessing T stage. PSA testing and Gleason scoring in the initial biopsy are important in staging and risk category assessment. Although patients with high-risk disease are likely to benefit from routine imaging (CT, MRI, or bone scan) for detection of metastatic disease, symptom-directed imaging is appropriate in patients with low-risk disease.

- Gleason grades range from 1 to 5. Grade 1 is assigned to well-differentiated and grade 5 to poorly differentiated gland pattern. **Gleason score** is the sum of the grades for the primary and secondary patterns seen on the biopsy.

- Risk categorization: Based on these characteristics, tumors are classified as low (PSA ≤10 ng/mL, Gleason score <7, and stage up to T2a), intermediate (PSA >10 to ≤20 ng/mL, Gleason score 7, and stage T2b), or high (PSA >20 ng/mL, Gleason score >7, and stage T2c) risk.

Staging

Early stage disease (T1-T2) is confined to the prostate, and locally advanced disease (T3-T4) is defined by local invasion. Stage IV disease is defined by nodal involvement and metastatic disease.

TREATMENT

The most important predictors of outcome are pretreatment PSA levels, Gleason score, and clinical TNM stage.

- **Early stage disease:** Outcomes are equivalent with radical prostatectomy, external-beam radiation, or brachytherapy. Late toxicities are variable but usually include incontinence and erectile dysfunction. Active surveillance is a suitable option for men with low-risk disease.
- **Locally advanced disease** is often treated with different combinations of surgical, radiation, and hormonal therapy. Surgery (if previous radiation), radiation (if previous prostatectomy), brachytherapy, and sometimes systemic hormonal therapy can be considered in patients who show an asymptomatic increase in PSA levels after surgery or radiation. Adjuvant or "salvage" radiation should be offered to patients with adverse pathologic features after prostatectomy even in the absence of a PSA recurrence.
- **Metastatic disease** is incurable and is initially treated with surgical or medical castration with an LHRH agonist or antagonist, termed androgen deprivation therapy (ADT), because testosterone/androgens play a major role in tumor growth. The antiandrogens flutamide or bicalutamide may be added for combined androgen blockade (CAB), which has shown marginal improvements in overall survival compared with LHRH monotherapy in meta-analyses. **Castration-resistant disease** is diagnosed in patients who experience disease progression on hormonal therapy. The term "castration resistance" does not necessarily imply complete resistance to therapies that block androgen stimulation. Chemotherapy with docetaxel, cabazitaxel, abiraterone, enzalutamide, radium-223, and sipuleucel-T are treatment options for these patients. Sipuleucel-T is an autologous cellbased vaccine targeting prostatic acid phosphatase.

Testicular Cancer and Germ Cell Tumors

GENERAL PRINCIPLES

Epidemiology

Testicular cancers are relatively rare tumors with about 8000 cases annually in the United States. However, they are the most common tumors diagnosed in men age 15-35 years. Nonseminomatous tumors are more common in younger men, whereas seminomas are more common after age 30 years. Incidence is higher in Caucasians than in patients of other ethnicities. Other risk factors include cryptorchidism and Klinefelter syndrome.

Pathology

Fifty percent of testicular cancers are seminomas, and the remainder are nonseminomas or of mixed histology. Nonseminomas include embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumors. Pure seminomas carry a better prognosis compared to nonseminomas or mixed histology tumors.

DIAGNOSIS

Clinical Presentation

The most common presentation is that of a painless testicular mass, but patients can also present with testicular pain, hydrocele, or gynecomastia. Advanced testicular cancer can present with back or flank pain, fevers, night sweats, and weight loss.

Diagnostic Testing

Tumor markers, including β-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH), should be ordered. In patients with pure seminomas, AFP is not elevated; thus, elevated AFP suggests a focus of undetected nonseminoma. Preoperative CT of the abdomen and pelvis

and CXR should be performed.

STAGING

Staging is based on TNM status and serum markers (S). In general, stage I represents disease confined to the scrotum, stage II indicates lymph node involvement, and stage III is defined by the presence of visceral metastases.

TREATMENT

- Stage I: The treatment of choice is orchiectomy. Adjuvant radiation to retroperitoneal nodes, retroperitoneal nodal dissection, chemotherapy with carboplatin, and active surveillance are possible adjuvant management approaches based on histology and other risk features such as lymphatic or vascular involvement.
- Stages II-III: Chemotherapy with BEP (bleomycin, etoposide, and cisplatin) results in high rates of cure, particularly in seminomas, and a minimum of three cycles is administered. Second-line chemotherapy regimens include VeIP (vinblastine, ifosfamide, cisplatin) and TIP (paclitaxel, ifosfamide, cisplatin). High-dose chemotherapy with stem cell therapy may be used in more advanced cases refractory to initial treatment.
- Sperm banking should be discussed with all patients prior to beginning treatment.

GYNECOLOGIC MALIGNANCIES

Cervical Cancer

GENERAL PRINCIPLES

Epidemiology and Etiology

Cervical cancer death rates have declined by almost 80% between 1930 and 2010 because of the widespread implementation of screening programs. In countries that lack a cervical cancer screening and prevention program, cervical cancer is the second most common cancer seen in women. The most important risk factor is persistent HPV infection, detected in >99% of tumors, usually HPV-16 and -18. Other risk factors include early onset of sexual activity, multiple sexual partners, high-risk partner, history of sexually transmitted disease, and chronic immunosuppression (HIV infection).

Pathology

The most common histology seen is squamous cell carcinoma followed by adenocarcinoma.

Prevention

The prophylactic quadrivalent HPV vaccine protects against types 6, 11, 16, and 18 (Gardasil), whereas the bivalent vaccine protects against HPV-16 and -18. Vaccinated women should continue routine Pap smears because the vaccine is not effective against all HPV subtypes. Cervical cancer screening should begin at age 21 years.

DIAGNOSIS

Clinical Presentation

Patients with early stage lesions are commonly asymptomatic and diagnosed incidentally on Pap smear, which underscores the importance of screening. Symptoms observed at presentation include irregular or heavy vaginal bleeding or postcoital bleeding. Patients with advanced disease may present with back pain, hematochezia from bowel involvement, or vaginal passage of urine or stool.

Diagnostic Testing

Diagnosis is obtained through cervical cytology and biopsy. A large cone biopsy is recommended in women without gross cervical lesions or with microinvasive disease to define depth of lesion. Clinical exam, CXR, IV pyelogram, proctosigmoidoscopy, and cystoscopy are required to assess International Federation of Gynecology and Obstetrics (FIGO) stage. CT, MRI, and PET imaging are used to guide treatment.

TREATMENT

Patients with early stage disease are treated with hysterectomy and/or pelvic radiation. Chemoradiation can be used in locally advanced tumors and as adjuvant therapy in highrisk patients following hysterectomy. Metastatic disease is treated with chemotherapy.

Endometrial Cancer

GENERAL PRINCIPLES

Epidemiology

Endometrial cancer is the most common gynecologic cancer in the United States, estimated to account for 54,870 new cases in 2015. Risk factors include obesity, unopposed estrogen, early menarche, late menopause, nulliparity, chronic anovulation, and tamoxifen use. Patients with hereditary cancer syndromes, such as Lynch syndrome, have increased incidence of endometrial cancer.

Pathology

There are two molecularly and morphologically distinct histologic subtypes:

- Type I: These are associated with exposure to unopposed estrogen (exogenous use, chronic anovulation, obesity, diabetes, nulliparity, and late menopause).
- Type II: These are more sporadic and not associated with the same risk factors as type I. These tumors show nonendometrioid histologies (serous, clear cell) and are associated with an aggressive behavior.

DIAGNOSIS

Clinical Presentation

The most common presentation is abnormal vaginal bleeding. Any vaginal bleeding in a postmenopausal woman, including spotting and staining, should be evaluated.

Diagnostic Testing

Tissue diagnosis is obtained through endometrial biopsy or through dilation and curettage. Cystoscopy, proctoscopy, and radiologic imaging might be necessary following clinical evaluation. Surgical exploration and staging are indicated in medically fit patients.

TREATMENT

- Surgery is indicated for staging and treatment.
- Patients with cervical extension (stage II) may benefit from adjuvant radiotherapy.
- Patients with extrauterine disease extension and those with distant metastases are treated with chemotherapy. Surgical cytoreduction prior to chemotherapy is a treatment option in a few women with metastatic disease.
- Chemotherapy, radiation, and hormone therapy are considered for patients in whom surgical staging and debulking is not feasible.

Ovarian Cancer

GENERAL PRINCIPLES

Epidemiology

Ovarian cancer is the leading cause of gynecologic mortality in the United States, with 14,180 deaths estimated in 2015. Risk factors include early menarche, late menopause, nulligravidity, family history, and familial syndromes including patients with *BRCA1* and *BRCA2* mutations and Lynch syndrome. Oral contraception use and pregnancy are associated with a low risk of ovarian cancer, suggesting a role for ovulation in malignant transformation.

Pathology

Most tumors are seen in patients between the ages of 40 and 65 years, and the majority of tumors are epithelial. Nonepithelial ovarian malignancies (germ cell, sex cord-stromal, and mixed) are seen in younger patients.

DIAGNOSIS

Clinical Presentation

Patients with early stage disease have nonspecific symptoms including bloating and abdominal discomfort. Patients usually have advanced disease at presentation and may have increasing abdominal girth, ascites, and abdominal pain.

Diagnostic Testing

- Cancer antigen 125 (CA-125) is elevated in most patients but is not specific.
- Surgical staging is an important aspect of management and is usually performed without prior histologic diagnosis for tumor debulking.

TREATMENT

- Stage I (without pelvic extension): Surgery is the preferred treatment.
- Stage II (extension to uterus, fallopian tubes, or other pelvic tissues): Treatment includes surgery and adjuvant chemotherapy.
- Stage III (peritoneal or lymph node involvement) and IV (distant metastasis): The treatment of choice is cytoreductive surgery and systemic chemotherapy with platinum and taxane agents administered intravenously (with or without intraperitoneal chemotherapy).

- Poly-ADP-ribose phosphorylase (PARP) inhibitors are associated with activity in patients with ovarian cancer carrying *BRCA* mutations. Olaparib is the first PARP inhibitor to be approved for use in ovarian cancer.
- **Germ cell ovarian cancers** are rare, typically occur in younger women, and are curable with chemotherapy.
- **Stromal tumors** usually present in early stages and are commonly cured with resection alone.

Cancer of Unknown Primary

GENERAL PRINCIPLES

Definition

Cancer of unknown primary site is defined as biopsy-proven malignancy for which the primary site of origin cannot be identified after a thorough history and physical examination, blood tests, and routine imaging studies.

Pathology

These malignancies are classified using light microscopy into adenocarcinoma (60%), poorly differentiated carcinoma/poorly differentiated adenocarcinoma (29%), squamous cell carcinoma (5%), poorly differentiated malignant neoplasm (5%), and neuroendocrine carcinoma (1%). Further identification usually requires specialized tests including IHC staining, electron microscopy, and genetic analysis.

DIAGNOSIS

In most cases, it is required to perform several studies to facilitate a diagnosis. Routine tests include pelvic and rectal examination, urinalysis, stool occult blood testing, and tumor marker testing in select patients (e.g., PSA in older men and β-hCG and AFP in younger men). CT of the chest, abdomen, and pelvis and symptom-oriented endoscopy are often warranted. PET scans are particularly useful in identifying the primary site in squamous cell carcinomas involving the cervical lymph nodes. IHC, electron microscopy, cytogenetic analysis for identifying characteristic abnormalities, and molecular profiling can yield important diagnostic clues and guide treatment.

TREATMENT

Treatment for favorable subgroups of patients with cancer of unknown primary is tailored to the likely primary site of origin (Table 22-5). Most patients who have unfavorable disease are treated with an empiric combination chemotherapy regimen, such as carboplatin and paclitaxel.

Melanoma

GENERAL PRINCIPLES

Epidemiology and Etiology

It is estimated that nearly 73,870 new cases of cutaneous melanoma will be diagnosed in 2015 in the United States. Lifetime risk of melanoma is higher among Caucasians (1 in 50) compared to African Americans (1 in

1000). Exposure to UV radiation, increased number of nevi (>50), history of >5 atypical nevi, large congenital nevi, immune suppression, and

familial risk (*CDKN2A* mutations) are known risk factors. Uveal (5%) and mucosal (1%) melanomas are rare.

TABLE 22-5 Treatment Recommendations for Selected Favorable Subgroups of Cancer of Unknown Primary

Subgroup	Treat for
Women with adenocarcinoma involving the axillary nodes	Stage II or III breast cancer
Women with papillary serous adenocarcinoma in the peritoneal cavity	Stage III ovarian carcinoma
Men with blastic bone metastases and elevated prostate-specific antigen	Prostate cancer
Men with poorly differentiated midline carcinoma	Extragonadal germ cell tumor
Squamous cell carcinoma of the cervical lymph nodes	Locally advanced head and neck cancer
Single metastasis	Local treatment with surgery or radiation therapy

Pathology

The most common types are superficial spreading (most common), nodular, lentigo maligna, acral lentiginous, and rare variants such as nevoid and desmoplastic. In most instances, histologic subtype does not influence staging or management (with the exception of desmoplastic melanoma, in which sentinel node biopsy may not be required). Breslow thickness, mitotic rate, ulceration, and presence or absence of disease at resection margins are important elements of histology that influence management and prognosis.

DIAGNOSIS

Clinical Presentation

Melanoma should be suspected in persons with pigmented skin lesions with **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, or **e**volution (change in characteristics) (ABCDEs of melanoma). Patients can present with pigmented lesions that itch, bleed, or show ulceration at diagnosis. Desmoplastic melanoma can present as a firm cutaneous mass.

Diagnostic Testing

The workup often involves adequate sampling of the lesion, IHC for markers of melanocytic origin (e.g., S100, MART1, HMB45), and genotype testing for detection of mutations in the *BRAF* gene (the V600E variant in particular). Primary lesions >0.75 mm in Breslow thickness, with ulceration, ≥1 mitoses/mm^2, or lymphovascular invasion, require a sentinel lymph node biopsy. CT imaging of chest, abdomen, and pelvis

with or without PET can be considered in patients with node-positive disease. Patients with metastatic disease require brain MRI.

TREATMENT

- **Localized disease:** The treatment of choice is resection with wide margins (0.5-2 cm depending on Breslow thickness). Patients with stage IIB-III benefit from adjuvant treatment with IFN-α2b. The role of newer therapies in the adjuvant setting is being investigated.
- **Metastatic disease:** There has been substantial progress in the management of metastatic melanoma.
  - ***BRAF* mutant:** About 50% of patients harbor the V600E mutation. These patients benefit from therapy with the BRAF inhibitors vemurafenib or dabrafenib, either alone or in combination with MEK inhibitors such as trametinib (*N Engl J Med 2015;372:30*).
  - **Immunotherapy:** Ipilimumab, an antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA4); nivolumab, a PD-1-directed antibody; and pembrolizumab, a PD-L1-directed antibody, are immunotherapies currently approved for use in patients with metastatic melanoma. Preliminary data support a role for concurrent therapy with nivolumab and ipilimumab (*N Engl J Med 2013;369:122*). Autoimmune endocrinopathies, pneumonitis, and colitis have been reported in patients treated with these drugs and may warrant treatment discontinuation if severe.

Central Nervous System Tumors

GENERAL PRINCIPLES

Epidemiology and Etiology

Brain and other central nervous system (CNS) tumors are estimated to be diagnosed in 22,850 patients in 2015. Ionizing radiation and familial cancer syndromes such as neurofibromatosis types 1 and 2, Li Fraumeni syndrome, and Von Hippel-Lindau syndrome are known risk factors.

Pathology

Meningiomas, gliomas, pituitary tumors, and embryonal tumors are the predominantly encountered primary CNS tumors in adults. The World Health Organization (WHO) classification further classifies gliomas based on their histology (e.g., astrocytoma, oligodendroglioma) and grade (I-IV).

DIAGNOSIS

Clinical Presentation

Patients with brain tumors typically present with a variety of symptoms ranging from headache, nausea, vomiting, seizures, and focal deficits to global neurologic dysfunction, based on the extent of mass effect and location of the tumor.

Diagnostic Testing

Workup includes MRI of the brain and molecular testing of the surgical biopsy or resected tumor specimen for *MGMT* methylation, 1p/19q co-deletion, and *IDH1* mutation, which may help guide therapy.

TREATMENT

- Gross total resection should be attempted in all patients, when possible. If resection is not feasible, a biopsy should be obtained for diagnosis and molecular testing.

- **Grade I tumors:** The treatment of choice is surgical excision.
- **Grade II tumors:** The treatment of choice is surgical excision. Recent data seem to favor treatment with adjuvant PCV (procarbazine, lomustine, and vincristine) and radiation in selected patients undergoing subtotal resection.
- **Grade III tumors:** The standard treatment is surgical excision followed by radiation and chemotherapy with either temozolomide or PCV.
- **Grade IV tumors/glioblastoma multiforme (GBM):** The treatment of choice is surgical excision or maximal debulking followed by concurrent chemoradiation with temozolomide and adjuvant temozolomide upon completion of chemoradiation. Bevacizumab is approved for recurrent GBM. Treatment is often individualized for elderly patients.
- **Meningioma:** Can be observed in asymptomatic patients for lesions that do not seem to be expanding. Surgical excision can be curative. Radiation is an option for inoperable tumors and in the adjuvant setting.

HEMATOLOGIC MALIGNANCIES

Myelodysplastic Syndrome

GENERAL PRINCIPLES

Epidemiology and Etiology

- Myelodysplastic syndromes (MDSs) comprise a heterogeneous group of myeloid neoplasms that are broadly characterized by cytopenias associated with a dysmorphic and usually cellular bone marrow and an increased risk of leukemic transformation. The median age at diagnosis is ≥65 years for de novo MDS. Cytopenias in MDS are due to clonal abnormalities of marrow cells affecting one or more cell lines. Therapy-related myeloid neoplasms, including acute myeloid leukemia (AML) and MDS, account for 10-20% of all myeloid neoplasms.
- Environmental factors such as exposure to chemicals, radiation, and chemotherapy, as well as genetic syndromes and benign hematologic disorders (such as paroxysmal nocturnal hemoglobinuria), have been associated with an increased risk of MDS.
- Chromosome abnormalities occur in up to 80% of cases, leading to accumulation of multiple genetic lesions, loss of tumor suppressor genes, and/or activating oncogene mutations.

Pathology

The current WHO classification system includes the following subclasses of MDS: refractory cytopenia with unilineage dysplasia (anemia, neutropenia, or thrombocytopenia); refractory cytopenia with multilineage dysplasia; refractory anemia with ring sideroblasts; refractory anemia with excess blasts (RAEB; 5-20%), which may be subdivided into RAEB-1 (5-9% blasts) and RAEB-2 (10-19% blasts); MDS with isolated deletion of 5q; and MDS unclassified.

DIAGNOSIS

Clinical Presentation

Symptoms can be related to bone marrow failure including fatigue, fever, bruising, or bleeding. Some cases are discovered incidentally through routine blood work. Leukopenia can be related to frequent infections. Sweet syndrome (acute febrile neutrophilic dermatosis) during the course of MDS may herald leukemic transformation.

Diagnostic Testing

Complete blood counts usually show anemia alone or as part of bicytopenia or pancytopenia. Macrocytosis is common. Platelet count can be normal or low. Peripheral blood smear can show dimorphic erythrocytes and large platelets. Neutrophils can be hypogranulated and have abnormally segmented nuclei (pseudo-Pelger-Huet cells). Obtaining a bone marrow aspirate and biopsy is important. The bone marrow is usually hypercellular. Cytogenetic analyses and FISH are required to identify chromosomal abnormalities, which aid in prognostication and planning therapy.

TREATMENT

- Therapy for MDS is generally unsatisfactory, and stem cell transplantation is the only curative option. A prognostic scoring system such as the Revised International Prognostic Scoring System (IPSS-R) (Table 22-6) is often used to determine patient risk category and influences treatment.
- Asymptomatic patients with low risk can be followed without specific therapy.
- Patients with very-low-risk or low-risk MDS and symptomatic anemia and a low erythropoietin level (<500 mU/mL) can be treated with erythropoiesis-stimulating agents. Treatment with immunosuppressive agents such as antithymocyte globulin and cyclosporine can be considered in patients with high erythropoietin levels. Patients who are young (age <60 years), have hypocellular MDS, express HLA-DR15, and demonstrate a paroxysmal nocturnal hemoglobinuria clone are more likely to respond to immunosuppression.
- Treatment with hypomethylating agents such as 5-azacytidine or decitabine can be considered in patients not suitable for immunosuppression. Treatment with 5-azacytidine has been associated with improved blood counts and a modest survival benefit compared to best supportive care.
- 5q-deleted MDS is associated with a good prognosis and higher probability of response to treatment with lenalidomide.
- Patients with high- and very-high-risk MDS are candidates for stem cell transplantation if eligible. Therapy with hypomethylating agents can be considered in those not eligible for transplant.

Acute Myeloid Leukemia

GENERAL PRINCIPLES

Epidemiology and Etiology

AML is the most common type of acute leukemia in adults. Median age at presentation is around 65 years. Risk factors are similar to those of MDS. Antecedent MDS increases the risk of AML.

Pathology

The current WHO classification (Table 22-7) includes the following categories: AML with recurrent genetic

abnormalities; AML with MDS-related changes; therapy-related AML; AML, not otherwise specified (NOS); myeloid sarcoma; myeloid proliferations related to Down syndrome; and blastic plasmacytoid dendritic neoplasms.

The AML NOS category includes the French-American-British (FAB) subtypes M0 (AML minimally differentiated), M1 (AML without maturation), M2 (AML with maturation), M4 (acute myelomonocytic leukemia), M5 (acute monocytic leukemia), M6 (acute erythroleukemia), and M7 (acute megakaryoblastic leukemia). FAB subtype M3 (acute promyelocytic leukemia [APL]) is classified as AML with recurrent genetic abnormalities due to the presence of t(15;17).

TABLE 22-6 Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes

Score	Cytogenetics	Marrow Blasts (%)	Hemoglobin (g/dL)	Neutrophils ($\times 10^9$/L)	Platelets ($\times 10^9$/L)
0	Very good: - Y, del(11q)	≤2	≥10	≥0.8	≥100
0.5				<0.8	50-99
1	Good: normal, del(5q), del(12p), del(20q), double including del(5q)	2.1-4.9	8-9.9		<50
1.5			<8		
2	Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones	5-10			
3	Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex with 3 abnormalities	>10			
4	Very poor: complex with >3 abnormalities				

Total Score	Risk Category	Median Overall Survival (years)	Median Time to 25% Acute Myeloid Leukemia Risk (years)
≤1.5	Very low	8.8	NR
2.0-	Low	5.3	10.8

3.0			
3.5-4.5	Intermediate	3	3.2
5.0-6.0	High	1.6	1.4
>6.0	Very high	0.8	0.73

TABLE 22-7 Acute Leukemias with Recurrent Genetic Abnormalities

Acute Myeloid Leukemia	Acute Lymphoblastic Leukemia (ALL)
Recurrent genetic abnormalities	**Recurrent genetic abnormalities**
t(8;21); *RUNX1-RUNX1T1*	t(9;22); *BCR1-ABL*
inv(16) or t(16;16); *CEFB-MYH11*	t(V;11); *V/MLL* (*MLL* rearranged)
t(15;17); *PML-RARA*	t(12;21); *TEL/AML1* (*ETV6-RUNX1*)
t(9;11); *MLLT3-MLL*	t(1;19); *E2A-PBX1*
t(6;9); *DEK-NUP214*	t(5;14); *IL3-IGH*
inv(3) or t(3;3); *RPN1-EVI1*	ALL with hyperdiploidy
t(1;22); *RBM15-MKL1*	Hypodiploid ALL
Provisional entities at molecular level	
NPM1 mutated	
CEBPA mutated	

DIAGNOSIS

Clinical Presentation

Symptoms are usually related to bone marrow failure, including fatigue, fever, bruising, or bleeding. Most patients present with pancytopenia and circulating blast forms. Patients with a high blast percentage are at risk for leukostasis, manifested by dyspnea, chest pain, headaches, confusion, and cranial nerve palsies.

Extramedullary tissue invasion by leukemic cells (most commonly with AML-M5) can result in hepatomegaly, splenomegaly, lymphadenopathy, rashes (leukemia cutis), gingival hypertrophy, CNS dysfunction, cranial neuropathies, or infiltrative masses (granulocytic sarcomas or chloromas).

Diagnostic Testing

In the WHO system, AML is defined by the presence of ≥20% blasts in the bone marrow and/or in the peripheral blood. AML with t(8;21), inv(16), and t(15;17) can be diagnosed irrespective of the blast percentage. Bone marrow specimens should be submitted for flow cytometry, molecular testing, and cytogenetics. This information is used to classify AML into prognostic groups and guide treatment (*Blood 2010;115:453*).

TREATMENT

- **Remission induction:** Induction chemotherapy consists of a 7 + 3 regimen that includes administration of cytarabine over 7 days in combination with an anthracycline (daunorubicin or idarubicin) on the first 3 days. Approximately 60-80% of AML patients achieve remission with induction chemotherapy. However, patients achieving remission eventually relapse without additional consolidation therapy.
- **Consolidation:** Options include high-dose cytarabine with or without subsequent stem cell transplantation. Optimal consolidation strategy is dependent on disease risk category (Table 22-8).
- Acute promyelocytic leukemia (AML-M3) is characterized by increased cure rates. Treatment includes the use of all-*trans*-retinoic acid (ATRA) and arsenic trioxide.

TABLE 22-8 Cytogenetic Abnormalities in Acute Myeloid Leukemia and Associated Prognosis

Risk Group	Cytogenetic and Molecular Features	Preferred Consolidation Strategy
Favorable	t(15;17), t(8;21), inv(16). Mutated *NPM1* without mutated *FLT3*-ITD, or mutated *CEBPA*	Chemotherapy
Intermediate	Normal cytogenetics. Mutated *FLT3*-ITD, t(9;22)	Allogeneic transplant
Unfavorable	Complex karyotype (defined as ≥3 abnormalities, excluding the favorablerisk cytogenetics), monosomal karyotype, inv(3), t(6;9), *MLL* rearranged, del(5q), -5, -7, +8	Allogeneic transplant

Acute Lymphoblastic Leukemia

GENERAL PRINCIPLES

Epidemiology and Etiology

Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia. The median age at presentation is 35 years with a bimodal distribution including one peak at 4-5 years and a second gradual increase after the age of 50 years. Advanced age is a poor prognostic factor.

Pathology

ALL can arise from B- or T-lymphocyte progenitors. The WHO classifies ALL into three categories: B cell with recurrent genetic abnormalities, T cell, and B cell, not otherwise specified (see Table 22-7).

DIAGNOSIS

Clinical Presentation

Symptoms include fatigue, fever, and bleeding. Leukostasis is uncommon, even with high white blood cell counts. Lymphadenopathy and splenomegaly are present in approximately 20% of cases. CNS may be involved at presentation, manifesting as headache or cranial nerve palsies.

Diagnostic Testing

Basic workup is similar to that required in AML. Immunophenotyping is often necessary to distinguish ALL from AML.

TREATMENT

- Several complex regimens such as the Berlin-Frankfurt-Munster (BFM); hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD); Cancer and Leukemia Group B (CALGB) 8811; and the German Multicenter ALL (GMALL) regimen have been described in ALL. Treatment is usually subdivided into induction, consolidation, and maintenance (usually administered over a course of 2 years) phases.

- Because of the high risk of CNS relapse, prophylactic intrathecal therapy is administered during the induction and consolidation phases.
- Allogeneic stem cell transplantation is an option in relapsed ALL and in patients with high-risk disease.

Chronic Myeloid Leukemia

GENERAL PRINCIPLES

Epidemiology and Etiology

Chronic myeloid leukemia (CML) accounts for nearly 14% of leukemias diagnosed in the United States, with a median age at diagnosis of 65 years.

Pathology

- CML is associated with the fusion of two genes, *BCR* on chromosome 22 and *ABL1* on chromosome 9, resulting in the *BCR-ABL1* fusion gene (Philadelphia chromosome). The fusion protein is associated with deregulated kinase activity.
- The natural history of CML is a triphasic process with a chronic phase, an accelerated phase, and a blast phase. Chronic phase is associated with an asymptomatic accumulation of differentiated myeloid cells in the marrow, spleen, and circulation. CML patients will invariably progress to accelerated and blast phases without

treatment.

DIAGNOSIS

Clinical Presentation

Patients can present in any of three phases, although the majority present in the chronic phase of their illness. Symptoms are usually related to splenomegaly (pain, left abdominal mass, early satiety) or anemia. Peripheral blood counts show increased white blood cells with all levels of granulocytic differentiation, from myeloblasts to segmented neutrophils. Transformation from chronic phase to blast phase can be insidious through the accelerated phase or abrupt.

Diagnostic Testing

The presence of the *BCR-ABL1* rearrangement by cytogenetics, FISH, or polymerase chain reaction (PCR) in the peripheral blood or bone marrow confirms the diagnosis of CML. Quantitative PCR (qPCR) is performed prior to treatment initiation to establish a baseline and then every 3 months to monitor response to treatment.

TREATMENT

- Most patients are initially treated with oral TKIs such as imatinib, dasatinib, and nilotinib. The choice of agent typically depends on treatment-related adverse effects and patient preference. Phase III trials comparing second-generation TKIs (dasatinib or nilotinib) to imatinib as initial therapy for CML in chronic phase have demonstrated faster and deeper responses with the former.
- Complete hematologic remission (CHR) is defined as normalization of peripheral blood counts and absence of splenomegaly, whereas complete cytogenetic response (CCyR) is defined by the absence of Philadelphia chromosome metaphases on bone marrow cytogenetic analysis; major molecular remission (MMR) is defined by qPCR when *BCR-ABL1* transcripts in the peripheral blood are ≤0.1% on the International Scale (IS). Complete molecular remission (CMR) defined by the absence of *BCR-ABL1* transcripts by qPCR is a misleading term because a very low burden of malignant clone may still be present in

  these patients, and therefore, it has been proposed to not use this term any more. CHR and/or *BCR-ABL1* transcripts in the marrow ≤10% (IS) by 3 months, CCyR and/or *BCR-ABL1* transcripts in the marrow ≤1% (IS) by 6 months, and *BCR-ABL1* transcripts in the marrow ≤0.1% (IS) by 12 months after starting a TKI constitute an optimal response to therapy (*Blood 2013;122:872*).
- Failure to achieve treatment milestones often requires switching therapies. Many patients who respond initially to first-line TKIs may eventually develop acquired resistance. For patients with resistance, ponatinib and omacetaxine are available, although they do not provide long-term disease control.
- Stem cell transplantation can be considered in patients who relapse after initial response to TKIs and/or who develop resistance to TKIs.
- Blast crises are more challenging to manage, and treatment often involves TKIs, chemotherapy, and stem cell transplantation.

Chronic Lymphocytic Leukemia

GENERAL PRINCIPLES

Epidemiology and Etiology

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Western countries. CLL carries the highest familial risk of all hematologic malignancies, highlighting the importance of inheritable risk factors. Monoclonal B lymphocytosis (MBL) precedes the development of CLL with a rate of 1.1% per year. MBL is characterized by the presence of less than 5000 monoclonal B cells/μL with no other features of a lymphoproliferative disorder (*N Engl J Med 2008;359:575*).

Pathology

The diagnosis of CLL requires the presence of more than 5000 lymphocytes/μL and characteristic cell surface markers including the B-cell antigens CD19, CD20, and CD23. Of note, CD5, a T-cell antigen, is found in virtually all cases of CLL.

STAGING

The classification of CLL, based on the extent of systemic infiltration of lymphocytes, is used to determine the prognosis and initiation of treatment (Table 22-9). Molecular and cytogenetic markers have become increasingly useful for prognostication.

TABLE 22-9 Chronic Lymphocytic Leukemia Clinical Staging

Rai	Binet
Stage 0: Lymphocytosis	Stage A: Lymphocytosis
Stage 1: Lymphadenopathy	Stage B: Lymphadenopathy in ≥3 areas
Stage 2: Splenomegaly	Stage C: Hgb <10 g/dL or platelets <100,000/μL
Stage 3: Hgb <11 g/dL	
Stage 4: Platelets <100,000/μL	

Hgb, hemoglobin.

DIAGNOSIS

Clinical Presentation

Most patients are diagnosed while asymptomatic. When present, symptoms include fatigue, weight loss, lymphadenopathy, anemia, thrombocytopenia, and infections. Patients can also present with a hemolytic anemia, immune thrombocytopenia, or Richter syndrome, which is a malignant transformation of CLL to diffuse large B-cell lymphoma.

Diagnostic Testing

Flow cytometry aids in the identification of CLL surface markers on B cells. FISH of the peripheral blood for evaluating 17p, 11q, and 13q deletion, and trisomy 12, mutation status of Ig heavy chain variable region

(IGHV), and assessing the expression of ZAP70 and CD38 are of prognostic importance.

TREATMENT

- Many patients do not require treatment at the time of initial diagnosis.
- **Active disease** as defined by the International Workshop on CLL is an indication for treatment. Active disease is characterized by progressive marrow failure, massive or symptomatic splenomegaly (>6 cm below costal margin) or lymphadenopathy (>10 cm in longest diameter), progressive lymphocytosis (>50% increase in 2 months or doubling time of <6 months), autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy, and the presence of constitutional symptoms (*Blood 2008;111:5446*).
- Treatment options include oral alkylating agents (chlorambucil, cyclophosphamide, bendamustine), purine analogues (fludarabine, cladribine), and monoclonal antibodies such as rituximab (anti-CD20), ofatumumab (anti-CD20), and alemtuzumab (anti-CD52), either as single agents or in combination. Idelalisib, a PI3K inhibitor, has been associated with improved survival and response rates in patients with relapsed CLL (*N Engl J Med 2014;370:997*).

Hairy Cell Leukemia

GENERAL PRINCIPLES

Epidemiology

Hairy cell leukemia is a rare disorder, most commonly seen in elderly men.

Diagnostic Testing

Peripheral blood leukocytes have the characteristic “hairy” appearance and are tartrateresistant acid phosphatase (TRAP) positive. Flow cytometry is positive for CD20, CD11c, CD103, CD123, cyclin D1, and annexin A1. The majority of patients with hairy cell leukemia harbor the *BRAF* V600E mutation.

DIAGNOSIS

Clinical Presentation

Most patients present with malaise and fatigue. Splenomegaly and hepatomegaly may be evident on exam. With more advanced disease, pancytopenia develops, and patients may present with bleeding or recurrent infections.

TREATMENT

- The decision to treat is based on the development of cytopenias, symptomatic splenomegaly, constitutional symptoms, and recurrent infections.
- Cladribine and pentostatin are typically used for treatment. However, both of these agents induce significant and prolonged immunosuppression.

Hodgkin Lymphoma

GENERAL PRINCIPLES

Epidemiology and Etiology

The incidence of Hodgkin lymphoma (HL) follows a bimodal distribution with the first peak at age 25 years and second peak after the age of 50 years. EBV and HIV infections, autoimmune conditions, and immunosuppressant use have been described as risk factors for HL.

Pathology

- HL is subdivided into nodular lymphocyte predominant (NLPHL) and classical HL (nodular sclerosis, lymphocyte-rich, mixed-cellularity, lymphocyte-depleted) subtypes.
- The Reed-Sternberg (RS) cells consistently express the CD30 and CD15 antigens. CD30 is a marker of lymphocyte activation that is expressed by reactive and malignant lymphoid cells. CD15 is a marker of late granulocytes, monocytes, and activated T cells that is not normally expressed by cells of B lineage. In contrast to the other histologic subtypes, RS cells are infrequent in NLPHL. Instead, “popcorn cells” are seen within a background of inflammatory cells in NLPHL.

DIAGNOSIS

Clinical Presentation

Most patients present with painless lymphadenopathy. B symptoms are more common in advanced stages.

Diagnostic Testing

FNA is often inadequate to make a diagnosis, and an excisional biopsy may be required. Workup includes history and physical, complete blood cell counts, chemistry, LDH, erythrocyte sedimentation rate (ESR), CT, PET, and bone marrow exam.

STAGING

The Ann Arbor staging system classifies lymphomas into four stages (Table 22-10). Patients with early stage disease (stages I-II) are further stratified into favorable and unfavorable risk categories. Favorable risk is defined by the presence of not more than two sites of disease, mediastinal width less than one-third of maximal thoracic diameter, ESR <50 mm/h (30 mm with B symptoms), and absence of extranodal extension (*N Engl J Med 2010;363:640*).

TREATMENT

The treatment of choice for HL is chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), with or without radiation, depending on the stage and risk category. Relapsed disease is treated with salvage chemotherapy with or without stem cell transplantation. Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has been recently approved for treatment of refractory and relapsed HL.

TABLE 22-10 Ann Arbor Staging of Lymphomas[a]

Stage	Description
I	Involvement of a single lymph node region (I) or single extralymphatic organ (IE).

II	Involvement of ≥2 lymph node regions in the same side of the diaphragm.
III	Involvement of lymph node regions in both sides of the diaphragm.
IV	Diffuse or disseminated involvement of one or more extralymphatic organs.

[a]Modifying features: A, absence of B features; B, presence of B features; E, involvement of a single extranodal site contiguous or proximal to the involved nodal site; S, spleen involvement; X, bulky disease defined as lymph node ≥10 cm than one-third of mediastinum.

Non-Hodgkin Lymphoma

GENERAL PRINCIPLES

Epidemiology and Etiology

Non-Hodgkin lymphoma (NHL) is the fifth most common malignancy in the United States with an estimated 71,850 new cases in 2015. Risk factors include immunodeficiency, autoimmune disorders, bacterial infections (*H. pylori*, *Borrelia burgdorferi*, and *Chlamydia psittaci*), viral infections (HIV, EBV, HHV8, and human T-lymphotropic virus-1), and immunosuppression in the setting of previous transplantation.

Pathology

NHL may be broadly divided into indolent (e.g., follicular, marginal, small lymphocytic), aggressive (e.g., diffuse large B cell, mantle cell, peripheral T cell, anaplastic T cell), and very aggressive (Burkitt lymphoma, lymphoblastic) tumors. Several recurrent chromosomal abnormalities have been described in patients with NHL (Table 22-11).

DIAGNOSIS

Clinical Presentation

Clinical manifestations depend on the histologic subtype and can be characteristic in some rare subtypes of NHL. For instance, pruritic plaques can be seen in mycosis fungoides (a primary cutaneous T-cell NHL), marked hepatosplenomegaly in mantle cell lymphoma, and isolated splenomegaly in splenic marginal zone lymphomas.

Diagnostic Testing

Essential workup often includes history, physical exam, complete blood cell count, chemistry, PET/CT, and bone marrow biopsy. The CSF evaluation is indicated in patients with high-grade lymphomas, HIV-related lymphomas, and involvement of the epidural space, nasopharynx, and paranasal sinuses. Patients suspected to have primary CNS lymphomas require an ophthalmologic exam. Occasionally, patients with aggressive lymphomas can present with a spontaneous tumor lysis syndrome (TLS) (Table 22-12).

STAGING

Patients are staged by the Ann Arbor classification. Patients with aggressive lymphoma are usually stratified according to the International Prognostic Index, which uses five adverse

prognostic factors: age >60 years, Ann Arbor stage III or IV, abnormal serum LDH, two or more extranodal sites involved, and Eastern Cooperative Oncology Group performance status of ≥2. Five-year survival rates for patients with 0-1, 2, 3, or 4-5 risk factors are 73%, 51%, 43%, and 26%, respectively (*N Engl J Med 1993;329:987*).

TABLE 22-11 Selected Chromosomal Abnormalities in B-Cell Non-Hodgkin Lymphomas

Cytogenetic Abnormality	Histology	Oncogene
t(14;18)	Follicular, DLBCL	*BCL2*
t(11;14)	Mantle cell	Cyclin D1
t(1;14)	MALT lymphoma	*BCL10*
t(11;18)	Marginal zone/extranodal marginal zone	
t(2;5)	ALK-positive anaplastic large-cell lymphoma	*ALK*
t(9;14)	Lymphoplasmacytic lymphoma	
8q24 translocations t(8;14) t(2;8) t(8;22)	Burkitt lymphoma	*MYC*

DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue.

TREATMENT

Indolent Lymphomas

Stage I-II

- Observation, involved-field radiotherapy (IFRT), single-agent rituximab, rituximab with chemotherapy, and combined-modality therapy with rituximab, chemotherapy, and IFRT are all options.
- Gastric mucosa-associated lymphoid tissue (MALT) lymphomas are related to *H. pylori* infection and respond well to *H. pylori*-directed therapy (*Gut 2012;61:507*).

Gastric MALT lymphomas that do not respond to or relapse after *H. pylori* therapy, and other isolated extranodal lymphomas (salivary gland, breast, conjunctiva) may be treated with IFRT.

TABLE 22-12 Defining Features of Tumor Lysis Syndrome

Manifestation	Features
Laboratory	1. Uric acid ≥8 mg/dL or 25% increase from baseline 2. Potassium ≥6 mEq/dL or 25% increase from baseline 3. Phosphorus ≥6.5 mg/dL or 25% increase from baseline 4. Calcium ≤7 mg/dL or 25% decrease from baseline
Clinical	1. Creatinine ≥1.5 × upper normal limit 2. Cardiac arrhythmia or sudden death 3. Seizure

Stage III-IV

There is no convincing evidence to support early intervention versus "watchful waiting" in asymptomatic patients (*Lancet Oncol 2014;15:424*). Older patients with low-volume disease and no symptoms can be observed. A combination of rituximab and chemotherapy or single-agent rituximab can be used for treatment.

Relapsed disease

First-line therapy can be repeated in patients who were in first remission for >1-2 years. Radioimmunotherapy (RIT) with ibritumomab (anti-CD20 antibody conjugated with yttrium-90), idelalisib, lenalidomide, and stem cell transplant are all effective options.

Aggressive Lymphomas

Diffuse Large B-Cell Lymphoma

Stage I-II

Limited-stage disease is managed with chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) with or without IFRT.

Stage III-IV

- Patients beginning therapy for aggressive lymphomas should be monitored closely for signs of TLS and should receive adequate IV hydration and appropriate prophylaxis with allopurinol and/or rasburicase.
- Chemotherapy with R-CHOP is the standard. Patients with *MYC* translocations, especially those with "double-hit" lymphomas (combined translocations of *MYC* and either *BCL2* or *BCL6*), have significantly worse outcomes.
- **CNS prophylaxis** with intrathecal chemotherapy or high-dose methotrexate should be considered for patients with testicular, orbital, epidural, paranasal sinus, or extensive bone marrow involvement with elevated LDH.
- Primary CNS lymphoma is treated with complex regimens that usually incorporate high-dose methotrexate, cytarabine, and rituximab with consideration for consolidation with stem cell transplantation (*J Clin Oncol 2013;31:3061*). Wholebrain radiation alone is reserved for elderly patients who are ineligible for aggressive chemotherapy.

Burkitt Lymphoma

Burkitt lymphomas are usually treated with complex multidrug protocols and CNS prophylaxis.

Mantle Cell Lymphoma

Chemotherapy regimens such as rituximab plus Hyper-CVAD alternating with high-dose methotrexate and

cytarabine, or brentuximab and rituximab are often used. Consolidation with stem cell transplantation can be considered in first remission. Maintenance rituximab is considered in select patients.

Relapsed disease

- Younger patients without significant comorbidities are candidates for stem cell transplantation at relapse. Several effective salvage regimens such as ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cisplatin, cytarabine), and ESHAP (etoposide, methylprednisone, cytarabine, cisplatin) are available. Rituximab can be added to patients with B-cell lymphomas.
- Allogeneic transplantation should be considered in patients with relapsed Burkitt or lymphoblastic lymphoma, refractory disease at relapse, or a duration of remission of <1 year after initial therapy.

Multiple Myeloma

GENERAL PRINCIPLES

Multiple myeloma (MM) is the second most frequent hematologic malignancy after NHL. The median age at diagnosis is 66 years. A small percentage of cases are familial.

DIAGNOSIS

Clinical Presentation

The most common presentation is anemia. Patients can also have bone pain, renal failure, fatigue, elevated creatinine, weight loss, and hypercalcemia. Patients with extramedullary plasmacytomas can present with radiculopathy, cord compression, or CNS involvement.

Diagnostic Testing

Initial evaluation includes routine blood work, β_2-microglobulin (B2M), serum and urine protein electrophoresis, serum free light chain estimation, skeletal survey, and bone marrow exam. The diagnosis is confirmed by the presence of 10% or more clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma, with evidence of end-organ damage (hypercalcemia, renal dysfunction, anemia, or bone lesions). A clonal marrow plasma cell percentage of ≥60%, κ or λ free light chain ratio of ≥100, and the presence of one or more focal lesions on MRI are also criteria for diagnosis of myeloma because they are associated with a high risk of progression to end-organ damage (*Lancet Oncol 2014;15:e538*).

STAGING

- The International Staging System for MM uses B2M and albumin to stratify patients into: stage I (B2M <3.5 mg/dL and albumin >3.5 g/dL), stage II (albumin <3.5 g/dL or B2M 3.5-5.5 mg/dL), and stage III (B2M >5.5 mg/dL).
- Cytogenetic features (Table 22-13) can be used for risk stratification and guiding treatment (*Am J Hematol 2014;89:999*).

TREATMENT

- Transplant-eligible patients are offered autologous stem cell transplantation following approximately 4 months of treatment with one of the previously mentioned regimens,

whereas initial therapy is continued for 12-18 months in transplant-ineligible patients.

TABLE 22-13 Risk Stratification in Myeloma Based on mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy) Model

Standard Risk	Intermediate Risk	High Risk
Trisomies, t(11;14), and t(6;14)	t(4;14), 1q gain, deletion 13, hypodiploidy, complex karyotype	17p del, t(14;16), and t(14;20) High-risk gene expression profile signature

Adapted from Mikhael JR1, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-76.

- Maintenance therapy with either lenalidomide or bortezomib is considered following initial therapy based on the patient's risk category.

Principles of Stem Cell Transplantation

GENERAL PRINCIPLES

Background

- Hematopoietic stem cell transplantation (HSCT) involves the infusion of either allogeneic (different donor) or autologous (patient's own) stem cells following administration of intense chemotherapy and/or radiation.
- Autologous transplantation involves collection, cryopreservation, and reinfusion of a patient's own stem cells. This allows administration of myelosuppressive doses of chemotherapy with the intent of maximizing the efficacy of therapy.
- Allogeneic transplantation refers to the infusion of stem cells collected from either HLAmatched or -mismatched donors. In addition to facilitating the administration of high doses of chemotherapy, allogeneic transplantation also allows for an immunologic effect mediated by donor T and natural killer (NK) cells (graft-versus-tumor effect).

Indications

- Stem cell transplantation can be considered for patients with progressive or residual disease that is thought to be chemoresponsive or susceptible to graft-versus-tumor effect. MM and lymphoma are the most common indications for autotransplantation, whereas MDS and leukemia are the most common indications for allotransplantation.
- Allogeneic transplantations are also considered in other nonmalignant disorders, such as congenital immune deficiencies, sickle cell anemia, thalassemia, and inborn errors of metabolism.

Donor Selection

Appropriate donor selection is crucial and is based on the following factors:

- HLA typing: Major histocompatibility class I and II alleles code for HLA proteins that are expressed on the cell surface and play a major role in immune recognition. Highresolution typing of 10 HLA alleles (e.g., HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1) is the current standard.
- The chance of any given sibling being a full HLA match is only 25%. Patients who lack HLA-identical siblings should have a search for HLA-matched donors through the National Marrow Donation Program (NMDP), although chances of finding an HLA-matched unrelated donor is significantly influenced by the patient's ethnicity.
- Partial HLA-mismatched transplantations, umbilical cord blood, and haploidentical transplantations (3/6 match) are alternate sources of marrow for patients without matched sibling or unrelated donors
- Cytomegalovirus (CMV)-negative donors are preferred for CMV-negative patients.

Source of Stem Cells

- Bone marrow can be obtained under anesthesia through repeated aspirations from the iliac crest.
- Stem cells can be collected from peripheral blood by leukopheresis after mobilization with granulocyte colony-stimulating factor (G-CSF) and plerixafor (CXCR4 antagonist).

Complications

- Hematopoietic transplantation is often preceded by the use of intense chemotherapy and sometimes total-body radiation to clear residual disease and immunosuppress the host. Depending on the extent of myelosuppression achieved as a result of this conditioning, regimens are classified as myeloablative, reduced intensity, or nonmyeloablative.
- **Graft-versus-host disease (GVHD):** Occurs when the donor T cells react with recipient tissues, leading to acute and/or chronic inflammation. The most common tissues affected are the skin, liver, gut, cornea, and lungs. Acute and chronic GVHD are associated with significant morbidity and mortality in allogeneic transplantation patients. Chronic GVHD can result in diarrhea and sclerodermatous-type skin changes. The prophylaxis and treatment of GVHD include the use of corticosteroids and a myriad of immunosuppressants including cyclosporine, methotrexate, sirolimus, mycophenolate, and tacrolimus.
- **Infections:** Due to the intense conditioning and heavy immunosuppression, transplant patients are susceptible to a variety of infections in the peritransplant setting. The postengraftment period is complicated by susceptibility to CMV, *Pneumocystis jirovecii* pneumonia, and *Aspergillus* infections.

ONCOLOGIC EMERGENCIES

The most common oncology emergencies are febrile neutropenia, TLS, malignant hypercalcemia, spinal cord compression, superior vena cava syndrome, and brain metastases with increased intracranial pressure (Table 22-14).

Febrile Neutropenia

GENERAL PRINCIPLES

- Febrile neutropenia (FN) is defined as an absolute neutrophil count (ANC) of <500/μL, with a single core temperature of >38.3°C or a persistent temperature (>1 hour) of >38.0°C.

- Risk of FN is proportional to the duration of neutropenia.
- Although most solid tumor chemotherapy regimens are associated with a brief (<5 day) duration of neutropenia, neutropenia with leukemia and transplantation regimens can be more persistent.
- Risk is also increased with regimens that cause mucositis (inflammation and ulceration of the oral and GI mucosa).

DIAGNOSIS

- Evaluation should include a complete physical exam including assessment of catheter sites, perianal region, and mucosal surfaces. DRE should not be performed, considering the potential risk for bacterial translocation.
- Cultures of blood and urine and CXR in all patients, along with stool and sputum cultures in symptomatic patients, should be obtained.

TREATMENT

- Emergent IV antibiotic therapy is critical to prevent life-threatening sepsis.
  - Antibiotics with coverage of gram-negative bacilli (including *Pseudomonas aeruginosa*) must be used.
  - Empiric coverage of methicillin-resistant *Staphylococcus aureus* (MRSA) with vancomycin or linezolid is not recommended unless patients are unstable or have active oral mucositis, evidence of a catheter-related infection, or a recent infection with MRSA.

TABLE 22-14 Oncologic Emergencies

Emergency	Etiology	Presentation	Management
Neutropenic fever	Infectious	Temperature >38.3°C or >38°C two times 1 h apart	1. Antibiotic coverage: gram-negative with pseudomonal activity, and gram-positive if risk factors (catheters, pneumonia, mucositis, *Staphylococcus* colonization, sepsis), and also fungal if unstable 2. IV hydration and supportive care as appropriate
Tumor lysis syndrome (TLS)	Massive lysis of cancer cells (mostly with chemotherapy)	Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, AKI, cardiac arrhythmias,	1. Prevention with IV fluids and prophylactic allopurinol or rasburicase based on estimated risk

		and/or seizures	of TLS 2. Treatment: Aggressive hydration, rasburicase, dialysis
Hypercalcemia	Humoral, PTHrP, bone metastasis, calcitriol mediated (lymphomas)	Dehydration, CNS symptoms, constipation, ileus, weakness, cardiac (bradycardia, short QT, prolonged PR, etc.)	1. IV hydration 2. Bisphosphonates or denosumab (if low creatinine clearance) 3. Calcitonin (if symptomatic, rapid onset) 4. Steroids can be useful
Spinal cord compression (SCC)	Metastatic or involvement of spine in SCC	SCC: pain, weakness, sensory loss, incontinence, ataxia	1. Steroids 2. Neurosurgery consultation 3. RT 4. Chemotherapy can be considered in few cases of SCC
Superior vena cava (SVC) syndrome	Obstruction of SVC by primary or metastatic cancer (mostly intrathoracic)	Dyspnea, stridor (laryngeal edema), facial and upper extremity swelling, risk of cerebral edema and herniation	1. Histologic diagnosis is important 2. Consider upfront endovascular stent and RT if comatose or respiratory compromise 3. Treatment depends on tumor type: SCLC, lymphoma, germ cell: chemotherapy; NSCLC: RT; thymic tumors: surgery
Hyperleukocytosis with leukostasis	Intravascular accumulation of blasts, with or without DIC	Chest pain, respiratory distress, stupor, TLS, DIC	1. Leukapheresis: symptomatic patients (count threshold AML >50 × 10^3/μL, ALL and CML >150 × 10^3/μL, CLL >500 × 10^3/μL); asymptomatic patients (AML >100 × 10^3/μL, ALL >200 × 103/μL) 2. Hydroxyurea for cytoreduction

AKI, acute kidney injury; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia;

CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; DIC, disseminated intravascular coagulation; NSCLC, non-small-cell lung cancer; PTHrP, parathyroid hormone-related protein; RT, radiotherapy; SCLC, small-cell lung cancer.

P.721

P.722

- Antimicrobial regimen should be tailored to treat the source of infection, if one is identified.
- Empiric antifungal therapy should be considered if fever persists for >72 hours.
- Gram-negative coverage should continue until ANC is >500/μL.
- Low-risk patients (afebrile for 24 hours after antibiotics, negative culture results, and expected duration of myelosuppression for <1 week) can be treated as outpatients with oral, broad-spectrum antibiotics such as fluoroquinolone, amoxicillin/clavulanic acid, or trimethoprim-sulfamethoxazole.
- Consuming raw fruits and vegetables is not associated with excessive risk for infection in neutropenic patients.

- White cell growth factors
  - G-CSF is the most commonly used growth factor and is given SC in doses of 5 μg/kg/d.
  - Although growth factors can reduce the duration of hospitalization for FN, they have not been shown to improve survival.
  - Growth factors should not be given within 24 hours after chemotherapy or during radiation because of the potential for increased myelosuppression.
  - Prophylactic growth factors are used when the predicted risk of FN is high and the neutropenia is predicted to result in chemotherapy delays.

Tumor Lysis Syndrome

GENERAL PRINCIPLES

- TLS is a group of metabolic disturbances resulting from significant tumor breakdown with release of intracellular products into the circulation.
- TLS occurs in tumors that grow rapidly and are sensitive to cytotoxic chemotherapy. The risk of TLS is high in patients with acute leukemias and high-grade lymphomas, bulky tumors, elevated pretreatment LDH and uric acid levels, and renal dysfunction.
- TLS can also be spontaneous (not treatment related).

DIAGNOSIS

TLS is characterized by the presence of certain laboratory and clinical criteria (see Table 22-14).

TREATMENT

- The most important intervention to prevent TLS is aggressive hydration to maintain a urine output of at least 100 mL/m^2/h.
- Prophylactic strategies include the use of the xanthine oxidase inhibitor allopurinol prior to treatment

initiation.

- Rasburicase is a recombinant enzyme that degrades uric acid that can be used for the prophylaxis and treatment of hyperuricemia. It is indicated in patients with an elevated uric acid level prior to treatment initiation and those at a high risk for developing hyperuricemia (predicted based on tumor type, tumor burden, and pretreatment LDH level).
- Hyperkalemia is an immediate threat and should be treated aggressively.
- Calcium administration should be restricted in symptomatic patients with hypocalcemia or hyperkalemia to prevent risk of metastatic calcification in the setting of hyperphosphatemia.
- Hyperphosphatemia should be treated with phosphate binders.
- Patients with persistent electrolyte abnormalities (hyperkalemia, hyperphosphatemia, and high calcium-phosphate products) and a pronounced decrease in urine output require renal replacement therapy.

Malignant Hypercalcemia

GENERAL PRINCIPLES

- Malignant hypercalcemia is a common paraneoplastic syndrome and occurs in nearly 10-20% of cancer patients.
- A serum total calcium level of >10.5 g/dL is generally considered elevated. Measuring ionized calcium can be necessary and helpful in patients with abnormal serum albumin levels.
- Osteolysis and humoral hypercalcemia through tumor production of parathyroid hormone (PTH), PTH-related protein (PTHrP), or vitamin D analogs are the predominant mechanisms of hypercalcemia.

DIAGNOSIS

Classic symptoms usually develop with total calcium levels above 12 mg/dL and include polyuria, polydipsia, anorexia, constipation, nausea, vomiting, and confusion. Patients are usually severely hypovolemic due to excessive fluid losses and limited intake.

TREATMENT

- Aggressive hydration with normal saline is important. Diuretics should not be used unless volume overload is present.
- IV bisphosphonates, pamidronate 90 mg or zoledronic acid 4 mg, inhibit bone resorption and are used in the management of severe or symptomatic hypercalcemia. Zoledronic acid is contraindicated in patients with severe renal dysfunction.
- Calcitonin can be used in patients with severe symptomatic hypercalcemia for short-term and immediate control of calcium levels.
- Hypercalcemia caused by tumor production of vitamin D analogs may respond to corticosteroids.

Malignant Spinal Cord Compression

GENERAL PRINCIPLES

Malignant spinal cord compression (MSCC) affects approximately 5-10% of patients with cancer and is commonly seen in patients with lung, breast, prostate, and lymphoid malignancies.

DIAGNOSIS

- The study of choice for MSCC is MRI of the entire spine.
- Most patients present with back pain and local tenderness in the involved region. Pain is worse in a recumbent position and aggravated by sneezing, coughing, or bearing down (Valsalva maneuver). Other symptoms include weakness, sensory loss, and bladder or bowel incontinence.
- Timely diagnosis and intervention are crucial to prevent permanent neurologic damage.

TREATMENT

- Patients suspected of having MSCC should be started on glucocorticoids. Treatment should not be delayed for imaging. The most commonly used corticosteroid regimen is a 10-mg dexamethasone loading dose, followed by 4 mg every 4-6 hours.

P.724

- Consultation from surgical and radiation oncology services should be obtained in a timely fashion. Outcomes are better with surgery compared to radiation therapy in patients who are surgical candidates.
- Systemic chemotherapy can be used to treat patients with chemosensitive tumors.

Superior Vena Cava Syndrome

GENERAL PRINCIPLES

- Cancer-related superior vena cava (SVC) syndrome results from obstruction of blood flow through the SVC through invasion, external compression, or thrombosis in the setting of a malignancy.
- The severity and rapidity of symptom onset depends on the rate at which the SVC is occluded and if there has been enough time for collateral venous drainage to develop.
- Lung cancer, lymphomas, thymic neoplasms, germ cell tumors, mesothelioma, and other solid tumors that cause mediastinal involvement are the cancers that are commonly associated with SVC syndrome.

DIAGNOSIS

- Symptoms can range from asymptomatic interstitial edema of the head and neck to lifethreatening complications, such as airway narrowing from upper airway or laryngeal edema and cerebral herniation and ischemia secondary to cerebral edema, as a consequence of venous outflow obstruction.
- Facial plethora, cyanosis, and arm edema are often observed. Physical exam can show presence of venous collaterals on the chest and neck. Close attention should be paid to detect stridor, headaches, or confusion.
- Contrast-enhanced CT scan of the chest allows identification of the underlying cause and level of obstruction.

TREATMENT

- Management of SVC depends on the presentation and underlying malignancy. Patients presenting with stridor from laryngeal edema and stupor from cerebral edema need emergent management with stent placement and/or radiation. Upfront radiation prior to obtaining a histologic diagnosis in patients who are stable can obscure a pathologic diagnosis and should not be pursued.
- Steroids have a role in the management of patients with steroid-responsive tumors such as lymphomas and thymomas. Their role in the management of other cancers is unclear and not recommended. Although steroids have anecdotally been used to control edema in patients with airway obstruction, they have not been systematically studied for use in this setting.
- Every effort should be made to obtain a pathologic diagnosis in a timely fashion because this information is crucial to plan management. Chemotherapy is the treatment of choice for patients with cancers such as SCLC, lymphomas, and germ cell tumors that tend to be chemosensitive.
- Stent placement and radiotherapy may be required for management and symptom relief of SVC syndrome in patients with less chemoresponsive tumors such as NSCLC. Anticoagulation is indicated in patients with SVC thrombosis.

Hyperleukocytosis with Leukostasis

Hyperleukocytosis refers to an elevated white blood cell count (often >100 × 10^9/L) as a result of leukemic proliferation. Leukostasis is a medical emergency as a result of

hypoperfusion due to the elevated blast count. The clinical features and emergent management of leukostasis have been summarized in Table 22-14.

Brain Metastases with Increased Intracranial Pressure

GENERAL PRINCIPLES

- Brain metastases are common in patients with malignancies. Patients with lung cancer, breast cancer, and melanoma have the highest incidence of brain metastases.
- Most lesions are supratentorial and located at the junction of gray and white matter.

DIAGNOSIS

- Headache, confusion, and focal neurologic deficits are the most common symptoms. However, nearly a third of these patients can be asymptomatic.
- CT scan of the head with IV contrast or a brain MRI is required for diagnosis.

TREATMENT

- Increased intracranial pressure from peritumoral edema or hemorrhage can lead to cerebral herniation and death in untreated patients.
- Symptomatic treatment with dexamethasone at an initial dose of 10 mg, followed by 4 mg every 6 hours, usually relieves symptoms.
- Treatment approach depends on several factors including the type of malignancy, its treatment responsiveness, location, number, and size.
- Neurosurgery, stereotactic radiosurgery or whole-brain radiation, and occasionally treatment with

chemotherapy or targeted therapies are the commonly employed modalities of treatment.

- Anticonvulsants are indicated only in patients with seizures.

MANAGEMENT OF TREATMENT TOXICITIES

Nausea

GENERAL PRINCIPLES

- Historically, nausea was one of the most debilitating side effects of chemotherapy. The advent and use of effective antiemetic therapies have made chemotherapy much more tolerable for cancer patients.
- Incidence of chemotherapy-induced nausea and vomiting (CINV) is widely variable and depends on both drug and dose used.
- CINV can be categorized as acute (<24 hours) or delayed (>24 hours). Acute CINV is an important predictor of delayed CINV.
- **Prevention** of CINV is more effective than treatment. Commonly used prophylactic agents include:
  - Dexamethasone, which has active antiemetic properties. It is frequently administered via IV prior to chemotherapy (premedication) and continued orally for 2-3 days with certain chemotherapy regimens.
  - 5-Hydroxytryptamine-3 (5-HT^3) receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron), which are highly effective and widely used as premedications.
  - Aprepitant, which is used with highly emetogenic regimens.

TREATMENT

- Posttreatment nausea should not be immediately assumed to be secondary to chemotherapy. Secondary causes, including bowel obstruction, brain metastasis with cerebral edema, constipation, narcotics, and gastroenteritis, should all be considered.
- Initial treatment with prochlorperazine is often effective. Lorazepam and other anxiolytics also have antiemetic properties. 5-HT_3 antagonists are less effective in treatment than in prevention but are frequently used. Olanzapine has also been studied and found to be active in treating CINV.

Diarrhea

GENERAL PRINCIPLES

- Diarrhea is a common side effect of many chemotherapies (irinotecan, 5FU, capecitabine), targeted agents (erlotinib, cetuximab, sunitinib, lapatinib), and newer immunotherapies (ipilimumab, nivolumab, pembrolizumab).
- Diarrhea can also be a symptomatic manifestation of the underlying cancer (such as carcinoid syndrome in neuroendocrine tumors).

DIAGNOSIS

- Obtaining a good history and accurately assessing the type of cancer a patient has, treatments received

and their timing, history of bone marrow transplantation (GVHD), immunosuppressant regimen and recent dose adjustments, and recent antibiotic use are all very crucial.

- Imaging of the abdomen, *Clostridium difficile* testing, and even obtaining a colonoscopy might be required in selected patients (e.g., ipilimumab-related colitis).
- Special attention should be paid to transplant patients because testing serum levels of immunosuppressants and testing for opportunistic infections constitute an important part of workup.

TREATMENT

- Hydration to avoid volume depletion is critical.
- Patients who test positive for *C. difficile* should be appropriately managed with suitable antibiotics such as metronidazole and/or oral vancomycin.
- Empiric and aggressive treatment with loperamide can be considered in patients with chemotherapy-related diarrhea. When loperamide is ineffective, diphenoxylate, atropine, or other similar agents can be used.
- Timely initiation of steroid therapy is important in immunotherapy and GVHD-related diarrhea.

SUPPORTIVE CARE: COMPLICATIONS OF CANCER

Cancer Pain

GENERAL PRINCIPLES

- The two main mechanisms for pain are nociceptive (somatic or visceral) and neuropathic.
  - Nociceptive pain is caused by stimulation of pain receptors and neuropathic pain by direct injury to the peripheral nervous system or CNS.

  - Somatic pain typically occurs with bone metastases, musculoskeletal inflammation, or after surgery and is characterized by a well-localized, dull, or aching pain.
  - Visceral pain results from tumor infiltration and compression or distention of viscera and is described as diffuse, deep, squeezing, and pressure-like sensation.
  - Neuropathic pain occurs due to tumor infiltration of peripheral nerves, roots, or spinal cord, as well as chemical injury caused by chemotherapy, radiotherapy, or surgery. This pain is described as a sharp or burning sensation.
- These three types of pain may occur alone or in combination in the same patient.
- Cancer pain in adults may be classified into three levels on the basis of a 0 to 10 numerical scale: mild pain (1-3), moderate pain (4-6), and severe pain (7-10).

TREATMENT

- Cancer pain is usually managed through a stepwise approach (the “WHO ladder”), according to the level of pain.
  - Step 1: Patients with mild pain and not taking opioids may be treated with nonopioid analgesics

including NSAIDs or acetaminophen.
    - Step 2: Patients with no response to nonopioids or moderate pain are treated with weak opioids such as codeine, hydrocodone, and oxycodone, either alone or in combination with acetaminophen.
    - Step 3: Severe pain is treated with opioids such as morphine, hydromorphone, methadone, or transdermal fentanyl.
- Tramadol, which has weak affinity to μ-opioid receptors and is considered a nonopioid drug, can be used in patients with mild to moderate pain not responding to NSAIDs and those who wish to defer opioid treatment.
- Co-analgesics should be considered in specific cases.
    - Systemic corticosteroids may be useful in pain caused by bone metastases, increased cranial pressure, spinal cord compression, and nerve compression or infiltration.
    - Tricyclic antidepressants, such as nortriptyline, and anticonvulsants, such as gabapentin, are commonly indicated in neuropathic pain.
    - Bisphosphonates (zoledronic acid and pamidronate) and radiolabeled agents (strontium-89 and samarium-153) may help in treating bone metastases-related pain.
- Common side effects of opioid therapy include constipation, nausea, respiratory depression, and sedation. Constipation should be prevented with the prophylactic use of combined stimulant laxative and stool softener. If symptoms persist, patients may benefit from the addition of a third agent, including lactulose, magnesium citrate, polyethylene glycol, or enema.
- Patients who experience inadequate pain control despite aggressive opioid therapy or who cannot tolerate opioid titration due to side effects may benefit from interventional therapies, such as regional infusion of analgesics and neuroablative or neurostimulatory procedures.
- Uncontrolled pain should be treated as a medical emergency. Patients in acute pain may often require opioids dosed through a patient-controlled analgesia delivery system. These patients require close monitoring.

Bone Metastasis

GENERAL PRINCIPLES

Commonly seen in patients with prostate, breast, lung, kidney, and bladder cancers and myeloma.

DIAGNOSIS

Bone scan (nuclear imaging with technetium-99m) is sensitive for blastic lesions but not lytic lesions). Concerning lesions on bone scan should be evaluated with plain radiograph films or CT to identify lesions at risk for pathologic fracture.

TREATMENT

- Pain should be managed aggressively with opioids. NSAIDs may offer additional relief.
- Lesions at risk for fracture should be treated surgically or with radiation therapy.
- Bisphosphonates and RANK ligand inhibitors may reduce the risk of fracture and reduce pain.

Pleural Effusion

GENERAL PRINCIPLES

Pleural effusions are common in patients with primary lung cancer, mesothelioma, advanced breast cancer, and lymphoma.

DIAGNOSIS

Routine thoracentesis with cytologic evaluation is typically adequate. Effusions with negative cytology can be further evaluated with pleuroscopy or open pleural biopsy (see Chapter 10, Pulmonary Diseases).

TREATMENT

- Prompt and complete drainage by therapeutic thoracentesis is necessary to avoid chronic fibrosis and trapped lung. Observation for rate of reaccumulation after initial drainage is appropriate for most patients. Rapidly reaccumulating effusions (<1 month) should be treated aggressively.
- Pleurodesis (obliteration of the pleural space by fibrosis) by complete drainage and instillation of a sclerosant (usually talc) can prevent recurrence of most malignant effusions.
- Placement of an indwelling pleural catheter for intermittent outpatient drainage is another alternative. Pleural fibrosis and resolution of the effusion occurs over several weeks in most patients.
- Medical therapy may be sufficient for managing effusions in breast cancer and lymphoma.

Fatigue

GENERAL PRINCIPLES

- Common symptom in cancer, occurring in an estimated 80% of patients with advanced disease.
- Close attention should be paid to any signs of underlying depression, which should be managed appropriately.

TREATMENT

- First step in the treatment is the identification of treatable contributing factors such as pain, poor nutrition, emotional distress, sleep disturbance, and comorbidities (anemia,

infection, organ dysfunction). Appropriate pain management, nutrition support, sleep therapy, exercise, and necessary supportive care can help address some of these issues.
- Transfusion support and erythropoietin may be helpful in selective patients with anemia.
- Psychostimulants such as methylphenidate or modafinil can prove helpful in some patients with severe symptoms.

Anorexia and Cachexia

GENERAL PRINCIPLES

- Anorexia is defined as loss of appetite with associated weight loss.

- Cachexia is a metabolic syndrome characterized by profound involuntary weight loss.

TREATMENT

- In addition to caloric supplementation, patients may benefit from pharmacologic therapy.
- Megestrol acetate is active, with symptomatic improvement in <1 week. Despite the quick increase in the appetite, it may take several weeks to achieve weight gain. Megestrol is also associated with an increased risk of thromboembolism.
- Dexamethasone provides a short-lived improvement, usually without significant weight gain.
- Dronabinol has limited benefits in anorexia and is associated with sedation.

23
Diabetes Mellitus and Related Disorders

Cynthia J. Herrick

Janet B. McGill

Diabetes Mellitus

GENERAL PRINCIPLES

- **Diabetes mellitus (DM)** is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In 2012, DM was present in 12.3% of persons over the age of 20 years in the United States and 25.9% of those over the age of 65 years. A substantial percentage of affected persons are not diagnosed. Type 2 diabetes (T2DM) represents 90-95% of all cases of diabetes, with type 1 diabetes (T1DM) and other causes representing the remaining 5-10% (*National Diabetes Statistics Report, 2014 http://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf*).
- Persons with diabetes are at risk for microvascular complications, including retinopathy, nephropathy, and neuropathy, and are at increased risk for macrovascular disease.
- T2DM is accompanied by hypertension (approximately 75%) and hyperlipidemia (>50%) in adult patients and is considered a “cardiac risk equivalent” because of the excess risk for macrovascular disease, cardiovascular disease (CVD) events, and mortality (*Diabetes Care 2012;35(suppl 1):S11*).

Classification

DM is classified into four clinical classes (*Diabetes Care 2015;38(suppl 1):S8*).

- T1DM accounts for <10% of all cases of DM and results from a cellular-mediated autoimmune destruction of the beta (β) cells of the pancreas.
- T2DM accounts for >90% of all cases of diabetes. T2DM is characterized by insulin resistance followed by reduced insulin secretion from β cells that are unable to compensate for the increased insulin requirements.
- **Other specific types of DM** include those that result from genetic defects in insulin secretion or action (monogenic diabetes such as neonatal diabetes and maturity-onset diabetes of the young), pancreatic surgery or disease of the exocrine pancreas (cystic fibrosis), endocrinopathies (e.g., Cushing syndrome, acromegaly), or drugs (corticosteroids, antiretroviral, atypical antipsychotics), and diabetes associated with other syndromes.
- **Gestational DM** (GDM) is glucose intolerance with onset or diagnosis during pregnancy. The prevalence of GDM depends on the criteria used for diagnosis and varies by age and ethnic group (generally from 5-6% of pregnancies to 15-20% of pregnancies). Diagnostic criteria for GDM vary based on practice location with a two-step method (50-g, 1-hour screen followed by 100-g, 3-h oral glucose tolerance test [OGTT]) used in the United States and a one-step method (75-g, 2-hour OGTT) more common internationally (*Diabetes Care 2015;38(suppl 1):S13*). About 60% of women with GDM will develop T2DM in the ensuing 5-10 years, and all remain at an increased risk for the development of T2DM later in life (*http://www.cdc.gov/diabetes/pubs*).
    - All patients with GDM should undergo diagnostic testing 6-12 weeks postpartum with a 2-h OGTT or fasting plasma glucose and every 1-3 years thereafter to determine whether abnormal carbohydrate metabolism has persisted or is recurrent (*Diabetes Care 2015;38(suppl 1):S79*).

    - Weight loss and exercise are encouraged to decrease the risk of persistent prediabetes or T2DM after delivery.

DIAGNOSIS

- Progression from impaired fasting glucose or impaired glucose tolerance to T2DM occurs at the rate of 2-22% (average, about 12%) per year depending on the population studied.
- Lifestyle modification, including a balanced hypocaloric diet to achieve 7% weight loss in overweight patients and regular exercise of ≥150 minutes per week, is recommended for persons with prediabetes to prevent progression to T2DM (*Diabetes Care 2015;38(suppl 1):S31*).
- Metformin may be considered in patients with prior GDM, those with body mass index ≥35, or those with progressive hyperglycemia (*Diabetes Care 2015;38(suppl 1):S32*).
- See Table 23-1.

TREATMENT

- **Goals of therapy** are alleviation of symptoms; achievement of glycemic, blood pressure, and lipid targets; and prevention of acute and chronic complications of diabetes.
- Glycemic control recommendations are the same for T1DM and T2DM: Fasting and preprandial capillary blood glucose (BG) 80-130 mg/dL (3.9 to 7.2 mmol/L), postprandial capillary BG <180 mg/dL (<10 mmol/L), and A1C <7% or as close to normal as possible while avoiding significant hypoglycemia (*Diabetes Care 2015;38(suppl 1):S37*). The American Association of Clinical Endocrinologists (AACE) and European Association for the Study of Diabetes (EASD) recommend an A1C target of <6.5% (*Endocr Pract 2011;17(suppl 2):1*). This degree of glycemic control has been associated with the lowest risk for microvascular complications in patients with T1DM (*N Engl J Med 1993;329:978*) as well as T2DM (*BMJ 2000;321:405*; *Lancet 1998;352:837*).

TABLE 23-1 Diagnosis of Diabetes

Prediabetes Diagnosis (increased risk for developing diabetes)	Diabetes Diagnosis
A1C 5.7-6.4%	A1C ≥6.5%[a]
Fasting plasma glucose (FPG) 100-125 mg/dL (5.6-6.9 mmol/L) (impaired fasting glucose)	FPG ≥126 mg/dL (7.0 mmol/L)[a]
Oral glucose tolerance test (OGTT): glucose 140-199 mg/dL (7.8-11.0 mmol/L) 2 h after 75-g glucose load (impaired glucose tolerance)	OGTT: glucose ≥200 mg/dL (11.1 mmol/L) 2 h after 75-g glucose load[a]
	Symptoms of diabetes (polyuria, polydipsia, fatigue, weight loss) and random plasma glucose level ≥200 mg/dL (11.1 mmol/L)

[a]Should be repeated unless unequivocal hyperglycemia is present.

- Intensive diabetes therapy leading to tight glycemic control in patients with risk factors for CVD has been associated with increased mortality (*N Engl J Med 2011;364:818*; *N Engl J Med 2008;359:1577*). Hypoglycemia was implicated as the cause of higher mortality in one, but not all, of the studies (*N Engl J Med 2008;359:1577*). Less tight glycemic goals may be appropriate for patients with a history of cardiovascular (CV) events or those at

high risk for CV events.

- The blood pressure target for patients with diabetes is <140/90 mm Hg, but a lower goal of <130/80 mm Hg may be considered for younger patients. The use of either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) is recommended as first-line therapy. For patients not at goal, a thiazide diuretic should be added if the glomerular filtration rate (GFR) is >30 mL/min/1.73 m^2 and a loop diuretic added if the GFR is <30 mL/min/1.73 m^2 (*Diabetes Care 2015;38(suppl 1):s49*; *JAMA 2014;311:511*).
- High-intensity statin therapy (atorvastatin 40-80 mg daily or rosuvastatin 20-40 mg daily) is recommended in all patients with diabetes and overt CVD as well as patients age 40-75 with CVD risk factors (10-year atherosclerotic CVD risk score ≥7.5%). Moderate-intensity statin therapy can be considered in patients age 40-75 with no other CVD risk factors and in patients <40 or >75 with CVD risk factors (*Circulation 2014;129(suppl 2):S11*).
- Aspirin therapy should be advised in patients with diabetes who are older than 40 years or who have other risk factors. Low doses (75-162 mg) are appropriate for primary prevention (*Diabetes Care 2015;38(suppl 1):S54*).
- **Assessment of glycemic control** consists of the following:
  - **Self-monitoring of blood glucose (SMBG)** is recommended for all patients who take insulin and provides useful information for those on noninsulin therapies. Patients using multiple daily injections or insulin pumps should test themselves three or more times daily. Less frequent testing may be appropriate for those on noninsulin therapies. Although most SMBG is done before meals and at bedtime, periodic testing 1-2 hours after eating may be necessary to achieve postprandial glucose targets (*Diabetes Care 2015;38(suppl 1):S33*).
  - **Continuous glucose monitoring (CGM)** has been shown to reduce A1C in adults older than 25 years on intensive insulin therapy. CGM measures interstitial glucose, which provides a close approximation of BG values. Hypoglycemia and hyperglycemia alarms may help patients with widely fluctuating BG levels or hypoglycemia unawareness. CGM is supplemental to SMBG (*N Engl J Med 2008;359:1464*).
  - **A1C** provides an integrated measure of BG values over the preceding 2-3 months. A1C should be obtained every 3 months in patients not at goal or when either diabetes therapy or clinical condition changes and twice yearly in well-controlled patients. A1C should confirm results of SMBG, and discordant values should be investigated. An A1C level that is higher than expected should be evaluated by a diabetes educator to ensure meter accuracy, appropriate technique, and frequency of testing. When the A1C is lower than expected, blood loss, transfusion, hemolysis, and hemoglobin variants should be considered. The correlation between A1C and mean plasma glucose is sufficiently strong that laboratory reports may include both the A1C result and the estimated average glucose (*Diabetes Care 2015;38(suppl 1):S34*).
  - **Ketones** can be detected in a fingerstick blood sample by measuring β-hydroxybutyrate with the handheld glucose/ketone meter, Precision Xtra. Urine ketones can be qualitatively identified, using Ketostix or Acetest tablets. Patients with T1DM should test for ketones during febrile illness, for persistent elevation of glucose (>300 mg/dL), or if signs of impending diabetic ketoacidosis (e.g., nausea, vomiting, abdominal pain) develop. Testing for β-hydroxybutyrate is useful in emergency departments to determine whether a patient with hyperglycemia has ketonemia (*Acad Emerg Med 2006; 13(6):683*). Hospital laboratories measure serum ketones including acetone, acetoacetate, and β-hydroxybutyrate.

MANAGEMENT

Comprehensive diabetes management includes coordinated diet, exercise, and medication plans. **Patient education** in medical nutrition therapy, exercise, SMBG, medication use, and insulin dosing and administration is integral to the successful management of diabetes.

Medical Nutrition Therapy

- Medical nutrition therapy includes dietary recommendations for a healthy, balanced diet to achieve adequate nutrition and maintain an ideal body weight (*Diabetes Care 2015;38(suppl 1):S21*).
- Caloric restriction is recommended for overweight individuals, with individualized targets that may be as low as 1000-1500 kcal/d for women and 1200-1800 kcal/d for men depending on activity level and starting body weight.
- Caloric intake is usually distributed as follows: 45-65% of total calories as carbohydrates, 10-30% as protein, and <30% as total fat (<7% saturated fat) with <300 mg/d of cholesterol.
- In patients with low-density lipoprotein cholesterol >100 mg/dL (2.6 mmol/L), total fat should be restricted to <25% of total calories, saturated fat to <7% of calories, and cholesterol to <200 mg/d.
- Patients with progressive kidney disease may benefit from restriction of protein intake to 0.8 g/kg/d. Patients with severe chronic kidney disease (CKD) will need additional restrictions of potassium- and phosphorus-containing foods.
- "Carbohydrate counting" is a useful skill for patients on intensified insulin therapy who adjust insulin doses based on the carbohydrate content of meals and snacks.

Exercise

Exercise improves insulin sensitivity, reduces fasting and postprandial BG levels, and offers numerous metabolic, CV, and psychological benefits in diabetic patients.

- In general, 150 minutes per week is recommended as part of a healthy lifestyle and has been shown to assist with the prevention and management of T2DM.
- Patients may need individualized guidance regarding exercise, and they are more likely to exercise when counseled by their physician to do so.

Diabetes Mellitus in Hospitalized Patients

GENERAL PRINCIPLES

Diabetes-specific indications for hospitalization

- **Diabetic ketoacidosis (DKA)** is characterized by a plasma glucose level of >250 mg/dL (14 mmol/L) in association with an arterial pH <7.30 or serum bicarbonate level of <15 mEq/L and moderate ketonemia or ketonuria (*Diabetes Care 2009;32:1336*).
- **Hyperosmolar hyperglycemic state (HHS)** includes marked hyperglycemia (≥600 mg/dL) and elevated serum osmolality (>320 mOsm/kg), often accompanied by impaired mental status (*Diabetes Care 2009;32:1336*).
- **Hypoglycemia** is an indication for hospitalization if it is induced by a sulfonylurea (SFU) medication, is due to a deliberate drug overdose, or results in coma, seizure, injury, or persistent neurologic change.
- **Newly diagnosed T1DM** or newly recognized GDM can be indications for hospitalization, even in the absence of ketoacidosis.
- **Patients with T2DM** are rarely admitted to the hospital for initiation or change in insulin therapy unless hyperglycemia is severe and associated with mental status change or other organ dysfunction.

Management of diabetes in hospitalized patients

- Hyperglycemia (BG ≥140 mg/dL [7.8 mmol/L]) is a common finding in hospitalized patients and may be due to previously diagnosed diabetes, undiagnosed diabetes, medications, or stress-induced hyperglycemia. Up to 40% of

general medical and surgical patients exhibit hyperglycemia, and approximately 80% of intensive care unit (ICU) patients will demonstrate transient or persistent hyperglycemia. Patients with T1DM should be clearly identified as such at the time of admission.

- A1C can help identify previously undiagnosed diabetes in hospitalized patients and may assist with the evaluation of prior glucose control. A1C is not accurate in patients who are severely anemic, bleeding, or hemolyzing or who have been transfused.
- Data are limited regarding use of noninsulin therapies in inpatients.
- Medication reconciliation on admission should include a careful assessment of home diabetes medications, level of glucose control, kidney function, expected diagnostic studies and treatments, and the possible need for insulin treatment.
- Patients who are required to fast for diagnostic testing or treatments should have all noninsulin therapies stopped.
- **Patients hospitalized for reasons other than diabetes and are eating normally** may continue or restart outpatient diabetes treatments, unless specifically contraindicated.
- Use of noninsulin therapies may be appropriate in psychiatric units, rehabilitation settings, or stable patients preparing for discharge.
- **Glucose targets for inpatients** aim to reduce morbidity and mortality, while minimizing hypoglycemia.
  - In critical care settings, the glucose target is 140-180 mg/dL (7.8-10.0 mmol/L) with frequent monitoring recommended to avoid hypoglycemia (*N Engl J Med 2009;360:1283*).
  - In noncritical care settings, the glucose target is <140 mg/dL (7.8 mmol/L) fasting and premeal and <180 mg/dL (10.0 mmol/L) postmeal or on a random glucose check with reassessment of the insulin regimen if glucose falls below 100 mg/dL (5.6 mmol/L) (*Endocr Pract 2009;15:353*; *J Clin Endocrinol Metab 2012;97:16*; *Diabetes Care 2015;38(suppl 1):S80*).

Management of hyperglycemia in critical care settings

- Variable IV insulin infusion is recommended for critical illness, emergency surgery, or major surgery. Numerous algorithms have been published that direct insulin dose adjustments based on capillary BG values performed hourly at the bedside.
- An IV infusion of a dextrose-containing solution or other caloric source should be provided to prevent hypoglycemia and ketosis. For fluid-restricted patients, 10% dextrose in water (D10W) can be infused at a rate of 10-25 mL/h to provide a steady, consistent source of calories.
- An intermediate- or long-acting insulin should be given 2 hours prior to insulin infusion discontinuation.

Management of hyperglycemia in non-critical care hospital settings

- BG should be checked on admission in all patients and monitored four times per day in hyperglycemic patients, especially in patients treated with insulin.
- Scheduled insulin with basal, nutritional, and correction components provides superior glycemic control compared with correction or “sliding scale” insulin alone (*Diabetes Care 2007;30:2181*; *Diabetes Care 2011;34:256*).
- For patients who are naïve to insulin, the starting dose of basal insulin should equal 0.2 units/kg or 0.1 units/lb. Scheduled premeal insulin should be 0.2 units/kg divided by three meals.

  Example: Your patient weighs 80 kg. The starting insulin dose should be 16 units of long-acting insulin plus 5 units of rapid-acting insulin before each meal. A correction dose of 1-2 units per 50 mg/dL of BG, beginning at 140 mg/dL, can be added to the premeal doses.

- Patients with T1DM should continue their home insulin doses and may continue the use of an insulin pump if there is

a hospital policy in place to do so. Insulin doses in patients with T2DM should be reduced by 20% on admission. If their home insulin dose is excessive compared to a weight-based dose of 0.4-0.5 units/kg or distribution between basal and premeal insulin is uneven, further reductions and adjustments may be necessary.

- Meal-time insulin doses should be given shortly before or immediately after meals, and the correction factor or sliding scale dose should be added to the premeal dose.
- The glucose threshold for sliding scale (corrective) insulin should be higher at bedtime, or corrective insulin should not be given at bedtime. Adjustments in the next-day basal or premeal insulin doses are indicated if correction doses of insulin are frequently required or if clinical status or medications change.
- Extreme hyperglycemia (≥300 mg/dL [16.7 mmol/L]) on more than one consecutive test should prompt testing for ketoacidosis with electrolytes and ketone measurements.
- Hypoglycemia should be treated promptly with oral or IV glucose, and the capillary BG should be repeated every 10 minutes until >100 mg/dL (5.5 mmol/L) and stable. Reevaluation of scheduled doses and assessment of risk factors for hypoglycemia (declining renal function, hepatic impairment, poor intake) should be undertaken for any BG <70 mg/dL (3.9 mmol/L) (*Endocr Pract 2006;12:458*).
- **Enteral nutrition** (*Mayo Clin Proc 1996;71:587*). Intermittent tube feeds should be matched by either short-acting (human regular) insulin or intermediate-acting (human NPH [Neutral Protamine Hagedorn]) insulin. Patients with baseline hyperglycemia may need a basal insulin dose in addition to the doses given to cover tube feeds. For example, nighttime enteral feeding lasting 6-8 hours should be managed with NPH, with or without a basal insulin dose. NPH can be given three to four times daily for continuous tube feeds, allowing a change in insulin dose if the feeding is interrupted.
- **Total parenteral nutrition (TPN).** Patients supported with TPN are likely to develop hyperglycemia, and some require large amounts of insulin. See Chapter 2, Nutrition Support, for insulin management of patients on TPN.

Diabetic Ketoacidosis

GENERAL PRINCIPLES

Epidemiology

DKA, a potentially fatal complication of diabetes, occurs in up to 5% of patients with T1DM annually and can occur in insulin-deficient patients with T2DM.

Pathophysiology

DKA is a catabolic condition that results from severe insulin deficiency, often in association with stress and activation of counter-regulatory hormones (e.g., catecholamines, glucagon).

Risk Factors

Precipitating factors for DKA include inadvertent or deliberate interruption of insulin therapy, sepsis, trauma, myocardial infarction (MI), and pregnancy. DKA may be the first presentation of T1DM and, rarely, T2DM.

Prevention

DKA can be prevented in many cases, and its occurrence suggests a breakdown in education, communication, and problem solving. Therefore, diabetes education should be reinforced at every opportunity, with special emphasis on (a) self-management skills during sick days; (b) the body's need for more, rather than less, insulin during such illnesses; (c) testing of blood or urine for ketones; and (d) procedures for obtaining timely and preventive medical advice.

DIAGNOSIS

History

- Patients may describe a variety of symptoms including polyuria, polydipsia, weight loss, nausea, vomiting, and vaguely localized abdominal pain generally in the setting of persistent hyperglycemia. A high index of suspicion is warranted because clinical presentation may be nonspecific.
- Tachycardia; decrease of capillary filling; rapid, deep, and labored breathing (Kussmaul respiration); and fruity breath odor are common physical findings.
- Prominent gastrointestinal (GI) symptoms and abdominal tenderness on exam may give rise to suspicion for intra-abdominal pathology.
- Dehydration is invariable, and respiratory distress, shock, and coma can occur.

Diagnostic Testing

- Anion gap metabolic acidosis.
- Positive serum β-hydroxybutyrate or ketones (a semiquantitative measurement of acetone, acetoacetate, and β-hydroxybutyrate) and positive urine ketones.
- Plasma glucose ≥250 mg/dL. Euglycemic DKA (plasma glucose <200 mg/dL) has been described in pregnancy, alcohol ingestion, fasting or starvation, during hospitalization, and in patients with both T1DM and T2DM treated with sodium-glucose cotransport (SGLT-2) inhibitors (*http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm446994.htm*).
- Hyponatremia, hyperkalemia, azotemia, and hyperosmolality are other possible findings.
- A focused search for a precipitating infection is recommended if clinically indicated.
- An ECG should be obtained to evaluate electrolyte abnormalities and for unsuspected myocardial ischemia.

TREATMENT

Management of DKA should preferably be conducted in an ICU (Table 23-2). **If treatment is conducted in a non-ICU setting, close monitoring is mandatory until ketoacidosis resolves and the patient's condition is stabilized.** The therapeutic priorities are fluid replacement, adequate insulin administration, and potassium repletion. Administration of bicarbonate, phosphate, magnesium, or other therapies may be advantageous in selected patients.

- **Monitoring of therapy**
  - BG levels should be monitored hourly, serum electrolyte levels every 2-4 hours, and arterial blood gas values as often as necessary for a severely acidotic or hypoxic patient.
  - Serum sodium tends to rise as hyperglycemia is corrected; failure to observe this trend suggests that the patient is being overhydrated with free water.
  - Serial serum ketone measurements are not necessary because ketonemia may persist after clinical recovery and because the most commonly used assays measure all ketones, not just β-hydroxybutyrate. Restoration of renal buffering capacity by normalization of the serum bicarbonate level and closure of the anion gap are more reliable indices of metabolic recovery.
  - Use of a flowchart is an efficient method of tracking clinical data (e.g., weight, fluid balance, mental status) and laboratory results during the management of DKA.
  - Telemetry is recommended given the propensity to electrolyte abnormalities.
- **IV antimicrobial therapy** should be started promptly for documented or suspected bacterial, fungal, and other treatable infections. Empiric broad-spectrum antibiotics can be started in septic patients pending results of blood

cultures. Note that DKA

is not typically accompanied by fever, so infection must be considered in a febrile patient.

TABLE 23-2 Treatment of Diabetic Ketoacidosis

IV Fluids Goals: First, replete circulating volume and then replenish total-body water deficit Estimate fluid deficit by subtracting current weight from recent dry weight Usually 7-9% of body weight Hypotension → >10% loss of body fluids (*Diabetes Care 2004;27:S94*)	Replete circulating volume 0.9% saline: 1 L bolus then 500-1000 mL/h if cardiac and renal function normal Replenish total-body water deficit 0.45% saline (0.9% saline if hyponatremic): 150-500 mL/h Adjust repletion according to BP, UOP, exam; no faster than 3 mOsm/kg/h; aim for positive fluid balance over 12-24 h
Insulin Goals: Turn off ketogenesis; correct hyperglycemia	Do not start until K >3.5 mmol/L Bolus: 0.1 units/kg Infusion: 0.1 units/kg/h (Regular insulin 100 units in 100 mL 0.9% saline at 10 mL/h = 10 units/h) Goal decrease in BG = 50-75 mg/dL/h Avoid correcting >100 mg/dL/h to reduce risk of osmotic encephalopathy Continue at 1-2 units per hour until HCO_3 >15 mEq/L, clinical improvement, AND anion gap closed Administer SC basal insulin 2 h prior to stopping insulin infusion
Dextrose (5%) Goal: Prevent hypoglycemia	Add when BG <250 mg/dL Consider giving glucose as a separate infusion of 50-100 mL/h (2-bag approach). Concurrently reduce insulin infusion to 0.05 units/kg/h
Potassium as KCl Goal: Prevent hypokalemia as insulin shifts potassium into the cell	Add to fluids at 10-20 mEq/h
Bicarbonate	NOT routinely recommended May consider if (a) shock/coma; (b) pH <6.9; (c) HCO_3 <5 mEq/L; (d) cardiac/respiratory dysfunction; or (e) severe hyperkalemia 50-100 mEq in 1 L 0.45% saline over 30-60 min; follow arterial pH Avoid hypokalemia by adding 10 mEq KCl
Phosphate and magnesium	NOT routinely recommended May give KPhos IV fluids if not eating May give 10-20 mEq of magnesium Sulfate IV with ventricular arrhythmias

BG, blood glucose; BP, blood pressure; HCO_3, bicarbonate; K, potassium; KCl, potassium chloride; KPhos, potassium phosphate; UOP, urine output.

COMPLICATIONS

Complications of DKA include life-threatening conditions that must be recognized and treated promptly.

- **Lactic acidosis** may result from prolonged dehydration, shock, infection, and tissue hypoxia in DKA patients. Lactic acidosis should be suspected in patients with refractory metabolic acidosis and a persistent anion gap despite optimal therapy for DKA. Management includes adequate volume replacement, control of sepsis, and judicious use of bicarbonate.
- **Arterial thrombosis** manifesting as stroke, MI, or an ischemic limb occurs with increased frequency in DKA. However, routine anticoagulation is not indicated except as part of the specific therapy for a thrombotic event.
- **Cerebral edema** is observed more frequently in children than in adults.
  - Symptoms of increased intracranial pressure (e.g., headache, altered mental status, papilledema) or a sudden deterioration in mental status after initial improvement in a patient with DKA should raise suspicion for cerebral edema.
  - Overhydration with free water and excessively rapid correction of hyperglycemia are known risk factors. Watch for a decrease in serum sodium level or failure to rise during therapy.
  - Neuroimaging with a CT scan can establish the diagnosis. Prompt recognition and treatment with IV mannitol is essential and may prevent neurologic sequelae in patients who survive cerebral edema.
- **Rebound ketoacidosis** can occur due to premature cessation of IV insulin infusion or inadequate doses of SC insulin after the insulin infusion has been discontinued. All patients with T1DM and patients with T2DM who develop DKA (indicating severe insulin deficiency) require both basal and premeal insulin in adequate doses to avoid recurrence of metabolic decompensation.

Hyperosmolar Hyperglycemic State

GENERAL PRINCIPLES

HHS is one of the most serious life-threatening complications of T2DM (*J Clin Endocrinol Metab 2008;93:1541*).

Epidemiology

- HHS occurs primarily in patients with T2DM, and in 30-40% of cases, it is the initial presentation of a patient's diabetes (*Emerg Med Clin North Am 2005;23:629*).
- HHS is significantly less common than DKA, with an incidence of <1 case per 1000 person-years.

Pathophysiology

- Ketoacidosis is absent because the ambient insulin level may effectively prevent lipolysis and subsequent ketogenesis yet is inadequate to facilitate peripheral glucose uptake and to prevent hepatic residual gluconeogenesis and glucose output.
- Precipitating factors include dehydration, stress, infection, stroke, noncompliance with medications, dietary indiscretion, and alcohol and cocaine abuse. Impaired glucose excretion is a contributory factor in patients with renal insufficiency or prerenal azotemia.

DIAGNOSIS

Clinical Presentation

In contrast to DKA, the onset of HHS is usually insidious. Several days of deteriorating glycemic control are followed by increasing lethargy. Clinical evidence of severe dehydration is the rule. Some alterations in consciousness and focal neurologic deficits may be found at presentation or may develop during therapy. Therefore, repeated neurologic assessment is recommended.

Differential Diagnosis

The differential diagnosis of HHS includes any cause of altered level of consciousness, including hypoglycemia, hyponatremia, severe dehydration, uremia, hyperammonemia, drug overdose, and sepsis. Seizures and acute stroke-like syndromes are common presentations.

Diagnostic Testing

Clinical findings include (a) hyperglycemia, often >600 mg/dL; (b) plasma osmolality >320 mOsm/L; (c) absence of ketonemia; and (d) pH >7.3 and serum bicarbonate level of >20 mEq/L. Prerenal azotemia and lactic acidosis can develop. Although some patients will have detectable urine ketones, most patients do not have a metabolic acidosis. Lactic acidosis may develop from an underlying ischemia, infection, or other cause.

TREATMENT

- See Table 23-3 for detailed treatment recommendations.
- **Underlying illness.** Detection and treatment of any underlying predisposing illness are critical in the treatment of HHS. Antibiotics should be administered early, after appropriate cultures, in patients in whom infection is known or suspected as a precipitant to HHS. A high index of suspicion should be maintained for underlying pancreatitis, GI bleeding, renal failure, and thromboembolic events, especially acute MI.

COMPLICATIONS

Complications of HHS include thromboembolic events (cerebral and MI, mesenteric thrombosis, pulmonary embolism, and disseminated intravascular coagulation), cerebral edema, adult respiratory distress syndrome, and rhabdomyolysis.

MONITORING/FOLLOW-UP

- **Monitoring of therapy.** Use of a flowchart is helpful for tracking clinical data and laboratory results.
- Initially, BG levels should be monitored every 30-60 minutes and serum electrolyte levels every 2-4 hours; frequency of monitoring can be decreased during recovery.
- Neurologic status must be reassessed frequently; persistent lethargy or altered mentation indicates inadequate therapy. On the other hand, relapse after initial improvement in mental status suggests too rapid correction of serum osmolarity.

Type 1 Diabetes

GENERAL PRINCIPLES

A comprehensive approach is necessary for successful management of T1DM. A team approach that includes the expertise of physicians, diabetes educators, dietitians, and other members of the diabetes care team offers the best chance of success.

TABLE 23-3 Treatment of Hyperosmolar Hyperglycemic State

IV Fluids Goals: Restore hemodynamic stability and intravascular volume by fluid replacement; this is the primary treatment and supersedes insulin; patients often require much more fluid than with diabetic ketoacidosis	**Replete circulating volume** 0.9% saline **Replenish total-body water deficit** 0.45% saline Aim for positive fluid balance over 24-72 h; may require 10-12 L
Potassium as KCl Goal: Prevent hypokalemia as insulin shifts potassium into the cell	Add to fluids at 10-20 mEq/h; begin as soon as urine output confirmed
Insulin Goals: Plays a secondary role; slowly corrects hyperglycemia	**Do not start until K >3.5 mmol/L** **Bolus: 5-10 units (if BG >600 mg/dL); smaller bolus if BG <600 mg/dL** **Infusion: 0.10-0.15 units/kg/h** Avoid correcting >100 mg/dL/h to reduce risk of osmotic encephalopathy **Administer SC basal insulin 2 h prior to stopping insulin infusion**
Dextrose (5%) Goal: Prevent hypoglycemia	Add when BG 250-300 mg/dL Can give as a separate infusion of 50-100 mL/h (two-bag approach) Concurrently reduce insulin infusion to 1-2 units/h
Bicarbonate	NOT routinely recommended May be required if concurrent lactic acidosis

BG, blood glucose; K, potassium; KCl, potassium chloride.

DIAGNOSIS

T1DM can present at any age, and because of the variable prodrome of hyperglycemia, the diagnosis can be challenging in adults.

- The rate of destruction of β cells is rapid in infants and children and slower in adults. Therefore, ketoacidosis as an initial presentation is more common in young patients.
- T1DM is characterized by severe insulin deficiency. Exogenous insulin is required to control BGs, prevent DKA, and preserve life. Ketosis develops in 8-16 hours and ketoacidosis in 12-24 hours without insulin.
- Early in the course of T1DM, some insulin secretory capacity remains, and the insulin requirement may be lower than expected (0.3-0.4 units/kg). Tight control of BG level from the onset has been shown to preserve the residual β-cell function and prevent or delay later complications.
- Latent autoimmune diabetes in adults (LADA) is characterized by mild to moderate hyperglycemia at presentation that often responds to noninsulin therapies initially. Adults with LADA will have one or more β cell-specific autoantibodies and tend to require insulin therapy sooner than patients with classic T2DM (months to years).
- T1DM should be suspected when there is a family history of T1DM, thyroid disease, or other autoimmune disease. Presentation with ketoacidosis suggests T1DM, but confirmatory tests may be useful to guide therapy.

- Autoantibodies include islet cell autoantibodies (ICA), antibodies to insulin, antibodies to glutamic acid decarboxylase (anti-GAD), antibodies to zinc transporter 8 (ZnT8), and antibodies to tyrosine phosphatases IA-2 and IA-2β. Measuring one or more of these autoantibodies along with a C-peptide can help to confirm the diagnosis of T1DM; however, 20% of insulin-deficient adults are antibody negative (*Diabetes Care 2015;38(suppl 1):S10*).

TREATMENT

Treatment of T1DM requires lifelong insulin replacement and careful coordination of insulin doses with food intake and activity.

- **Insulin preparations.** After SC injection, there is individual variability in the duration and peak activity of insulin preparations and day-to-day variability in the same subject (Table 23-4).
- **SC insulin administration.** The abdomen, thighs, buttocks, and upper arms are the preferred sites for SC insulin injection. Absorption is fastest from the abdomen, followed by the arm, buttocks, and thigh, probably as a result of differences in blood flow. Injection sites should be rotated within the regions, rather than randomly across separate regions, to minimize erratic absorption. Exercise or massage over the injection site may accelerate insulin absorption.

TABLE 23-4 Approximate Kinetics of Insulin Preparations

Insulin Type	Onset of Action (h)	Peak Effect (h)	Duration of Activity (h)
Rapid acting			
Lispro, aspart, glulisine	0.25-0.50	0.50-1.50	3-5
Regular	0.50-1.00	2-4	6-8

Technosphere insulin	0.25-0.5	1.0-1.5	2-3
Intermediate acting			
NPH	1-2	6-12	18-24
Lente[a]	1-2	6-12	18-24
Long acting[b]			
Detemir	3-4	8-12	18-24
Glargine	4-6	Possible[c]	20-24
Ultralente[a]	3-4	Variable	18-24
PZI[a]	3-4	Unclear	18-24

PZI, protamine zinc insulin.

[a]Not available in the United States; possibly generic manufacturers.

[b]Some patients with type 1 diabetes have improved control when the long-acting basal insulin is given twice a day rather than once daily.

[c]Insulin dosage and individual variability in absorption and clearance rates affect pharmacokinetic data. Duration of insulin activity is prolonged in renal failure. After a lag time of approximately 5 hours, insulin glargine generally has a flat peakless effect over a 22- to 24-hour period; however, broad peaks can occur.

- **Regular human insulin is now available in an inhaled form as technosphere insulin (Afrezza).** This comes in four- and eight-unit cartridges for rapid-acting insulin administration. Onset occurs at 0.2-0.25 hour with peak effect within the first hour and a duration of action of 3 hours. It is contraindicated in patients with asthma or chronic obstructive pulmonary disease because of risk of bronchospasm. Pulmonary function tests are required prior to starting and at regular intervals during therapy.
- A regimen of **multiple daily insulin injections** that include basal, premeal, and correction doses is preferred to obtain optimal control in both hospitalized patients and outpatients. This regimen implies that capillary glucose monitoring will occur four times daily, 10-30 minutes before meals and at bedtime.
  - The **insulin requirement** for optimal glycemic control is approximately 0.5-0.8 units/kg/d for the average nonobese patient. A conservative total daily dose (TDD) of 0.4 units/kg/d is given initially to a newly diagnosed patient; the dose is then adjusted, using SMBG values. Higher doses may be required in obese or insulin-resistant patients, in adolescents, and in the latter part of pregnancy.
  - Basal insulin (administered as NPH twice daily, detemir once or twice daily, or glargine once daily) should provide 40-50% of the TDD of insulin and should be adjusted by 5-10% daily until the fasting glucose is consistently <130 mg/dL. In general, basal insulin is given regardless of nothing by mouth (NPO) or dietary

status and should not be held without a direct order.

- Premeal or bolus doses of insulin (given only if eating) are adjusted according to the BG, the anticipated carbohydrate intake, and anticipated activity level. The total premeal complement should roughly equal the total basal dose, with one-third given before or after each meal. Rapid-acting insulins (lispro, aspart, or glulisine) are preferred, but regular human insulin can be used.
- The third component of a comprehensive insulin regimen is “correction factor” insulin, which is similar to sliding scale, adjusted according to the premeal fingerstick glucose testing and the patient's estimated insulin sensitivity. In general, thinner patients should use a less aggressive scale than heavier or more insulin-resistant patients. Correction factor and premeal doses should use the same insulin and be given together in the same syringe.

- **Continuous SC insulin infusion** using an insulin pump is widely used for insulin delivery in patients with T1DM and increasingly in T2DM. It is a useful tool but does not automatically improve glucose control without patient self-management.
  - A typical regimen provides 50% of total daily insulin as basal insulin and the remainder as multiple preprandial boluses of insulin, using a programmable insulin pump. A rapid-acting insulin (aspart, lispro, or glulisine) is used to fill the pump and is infused continuously to provide basal insulin.
  - Insulin pumps have advanced features that allow patients to fine-tune their basal and bolus doses but require diabetes education to use the pump to its full potential. Patients must check their blood sugars regularly because DKA can occur rapidly if the insulin infusion is disrupted (i.e., faulty infusion set).

Type 2 Diabetes

GENERAL PRINCIPLES

- T2DM results from defective insulin secretion followed by loss of β-cell mass in response to increased demand as a result of insulin resistance (*Diabetes 1988;37:667*).
- T2DM is usually diagnosed in adults, with both incidence and prevalence increasing with age; however, T2DM now accounts for up to one-third of new cases of diabetes diagnosed between the ages of 5 and 15 years.

- T2DM is associated with obesity, family history of diabetes, history of GDM or prediabetes, hypertension, physical inactivity, and race/ethnicity. African Americans, Latinos, Asian Indians, Native Americans, Pacific Islanders, and some groups of Asians have a greater risk of developing T2DM than Caucasians.
- T2DM may be asymptomatic and, therefore, can remain undiagnosed for months to years.
- The loss of pancreatic β cells is progressive. Insulin secretion is usually sufficient to prevent ketosis, but DKA or HHS can develop during severe stress. T2DM in patients who present with or later develop ketosis or DKA, but who do not require insulin between episodes, is termed ketosis-prone T2DM.
- The mechanisms underlying the β-cell loss in T2DM are unknown, but programmed cell death in response to genetic and environmental factors has been demonstrated in animal models (*Diabetes 2003;52:2304*).

TREATMENT

Medications

- The achievement of glycemic control requires individualized therapy and a comprehensive approach that incorporates lifestyle and pharmacologic interventions. Guidelines have been published by several professional organizations regarding the choice and sequence of antidiabetic therapy (*Endocr Pract 2015;15:e6*; *Diabetes Care 2015:38 (supplement 1)*).
- Considerations for selecting noninsulin therapy (Table 23-5) in patients with T2DM include the following:

- Oral therapy should be initiated early in conjunction with diet and exercise.
- Metformin is the recommended first-line therapy if tolerated.
- Monotherapy with maximum doses of insulin secretagogues, metformin, or thiazolidinediones (TZDs) yields comparable glucose-lowering effects.
- The glucose-lowering effects of metformin, insulin secretagogues, and DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) analogs are observed within days to weeks, whereas the maximum effect of TZDs may not be observed for several weeks to months.
- Combination therapy with two or more oral or injectable agents may be needed at the time of diagnosis to achieve A1C and glucose targets in patients presenting with significant hyperglycemia and will likely be needed as β-cell function deteriorates over time. The AACE recommends dual therapy for initial A1C ≥7.5% and triple therapy or insulin for initial A1C >9%. A preference for medications with lower risk of hypoglycemia (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors) is indicated (*Endocr Pract 2015;15:e6*). The American Diabetes Association (ADA) recommends proceeding to two-drug, three-drug, and injectable combinations if the A1C goal is not achieved in 3-month increments. Dual therapy is recommended at the time of diagnosis if the A1C is >9%. A particular order of therapy after metformin is not specified and will depend on patient comorbidities and preferences (*Diabetes Care 2015;38:145*).
- About 60% of patients on monotherapy may have worsening of metabolic control during the first 5 years of therapy, and concurrent use of two or more medications with different mechanisms of action may be necessary (*Am J Med 2010;123(suppl 3):S38*).
- Insulin therapy should be considered for patients presenting in DKA or with very high glucose levels (A1C >10%). Insulin therapy can sometimes be stopped after glucose toxicity is corrected but may need to be continued in patients with persistent insulin deficiency.
- Because pancreatic β-cell function is required for the glucose-lowering effects of all noninsulin therapies, many patients will require insulin replacement therapy at some point. Insulin therapy can be initiated with basal insulin in addition to other therapies. Nonsecretagogue therapies can be continued with premixed insulin or with a basal/bolus regimen.

P.744
P.745
P.746
P.747

TABLE 23-5 Noninsulin Medications for Diabetes

	Renal Dosing Necessary?	Main Adverse Effects
Oral therapies		
Biguanide: inhibits hepatic glucose output and stimulates glucose uptake by peripheral tissues. Weight neutral. Hold for 48 h after radiographic contrast procedure. Avoid in patients with cardiogenic or septic shock, CHF, severe liver disease, hypoxemia, and tissue hypoperfusion.		
Metformin (available in liquid and long-acting formulations)	Avoid if serum Cr ≥1.4 mg/dL in women or ≥1.5 mg/dL in men	GI symptoms (20-30%); lactic acidosis (3/100,000 patient-years)

Sulfonylureas (SFU): increase insulin secretion by binding specific β-cell receptors. Give 30-60 min before food. NEVER give if fasting. Start with lowest dose and increase over days to weeks to optimal dose (usually half the maximum approved dose).

Glyburide (glibenclamide)	Avoid if CrCl <50 mL/min	Hypoglycemia, weight gain; avoid with renal insufficiency; caution in elderly
Glipizide	Yes; if CrCl <50 mL/min	Same; fewer problems in kidney disease
Glimepiride	Start lowest dose and titrate slowly	Same; fewer problems in kidney disease
Gliclazide[a]		Same; fewer problems in kidney disease

Meglitinides: increase insulin secretion; much shorter onset and half-life than SFUs. Dose before each meal. NEVER give if fasting.

Nateglinide	No	Hypoglycemia, weight gain; not as severe as SFUs

- Give 10 minutes before meal
- Metabolized by cytochrome P450

Repaglinide	Yes; if CrCl ≤40 mL/min	Same

- Give 30 minutes before meal

Mitiglinide[a]		Same

α-Glucosidase inhibitors: block polysaccharide and disaccharide breakdown and decrease postprandial hyperglycemia. Give with food. Start with low dose and increase weekly. Do not use in patients with intestinal disease.

Acarbose	Avoid if serum Cr >2.0 mg/dL	Gas, bloating, diarrhea, abdominal pain (25-50%); transaminase elevations
Miglitol	Avoid if serum Cr >2.0 mg/dL	Gas, bloating, diarrhea, abdominal pain (25-50%)
Voglibose[a]	No; Not renally excreted; not studied in CKD	Same

Thiazolidinediones: increase insulin sensitivity in muscle, adipose tissue, and liver. Start with low

dose and increase after several weeks. Avoid in patients with New York Heart Association class III/IV heart failure. Caution in patients with coronary artery disease, hypertension, long-standing diabetes, left ventricular hypertrophy, preexisting edema or edema on therapy, insulin use, advanced age, renal failure, and aortic or mitral valve disease (*Diabetes Care 2004;27:256*).

Pioglitazone ■ Alters levels of medicines metabolized by CYP3A4	No	Edema, heart failure, fractures in women, increased risk of bladder cancer?—not seen in recent analysis of >1 million patients (*Diabetologia 2015;58(3):49*); rare hepatotoxicity; mild pancytopenia

DPP-4 inhibitors: inhibit enzyme that breaks down endogenous GLP (incretin secreted from intestinal L cells). Increased GLP reduces blood glucose by inhibiting glucagon release and stimulating insulin secretion. Avoid in patients with a history of pancreatitis.

Alogliptin	Yes; if CrCl <60 mL/min	Anaphylaxis, angioedema, skin reactions, liver injury, URI
Linagliptin	No	Anaphylaxis, angioedema, exfoliative skin reactions, URI
Saxagliptin	Yes; if CrCl ≤50 mL/min	Urticaria, facial edema, URI
Sitagliptin	Yes; if CrCl <50 mL/min	AKI, ESRD, anaphylaxis, angioedema, exfoliative skin reactions, URI
Vildagliptin[a] (not indicated in severe hepatic impairment, LFT >3× upper limit of normal)	Yes; if CrCl <50 mL/min; not indicated in severe renal impairment	Blistering skin lesions in animals, increased LFTs

SGLT-2 inhibitors: inhibit sodium glucose cotransporter 2 in the proximal renal tubule, decreasing glucose reabsorption by the kidney.

Canagliflozin	Yes; if eGFR 45 to <60 mL/min/1.73 m^2	Female genital mycotic infections, urinary tract infections, polyuria; hypotension, volume depletion, renal failure; increased LDL-C
	Not indicated for eGFR <45 mL/min/1.73 m^2	
Dapagliflozin	Not indicated for eGFR <60 mL/min/1.73 m^2	Same; possible increased risk for bladder cancer

Empagliflozin	Not indicated for eGFR <45 mL/min/1.73 m^2	Same
Bile acid sequestrants		
Colesevelam hydrochloride (contraindicated in bowel obstruction or GI motility disorders; pregnancy class B; can be used in renal and hepatic disease; take on an empty stomach)	No	Constipation, reduced absorption of some medications; raises triglycerides
Dopamine agonists		
Bromocriptine mesylate (do not use with other dopamine agonists or antagonists)	No	Nausea, asthenia, dizziness, headache, constipation, diarrhea
<u>SC injectable therapies</u>		
GLP-1 analogs: structurally similar to endogenous GLP-1 but resist breakdown by DPP-4. They have a longer half-life and reach higher levels in blood and tissues. They are given by injection and can improve satiety and result in weight loss. Avoid in patients with history of pancreatitis. Avoid in patients with history of medullary thyroid cancer or MEN2 given increased C-cell tumors in rodents (all except immediate-release exenatide).		
Albiglutide (dosed weekly)	No; monitor for GI side effects in patients with renal impairment	URI, diarrhea, nausea, injection site reaction
Dulaglutide (dosed weekly)	No; monitor for GI side effects in patients with renal impairment	Diarrhea, nausea, vomiting, abdominal pain, decreased appetite
Exenatide (dosed twice daily)	Do not use in severe renal impairment or ESRD; caution with moderate renal impairment or history of renal transplant	Nausea, vomiting, GI distress, reported cases of pancreatitis
Exenatide extended release (dosed weekly)	Do not use in severe renal impairment or ESRD; caution with moderate renal impairment or history	Nausea, vomiting, injection site reaction, headache, diarrhea, dyspepsia

	of renal transplant	
Liraglutide (dosed once daily)	Caution when initiating or escalating dose in patients with renal impairment	Headache, nausea, diarrhea, urticaria
Amylin analogs: blunt postprandial blood glucose response		
Pramlintide acetate (given as a separate injection with meals; insulin dose reduction is required when starting)	Not defined with CrCl <20 mL/min	Nausea, vomiting, diarrhea, headache, hypoglycemia

AKI, acute kidney injury; CKD, chronic kidney disease; CHF, congestive heart failure; Cr, creatinine; CrCl, creatinine clearance; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; GLP, glucagon-like peptide; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test; MEN2, multiple endocrine neoplasia type 2; URI, upper respiratory infection. Please refer to country-specific prescribing information before using any of the antidiabetes therapies.

[a]Not available in the United States.

- The toxicity profile of some oral and injectable antidiabetic agents may preclude their use in patients with preexisting illnesses.

- **Insulin therapy** in T2DM is indicated in the following:
  - Patients in whom oral or injectable agents have failed to achieve or sustain glycemic control
  - Metabolic decompensation: DKA, HHS
  - Newly diagnosed patients with severe hyperglycemia
  - Pregnancy and other situations in which oral agents are contraindicated
- **The success of insulin therapy** depends on both the adequacy of the insulin TDD (0.6 to >1.0 units/kg of body weight per day) and the appropriateness of the insulin regimen for a given patient to achieve target glucose and A1C values.
  - A once-daily injection of intermediate- or long-acting insulin at bedtime or before breakfast (basal insulin) added to oral or injectable agents may achieve the target A1C goal.
  - Premeal insulin may be required if basal insulin plus other agents is not adequate. Short- or rapid-acting insulin administered before meals can be added to a basal insulin. Alternatively, a premixed insulin can be given twice daily before breakfast and dinner. In general, the secretagogues are discontinued when premeal insulin is added, but sensitizing and other agents are continued on the basis of the individual patient needs.
  - The TDD of insulin required to achieve glycemic targets varies widely in patients with T2DM and is based on body mass index, the continuation of oral agents, and the presence of comorbid conditions. Large doses of insulin (>100 units/d) may be required for optimal glycemic control. Weight gain with insulin use is a concern.
  - Insulin-induced hypoglycemia, the most dangerous side effect, may increase CV event rates and death. Avoidance of hypoglycemia while achieving an A1C as low as can be safely achieved requires close collaboration between physician, patient, and diabetes educators. The frequency of hypoglycemia increases

as patients approach normal A1C levels or when deterioration of kidney function occurs.

- **Concentration.** The standard insulin concentration is 100 units/mL (U-100), with vials containing 1000 units in 10 mL. A highly concentrated form of regular insulin containing 500 units/mL (Humulin U-500) is available for the rare patient with severe insulin resistance (usually T2DM). The vial size for U-500 insulin is 20 mL. A newly approved insulin glargine formulation that is 300 units/mL (U-300) is being marketed as Toujeo. It should be noted that Toujeo has less glucose-lowering effect when compared unit by unit to Lantus (i.e., the Toujeo dose required to achieve the same blood sugars will be more than the Lantus dose divided by 3).
- **Mixed insulin therapy.** Short- and rapid-acting insulins (regular, lispro, aspart, and glulisine) can be mixed with NPH insulin in the same syringe for convenience. The rapid-acting insulin should be drawn first, cross-contamination should be avoided, and the mixed insulin should be injected immediately. Commercial premixed insulin preparations do not allow dose adjustment of individual components but are convenient for patients who are unable or unwilling to do the mixing themselves. Premixed insulins are an option for patients with T2DM who have a regular eating and activity schedule and, in general, should not be used in T1DM.

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

- Prevention of long-term complications is one of the main goals of diabetes management. Appropriate treatment of established complications may delay their progression and improve quality of life.

- **Microvascular complications** include diabetic retinopathy, nephropathy, and neuropathy. These complications are directly related to hyperglycemia. Tight glycemic control has been shown to reduce the development and progression of these complications.

Diabetic Retinopathy

GENERAL PRINCIPLES

Classification

- Diabetic retinopathy (DR) is classified as background retinopathy (microaneurysms, retinal infarcts, lipid exudates, cotton wool spots, and/or microhemorrhages) with or without macular edema and proliferative retinopathy. Background DR is also known as preproliferative retinopathy.
- Other ocular abnormalities associated with diabetes include cataract formation, dyskinetic pupils, glaucoma, optic neuropathy, extraocular muscle paresis, floaters, and fluctuating visual acuity. The latter may be related to changes in BG levels.
- The presence of floaters may be indicative of preretinal or vitreous hemorrhage; immediate referral for ophthalmologic evaluation is warranted.

Epidemiology

The incidence of DR and vision impairment has dropped significantly with improved management of glycemia, blood pressure, and lipids in patients with both T1DM and T2DM. Early identification and treatment of DR have further reduced vision impairment once it is diagnosed. DR is less frequent in T2DM, but maculopathy may be more severe. DR is still the leading cause of vision loss in adults younger than age 65 years (*N Engl J Med 2012;366:1227*).

DIAGNOSIS

Annual examination by an ophthalmologist is recommended at the time of diagnosis of all T2DM patients and at the beginning of puberty or 3-5 years after diagnosis for patients with T1DM. Dilated eye examination should be repeated annually by an optometrist or ophthalmologist because progressive DR can be completely asymptomatic until sudden loss of vision occurs. Early detection of DR is critical because therapy is more effective before severe

maculopathy or proliferation develops. Any diabetic patient with visual symptoms should be referred for ophthalmologic evaluation (*Diabetes Care 2012;35(suppl 1):S64*).

TREATMENT

The first line of treatment is glycemic control, which has been shown to reduce the incidence and progression of DR in patients with T1DM or T2DM. Blood pressure control was also shown to be effective in the United Kingdom Prospective Diabetes Study (UKPDS), and treatment with either an ACE inhibitor (ACE-I) or ARB has demonstrated additional utility in preventing DR. Fenofibrate, used with simvastatin, reduced the risk of progression of DR in the ACCORD and FIELD clinical trials (*N Engl J Med 2012;366:1227*). Background retinopathy is not usually associated with loss of vision unless macular edema is present (25% of cases). The development of macular edema or proliferative retinopathy (particularly new vessels near the optic disk) requires elective laser photocoagulation therapy to preserve vision. Intraocular injections of vascular endothelial growth factor (VEGF)-neutralizing antibodies or glucocorticoids improve vision outcomes in macular edema but have side effects. Vitrectomy is indicated for patients with vitreous hemorrhage or retinal detachment.

Diabetic Nephropathy

GENERAL PRINCIPLES

Epidemiology

Approximately 25-45% of patients with either type of diabetes develop clinically evident diabetic nephropathy during their lifetime. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States and a major cause of morbidity and mortality in patients with diabetes (*Med Clin North Am 2004;88:1001*).

Risk Factors

The newest ADA guidelines no longer distinguish between microalbuminuria and macroalbuminuria, defining albuminuria as urinary albumin-to-creatinine ratio ≥30 mg/g (*Diabetes Care 2015;38(suppl 1):S58*). The mean duration from diagnosis of T1DM to the development of overt proteinuria has increased significantly and is now >25 years. The time from the occurrence of proteinuria to ESRD has also increased and is now >5 years. In T2DM, albuminuria can be present at the time of diagnosis. Poor glycemic control is the major risk factor for diabetic nephropathy, but hypertension and smoking are contributors. Obesity may contribute to kidney damage in T2DM. Due to the widespread use of ACE inhibitor and ARB agents for the treatment of hypertension, impaired kidney function may occur in the absence of albuminuria (*Diabetes Care 2015;38(suppl 1):S60*).

Prevention

Prevention of diabetic nephropathy starts at the time of diagnosis with achievement of glycemic, blood pressure, and lipid targets. Smoking cessation is also important. Annual screening for albuminuria and measurement of serum creatinine identify those with early damage who are at risk of progression. Annual screening should be performed in T1DM patients who have had diabetes for >5 years and all T2DM patients starting at diagnosis.

Associated Conditions

- Patients with proteinuria (albumin/creatinine >300 mg/g) are at higher risk for anemia due to loss of transferrin and poor production of erythropoietin and should be screened at any stage of CKD and treated.
- **Patients with CKD are at higher risk for CVD and mortality**, so management of other CV risk factors is

particularly important in this group of patients.

- Hypovitaminosis D should be corrected, and secondary hyperparathyroidism should be prevented or treated as early as possible.
- Diabetic patients with CKD may be at risk for hyperkalemia and metabolic acidosis, which should be identified and managed accordingly.

DIAGNOSIS

Diagnostic Testing

- Measurement of the albumin-to-creatinine ratio (normal, <30 mg of albumin/g of creatinine) in a random urine sample is recommended for screening. At least two to three measurements within a 6-month period should be performed to establish the diagnosis of diabetic nephropathy (*Diabetes Care 2003;26:S94*).
- Measurement of serum creatinine and serum urea nitrogen should be performed annually, along with calculation of the estimated GFR. Patients with diabetes may have reduced kidney function without manifesting albumin in their urine. Testing and treatment of

associated disorders such as anemia, secondary hyperparathyroidism, hyperkalemia, and acid-base disturbances should begin when the estimated GFR is <60 mL/min/1.73 m^2, or during stage 3 CKD (see Chapter 13, Renal Diseases).

TREATMENT

Intensive control of both diabetes and hypertension is important to reduce the rate of progression of CKD due to diabetes. The current guideline by the Eighth Joint National Committee suggests treating to a target blood pressure of <140/90 mm Hg in patients with diabetes, including those with evidence of CKD (*JAMA 2014;311:511*).

Medications

- Antihypertensive treatment with ACE inhibitor or ARB drugs is recommended as first-line therapy for all patients with diabetes and hypertension. These agents have been shown to reduce progression of both retinopathy and nephropathy and may be considered in patients with normal blood pressure or prehypertension.
- Diuretics are considered second line, followed by calcium channel blockers, β-blockers, or centrally acting agents (*JAMA 2014;311:511*).

Lifestyle/Risk Modification

- Dietary protein intake of 0.8 g/kg/d (based on ideal body weight) is recommended. Further reduction does not alter glycemic control, CVD risk, or kidney function decline (*Diabetes Care 2015;38(suppl 1):S58*).
- Avoidance of renal toxins is important for preservation of kidney function.

Diabetic Neuropathy

GENERAL PRINCIPLES

Classification

Diabetic neuropathy can be classified as (a) subclinical neuropathy, determined by abnormalities in electrodiagnostic and quantitative sensory testing; (b) diffuse symmetrical polyneuropathy with distal symmetric sensorimotor losses ± autonomic syndromes; and (c) focal syndromes.

Epidemiology

Distal symmetric polyneuropathy (DPN) is the most common neuropathy in developed countries and accounts for more

hospitalizations than all the other diabetic complications combined. Sensorimotor DPN is a major risk factor for foot trauma, ulceration, and Charcot arthropathy, and is responsible for 50-75% of nontraumatic amputations (*Med Clin N Am 2004;88:947*).

Prevention

- Sensation in the lower extremities should be documented at least annually, using a combination of modalities such as a light-touch monofilament, tuning fork (frequency of 128 Hz), pinprick, or temperature.
- Foot examination should be conducted at least annually to evaluate the presence of musculoskeletal deformities, skin changes, and pulses, in addition to the sensory examination.

TREATMENT

- **Painful peripheral neuropathy** responds variably to treatment with tricyclic antidepressants (e.g., amitriptyline 10-150 mg PO at bedtime), topical capsaicin (0.075% cream), or anticonvulsants (e.g., carbamazepine 100-400 mg PO bid, gabapentin 900-3600 mg/d,

or pregabalin 150-300 mg/d). Patients should be warned about adverse effects, including sedation and anticholinergic symptoms (tricyclics), burning sensation (capsaicin), and blood dyscrasias (carbamazepine). α-Lipoic acid (600 mg bid) and high-dose thiamine (50-100 mg tid) have been tested in early DPN. Vitamin B_{12} should be checked and replaced if low.
- **Orthostatic hypotension** is a manifestation of autonomic neuropathy, but other etiologies (e.g., dehydration, anemia, medications) should be excluded. Treatment is symptomatic and includes postural maneuvers, use of compressive garments (e.g., Jobst stockings), and intravascular expansion using sodium chloride 1-4 g PO qid and fludrocortisone 0.1-0.3 mg PO daily. Hypokalemia, supine hypertension, and congestive heart failure (CHF) are some adverse effects of fludrocortisone.
- **Intractable nausea and vomiting** may be manifestations of impaired GI motility from autonomic neuropathy. **DKA** should be ruled out when nausea and vomiting are acute. Other causes of nausea and vomiting, including adrenal insufficiency, should be excluded.
  - **Management of diabetic gastroenteropathy** can be challenging. Frequent, small meals (six to eight per day) of soft consistency that are low in fat and fiber provide intermittent relief. Parenteral nutrition may become necessary in refractory cases.
  - **Pharmacologic therapy** includes the prokinetic agent metoclopramide, 10-20 mg PO (or as a suppository) before meals and at bedtime, and erythromycin, 125-500 mg PO qid. Extrapyramidal side effects (tremor and tardive dyskinesia) from the antidopaminergic actions of metoclopramide may limit therapy.
  - **Cyclical vomiting** that is unrelated to a GI motility disorder or other clear etiology may also occur in diabetic patients and appears to respond to amitriptyline 25-50 mg PO at bedtime.
- **Diabetic cystopathy**, or bladder dysfunction, results from impaired autonomic control of detrusor muscle and sphincteric function. Manifestations include urgency, dribbling, incomplete emptying, overflow incontinence, and urinary retention. Recurrent urinary tract infections are common in patients with residual urine. Treatment with bethanechol 10 mg tid or intermittent self-catheterization may be required to relieve retention.
- **Chronic, persistent diarrhea** in patients with diabetes is probably multifactorial. Celiac disease and inflammatory bowel diseases should be ruled out, particularly in patients with T1DM. Pancreatic mass is reduced with long-standing diabetes, so the possibility of exocrine pancreatic dysfunction should be considered. Bacterial overgrowth has been considered as an etiology but is difficult to diagnose. Empiric treatment with broad-spectrum antibiotics (e.g., azithromycin, tetracycline, cephalosporins) along with metronidazole may be beneficial. Antifungal agents and probiotic replacement can be tried. If diarrhea persists, loperamide or

octreotide 50-75 mg SC bid can be effective in patients with intractable diarrhea.

MACROVASCULAR COMPLICATIONS OF DIABETES MELLITUS

Coronary Heart Disease

GENERAL PRINCIPLES

- Coronary heart disease (CHD), stroke, and peripheral vascular disease (PVD) are responsible for 80% of deaths in persons with diabetes (*Lancet 1997;350(suppl 1):SI23*) (see Chapter 4, Ischemic Heart Disease).

- **Coronary artery disease (CAD)** occurs at a younger age and may have atypical clinical presentations in patients with diabetes (*Lancet 1997;350(suppl 1):SI23*).
  - MI carries a worse prognosis, and angioplasty gives less satisfactory results in diabetic patients.
  - Persons with diabetes have an increased risk of ischemic and nonischemic heart failure and sudden death.

Risk Factors

Risk factors for macrovascular disease that are common in persons with diabetes include insulin resistance, hyperglycemia, albuminuria, hypertension, hyperlipidemia, cigarette smoking, and obesity.

Prevention

- CV risk factors should be assessed at least annually and treated aggressively (see treatment goals in the following text). ECG should be obtained yearly. Stress tests, with or without imaging, should be reserved for those with typical or atypical chest pain or those with abnormalities on ECG (*Diabetes Care 2012;35(suppl 1):S64*).
- Screening asymptomatic persons with cardiac stress test has not been shown to reduce mortality or events in asymptomatic patients with T2DM (*JAMA 2009;301:1547*).
- Aspirin 81-325 mg/d has proven beneficial in secondary prevention of MI or stroke in diabetic patients and may be considered for persons over age 40 years with diabetes.

TREATMENT

- Aggressive risk factor reduction lowers the risk of both microvascular and macrovascular complications in patients with diabetes.
  - Glycemic control should be optimized to A1C <7% and as close to normal as possible in the first few years after diagnosis. Patients with long-standing T2DM may have increased risk of mortality with very tight glycemic control (A1C <6.5%), particularly if multiple agents are required and the risk of hypoglycemia increases.
  - Hypertension should be controlled to a target blood pressure of <140/90 mm Hg (or <130/80 mm Hg if this can be achieved without adverse effects).
  - Hyperlipidemia should be treated appropriately, with a high-intensity statin in patients with known CHD. High-density lipoprotein cholesterol levels of >50 mg/dL and triglyceride levels of <150 mg/dL should be achieved.
  - Cigarette smoking should be actively discouraged, and weight loss should be promoted in obese patients.
- **Management of diabetes after acute MI**

  Hyperglycemia (glucose >110 mg/dL), with or without a history of diabetes, is an independent predictor of in-hospital mortality and CHF in patients admitted for acute MI (*Lancet 2000;355:773*). However, the results of the

studies that investigated tight glucose control with insulin in the setting of acute MI in T2DM patients are inconclusive (*BMJ 1997;314:1512*; *J Am Coll Cardiol 1995;26:57*; *Eur Heart J 2005;26:650*). Nevertheless, given the consistent epidemiologic association, it is reasonable to expect that glucose-lowering effects in acute conditions could lead to clinical benefit.

Peripheral Vascular Disease

GENERAL PRINCIPLES

Diabetes and smoking are the strongest risk factors for PVD. In diabetic patients, the risk of PVD is increased by age, duration of diabetes, and presence of peripheral neuropathy.

PVD is a marker for systemic vascular disease involving coronary, cerebral, and renal vessels. Diabetic patients with PVD have increased risk for subsequent MI or stroke regardless of the PVD symptoms.

DIAGNOSIS

Clinical Presentation

Symptoms of PVD include intermittent claudication, rest pain, tissue loss, and gangrene, but patients with diabetes may have fewer symptoms due to concomitant neuropathy.

Physical Examination

Physical examination findings include diminished pulses, dependent rubor, pallor on elevation, absence of hair growth, dystrophic toenails, and cool, dry, fissured skin.

Diagnostic Testing

- The ankle-to-brachial index (ABI), defined as the ratio of the systolic blood pressure in the ankle divided by the systolic blood pressure at the arm, is the best initial diagnostic test. An ABI <0.9 by a handheld, 5- to 10-MHz Doppler probe has a 95% sensitivity for detecting angiogram-positive PVD (*Int J Epidemiol 1988;17:248*).
- ABI should be performed in diabetic patients with signs or symptoms of PVD.

TREATMENT

- Risk factors should be controlled, with similar goals described for CAD (see the previous text).
- Antiplatelet agents such as clopidogrel (75 mg/d) have additional benefits when compared with aspirin in diabetic patients with PVD (*Diabetes Care 2003;26:3333*).
- Patients with intermittent claudication could also benefit from exercise rehabilitation and cilostazol (100 mg bid). This medication is contraindicated in patients with CHF.

MISCELLANEOUS COMPLICATIONS

Erectile Dysfunction

GENERAL PRINCIPLES

Epidemiology

It is estimated that 40-60% of men with diabetes have erectile dysfunction (ED), and the prevalence varies depending on the age of the patient and duration of diabetes. In addition to increasing age, ED is associated with smoking, poor glycemic control, low high-density lipoprotein, neuropathy, and retinopathy.

Etiology

ED in diabetic patients is multifactorial. It can result from nerve damage, impaired blood flow (vascular

insufficiency), adverse drug effects, low testosterone, psychological factors, or a combination of these etiologies.

DIAGNOSIS

Evaluation should include a measurement of total or bioavailable testosterone. If the total testosterone is <300 mg/dL, the test should be repeated in the morning (does not have to

be fasting, but a blood draw before 9:00 a.m. is appropriate) along with a prolactin and prostate-specific antigen (PSA).

TREATMENT

- If testosterone is low, and both PSA and prostate examination are normal, then testosterone replacement can be tried with either testosterone enanthate, 200 mg every 2-3 weeks, or a topical gel (AndroGel or Testim).
- A trial of phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil) is often warranted in addition to hormonal correction (if indicated). Typical doses include sildenafil 50-100 mg, vardenafil 10 mg, or tadalafil 10 mg 1 hour prior to sexual activity. Tadalafil can also be administered as a daily medication at lower doses (2.5 to 5 mg/d). Referral to a urology specialist should be considered if the problem persists. CV status should be considered before starting these agents. **This drug class should not be used concurrently with nitrates** to prevent severe and potentially fatal hypotensive reactions. Macular edema should also be ruled out before starting these agents.

Hypoglycemia

GENERAL PRINCIPLES

Classification

Hypoglycemia is uncommon in patients not treated for diabetes. Iatrogenic factors usually account for hypoglycemia in the setting of diabetes, whereas hypoglycemia in the nondiabetic population could be classified as fasting or postprandial hypoglycemia. **Iatrogenic hypoglycemia** complicates therapy with insulin or SFUs and is a limiting factor to achieving glycemic control during intensive therapy in patients with DM (*Diabetes Care 2003;26:1902*).

Risk Factors

Hypoglycemia resulting from too intensive diabetes management may increase the risk of mortality in older patients with a long duration of diabetes and should be avoided.

- Risk factors for iatrogenic hypoglycemia include skipped or insufficient meals, unaccustomed physical exertion, misguided therapy, alcohol ingestion, and drug overdose.
- Recurrent episodes of hypoglycemia impair recognition of hypoglycemic symptoms, thereby increasing the risk for severe hypoglycemia (hypoglycemia unawareness).
- Hypoglycemia unawareness results from defective glucose counterregulation with blunting of autonomic symptoms and counterregulatory hormone secretion during hypoglycemia. Seizures or coma may develop in such patients without the usual warning symptoms of hypoglycemia.
- Hypoglycemia unrelated to diabetes therapy is an infrequent problem in general medical practice.

DIAGNOSIS

Clinical Presentation

- Hypoglycemia is a clinical syndrome in which low serum (or plasma) glucose levels lead to symptoms of sympathetic-adrenal activation (sweating, anxiety, tremor, nausea, palpitations, and tachycardia) from

increased secretion of counterregulatory hormones (e.g., epinephrine).

- Neuroglycopenia occurs as the glucose levels decrease further (fatigue, dizziness, headache, visual disturbances, drowsiness, difficulty speaking, inability to concentrate, abnormal behavior, confusion, and ultimately loss of consciousness or seizures).

Differential Diagnosis

Plasma or capillary BG values should be obtained, whenever feasible, to confirm hypoglycemia.

- Any patient with a serum glucose concentration of <60 mg/dL should be suspected of having a hypoglycemic disorder, and further evaluation is required if the value is <50 mg/dL.
- Absence of symptoms with these levels of glucose suggests the possibility of artifactual hypoglycemia. These levels are usually accompanied by symptoms of hypoglycemia. Detailed evaluation is usually required in a healthy-appearing patient, whereas hypoglycemia may be readily recognized as part of the underlying illness in a sick patient (*N Engl J Med 1986;315:1245*). Major categories include fasting and postprandial hypoglycemia.
- **Fasting hypoglycemia** can be caused by inappropriate insulin secretion (e.g., insulinoma), alcohol abuse, severe hepatic or renal insufficiency, hypopituitarism, glucocorticoid deficiency, or surreptitious injection of insulin or ingestion of an SFU.
  - These patients present with neuroglycopenic symptoms, but episodic autonomic symptoms may be present. Occasionally, patients with recurrent seizures, dementia, and bizarre behavior are referred for neuropsychiatric evaluation, which may delay timely diagnosis of hypoglycemia.
  - **Definitive diagnosis** of fasting hypoglycemia requires hourly BG monitoring during a supervised fast lasting up to 72 hours and measurement of plasma insulin, C-peptide, and SFU metabolites if hypoglycemia (<50 mg/dL) is documented. Patients who develop hypoglycemia and have measurable plasma insulin and C-peptide levels without SFU metabolites require further evaluation for an insulinoma.
- **Postprandial hypoglycemia** often is suspected, but seldom proven, in patients with vague symptoms that occur 1 or more hours after meals.
  - **Alimentary hypoglycemia** should be considered in patients with a history of partial gastrectomy or intestinal resection in whom recurrent symptoms develop 1-2 hours after eating. The mechanism is thought to be related to too rapid glucose absorption, resulting in a robust insulin response. These symptoms should be distinguished from dumping syndrome, which is not associated with hypoglycemia and occurs in the first hour after food intake. Frequent small meals with reduced carbohydrate content may ameliorate symptoms.
  - **Functional hypoglycemia.** Symptoms that are possibly suggestive of hypoglycemia, which may or may not be confirmed by plasma glucose measurement, occur in some patients who have not undergone GI surgery. This condition is referred to as “functional hypoglycemia.” The symptoms tend to develop 3-5 hours after meals. Current evaluation and management of functional hypoglycemia are imprecise; some patients show evidence of impaired glucose tolerance and may respond to dietary therapy.

TREATMENT

Isolated episodes of mild hypoglycemia may not require specific intervention. Recurrent episodes require a review of lifestyle factors; adjustments may be indicated in the content, timing, and distribution of meals, as

well as medication dosage and timing. Severe hypoglycemia is an indication for supervised treatment.

- **Readily absorbable carbohydrates** (e.g., glucose and sugar-containing beverages) can be administered orally to conscious patients for rapid effect. Alternatively, milk, candy bars, fruit, cheese, and crackers may be used in some patients with mild hypoglycemia. Hypoglycemia associated with acarbose or miglitol therapy should preferentially be treated with glucose. Glucose tablets and carbohydrate supplies should be readily available to patients with DM at all times.
- **IV dextrose** is indicated for severe hypoglycemia, in patients with altered consciousness, and during restriction of oral intake. An initial bolus, 20-50 mL of 50% dextrose, should

be given immediately, followed by infusion of 5% dextrose in water (D5W) (or D10W) to maintain BG levels above 100 mg/dL. Prolonged IV dextrose infusion and close observation are warranted in SFU overdose, in the elderly, and in patients with defective counterregulation.

- **Glucagon**, 1 mg IM (or SC), is an effective initial therapy for severe hypoglycemia in patients unable to receive oral intake or in whom an IV access cannot be secured immediately. Vomiting is a frequent side effect, and therefore, care should be taken to prevent the risk of aspiration. A glucagon kit should be available to patients with a history of severe hypoglycemia; family members and roommates should be instructed in its proper use.

PATIENT EDUCATION

- **Education** regarding etiologies of hypoglycemia, preventive measures, and appropriate adjustments to medication, diet, and exercise regimens is an essential task to be addressed during hospitalization for severe hypoglycemia.
- **Hypoglycemia unawareness** can develop in patients who are undergoing intensive diabetes therapy. These patients should be encouraged to monitor their BG levels frequently and take timely measures to correct low values (<60 mg/dL). In patients with very tightly controlled diabetes, slight relaxation in glycemic control and scrupulous avoidance of hypoglycemia may restore the lost warning symptoms.

24
Endocrine Diseases

William E. Clutter

DISORDERS OF THE THYROID GLAND

Evaluation of Thyroid Function

GENERAL PRINCIPLES

The major hormone secreted by the thyroid is **thyroxine (T_4)**, which is converted by deiodinases in many tissues to the more potent **triiodothyronine (T_3)**. Both are bound reversibly to plasma proteins, primarily **thyroxine-binding globulin (TBG)**. Only the free (unbound) fraction enters cells and produces biologic effects. T_4 secretion is stimulated by **thyroid-stimulating hormone (TSH)**. In turn, TSH secretion is inhibited by T_4, forming a negative feedback loop that keeps free T_4 levels within a narrow normal range. Diagnosis of thyroid disease is based on clinical findings, palpation of the thyroid, and measurement of plasma TSH and thyroid hormones.

DIAGNOSIS

Clinical Presentation

Thyroid palpation determines the size and consistency of the thyroid and the presence of nodules, tenderness, or a thrill.

Diagnostic Testing

- **Plasma TSH is the best initial test in most patients with suspected thyroid disease**. TSH levels are elevated in very mild primary hypothyroidism and are suppressed in very mild hyperthyroidism. Thus, **a normal plasma TSH level excludes hyperthyroidism and primary hypothyroidism**. Because even slight changes in thyroid hormone levels affect TSH secretion, **abnormal TSH levels are not specific for clinically important thyroid disease**. Changes in plasma TSH lag behind changes in plasma T_4, and TSH levels may be misleading when plasma T_4 levels are changing rapidly, as during treatment of hyperthyroidism.
  - TSH levels may be suppressed in severe nonthyroidal illness, in mild (or subclinical) hyperthyroidism, and during treatment with dopamine or high doses of glucocorticoids. Also, TSH levels remain suppressed for some time after hyperthyroidism is corrected.
  - Plasma TSH is mildly elevated (up to 20 microunits/mL) in some euthyroid patients recovering from nonthyroidal illnesses and in mild (or subclinical) hypothyroidism.
  - TSH levels are usually within the reference range in secondary hypothyroidism and cannot diagnose this rare form of hypothyroidism.
- **Plasma free T_4** confirms the diagnosis and assesses the severity of hyperthyroidism when plasma TSH is <0.1 microunits/mL. It is also used to diagnose secondary hypothyroidism and adjust thyroxine therapy in patients with pituitary disease. Most laboratories measure free T_4 by immunoassay.
- **Free T_4 measured by equilibrium dialysis** is the most reliable measure of unbound T_4, but results are seldom rapidly available. It is needed only in rare cases in which the diagnosis is not clear from

measurement of plasma TSH and free T_4 by immunoassay.

- **Effect of nonthyroidal illness on thyroid function tests.** Many illnesses alter thyroid tests without causing true thyroid dysfunction (the nonthyroidal illness or euthyroid sick syndrome). These changes must be recognized to avoid mistaken diagnosis.
  - **The low T_3 syndrome** occurs in many illnesses, during starvation, and after trauma or surgery. Conversion of T_4 to T_3 is decreased, and plasma T_3 levels are low. Plasma free T_4 and TSH levels are normal. This may be an adaptive response to illness, and thyroid hormone therapy is not beneficial.
  - **The low T_4 syndrome** occurs in severe illness. TSH levels decrease early in severe illness, sometimes to <0.1 microunits/mL. In prolonged illness, free T_4 may also fall below normal. During recovery, TSH rises, sometimes to levels slightly above the normal range (rarely >20 microunits/mL).
  - Some drugs affect thyroid function tests (see Table 24-1). Iodine-containing drugs (**amiodarone** and radiographic contrast media) may cause hyperthyroidism or hypothyroidism in susceptible patients. In general, plasma TSH levels are a reliable guide to whether true hyperthyroidism or hypothyroidism is present.

TABLE 24-1 Effects of Drugs on Thyroid Function Tests

Effect	Drug
Decreased free and total T_4	
True hypothyroidism (TSH elevated)	Iodine (amiodarone, radiographic contrast) Lithium Some tyrosine kinase inhibitors Some immune modulators (e.g., interferon-α)
Inhibition of TSH secretion	Glucocorticoids Dopamine
Multiple mechanisms (TSH normal)	Phenytoin
Decreased total T_4 only	
Decreased TBG (TSH normal)	Androgens
Inhibition of T_4 binding to TBG (TSH normal)	Furosemide (high doses) Salicylates
Increased free and total T_4	
True hyperthyroidism (TSH <0.1 microunits/mL)	Iodine (amiodarone, radiographic contrast)

	Some immune modulators (e.g., interferon-α)
Inhibited T_4 to T_3 conversion (TSH normal)	Amiodarone
Increased free T_4 only	
Displacement of T_4 from TBG in vitro (TSH normal)	Heparin, low-molecular-weight heparin
Increased total T_4 only	
Increased TBG (TSH normal)	Estrogens, tamoxifen, raloxifene

T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone.

Hypothyroidism

GENERAL PRINCIPLES

Etiology

- **Primary hypothyroidism** (due to disease of the thyroid itself) accounts for >90% of cases.
- **Chronic lymphocytic thyroiditis (Hashimoto disease)** is the most common cause and may be associated with Addison disease and other endocrine deficits. Its prevalence is greater in women and increases with age.
- **Iatrogenic hypothyroidism** due to thyroidectomy or radioactive iodine (RAI; iodine-131) therapy is also common.
- Transient hypothyroidism occurs in postpartum thyroiditis and subacute thyroiditis, usually after a period of hyperthyroidism.
- **Drugs that may cause hypothyroidism** include iodine-containing drugs, lithium, interferon (IFN)-α, IFN-β, interleukin-2, thalidomide, bexarotene, and sunitinib.
- Secondary hypothyroidism due to TSH deficiency is uncommon but may occur in any disorder of the pituitary or hypothalamus. However, it rarely occurs without other evidence of pituitary disease.

DIAGNOSIS

Clinical Presentation

History

Most symptoms of hypothyroidism are nonspecific and develop gradually. They include cold intolerance, fatigue, somnolence, poor memory, constipation, menorrhagia, myalgias, and hoarseness. Hypothyroidism is readily treatable and should be suspected in any patient with compatible symptoms.

Physical Examination

Signs include slow tendon reflex relaxation, bradycardia, facial and periorbital edema, dry skin, and nonpitting edema (myxedema). Mild weight gain may occur, but hypothyroidism does not cause marked obesity. Rare manifestations include hypoventilation, pericardial or pleural effusions, deafness, and carpal tunnel syndrome.

Diagnostic Testing

- Laboratory findings may include hyponatremia and elevated plasma levels of cholesterol, triglycerides, and creatine kinase.
- In suspected primary hypothyroidism, plasma TSH is the best initial test.
  - A normal value excludes primary hypothyroidism, and a markedly elevated value (>20 microunits/mL) confirms the diagnosis.
  - Mild elevation of plasma TSH (<20 microunits/mL) may be due to recovery from nonthyroidal illness, but usually indicates mild (or subclinical) primary hypothyroidism, in which thyroid function is impaired but increased secretion of TSH maintains normal plasma free T_4 levels. These patients may have nonspecific symptoms that are compatible with hypothyroidism and a mild increase in serum cholesterol and low-density lipoprotein cholesterol. They develop clinical hypothyroidism at a rate of 2.5% per year.
- If secondary hypothyroidism is suspected because of evidence of pituitary disease, plasma free T_4 should be measured. Plasma TSH levels are usually within the reference range in secondary hypothyroidism and cannot be used alone to make this diagnosis. Patients with secondary hypothyroidism should be evaluated for other pituitary hormone deficits and for a mass lesion of the pituitary or hypothalamus (see Disorders of Anterior Pituitary Function section).

- **In severe nonthyroidal illness**, the diagnosis of hypothyroidism may be difficult. Plasma free T_4 measured by routine assays may be low.
  - **Plasma TSH is the best initial diagnostic test.** A normal TSH value is strong evidence that the patient is euthyroid, except when there is evidence of pituitary or hypothalamic disease or in patients treated with dopamine or high doses of glucocorticoids. Marked elevation of plasma TSH (>20 microunits/mL) establishes the diagnosis of primary hypothyroidism.
  - Moderate elevations of plasma TSH (<20 microunits/mL) may occur in euthyroid patients recovering from nonthyroidal illness and are not specific for hypothyroidism. Plasma free T_4 should be measured if TSH is moderately elevated or if secondary hypothyroidism is suspected, and patients should be treated for hypothyroidism if plasma free T_4 is low. Thyroid function in these patients should be reevaluated after recovery from illness.

TREATMENT

Thyroxine is the drug of choice. The average replacement dose is 1.6 µg/kg PO daily, and most patients require doses between 75-150 µg/d. In elderly patients, the average replacement dose is lower. The need for lifelong treatment should be emphasized. Thyroxine should be taken 30 minutes before a meal, because some foods interfere with its absorption, and should not be taken with medications that affect its absorption (see the following text).

- **Initiation of therapy.** Young and middle-aged adults should be started on 1.6 µg/kg/d. This regimen

gradually corrects hypothyroidism, because several weeks are required to reach steady-state plasma levels of T_4. In otherwise healthy elderly patients, the initial dose should be 50 µg/d. Patients with cardiac disease should be started on 25 µg/d and monitored carefully for exacerbation of cardiac symptoms.

- **Dose adjustment and follow-up**
  - **In primary hypothyroidism, the goal of therapy is to maintain plasma TSH within the normal range.** Plasma TSH should be measured 6-8 weeks after initiation of therapy. The dose of thyroxine should then be adjusted in 12- to 25-µg increments at intervals of 6-8 weeks until plasma TSH is normal. Thereafter, annual TSH measurement is adequate to monitor therapy. TSH should also be measured in the first trimester of pregnancy, because the thyroxine dose requirement often increases at this time (see the following text). Overtreatment, indicated by a subnormal TSH, should be avoided because it increases the risk of osteoporosis and atrial fibrillation.
  - **In secondary hypothyroidism, plasma TSH cannot be used to adjust therapy.** The goal of therapy is to maintain the **plasma free T_4** near the middle of the reference range. The dose of thyroxine should be adjusted at 6- to 8-week intervals until this goal is achieved. Thereafter, annual measurement of plasma free T_4 is adequate to monitor therapy.

COMPLICATIONS

- **Situations in which thyroxine dose requirements change.** Difficulty in controlling hypothyroidism is most often due to **poor compliance** with therapy. Other causes of increasing thyroxine requirement include:
  - Malabsorption due to intestinal disease or drugs that interfere with thyroxine absorption (e.g., calcium carbonate, ferrous sulfate, cholestyramine, sucralfate, aluminum hydroxide)
  - Drug interactions that increase thyroxine clearance (e.g., estrogen, rifampin, carbamazepine, phenytoin) or block conversion of T_4 to T_3 (amiodarone)
  - Pregnancy, in which thyroxine requirements often increase in the first trimester (see the following text)
  - Gradual failure of remaining endogenous thyroid function after RAI treatment of hyperthyroidism

- **Pregnancy.** Thyroxine dose increases by an average of 50% in the first half of pregnancy (*J Clin Endocrinol Metab 2012;97:2543*). In women with primary hypothyroidism, plasma TSH should be measured as soon as pregnancy is confirmed and monthly thereafter through the second trimester. The thyroxine dose should be increased as needed to maintain plasma TSH within the lower half of the normal range to avoid fetal hypothyroidism.
- **Subclinical hypothyroidism** should be treated if any of the following are present: (a) symptoms compatible with hypothyroidism, (b) goiter, (c) hypercholesterolemia that warrants treatment, or (d) plasma TSH >10 microunits/mL (*Thyroid 2014;24:1670*). Untreated patients should be monitored annually, and thyroxine should be started if symptoms develop or serum TSH increases to >10 microunits/mL.
- **Urgent therapy** for hypothyroidism is rarely necessary. Most patients with hypothyroidism and concomitant illness can be treated in the usual manner. However, hypothyroidism may impair survival in critical illness by contributing to hypoventilation, hypotension, hypothermia, bradycardia, or hyponatremia.
  - Hypoventilation and hypotension should be treated intensively, along with any concomitant diseases.

Confirmatory tests (plasma TSH and free T_4) should be obtained before thyroid hormone therapy is started.

- **Thyroxine, 50-100 µg IV, can be given q6-8h for 24 hours**, followed by 75-100 µg IV daily until oral intake is possible. No clinical trials have determined the optimum method of thyroid hormone replacement, but this method rapidly alleviates hypothyroidism while minimizing the risk of exacerbating underlying coronary disease or heart failure. **Rapid correction is warranted only in extremely ill patients. Vital signs and cardiac rhythm should be monitored carefully to detect early signs of exacerbation of heart disease. Hydrocortisone**, 50 mg IV q8h, is recommended during rapid replacement of thyroid hormone, because this therapy may precipitate adrenal crisis in patients with adrenal failure.

Hyperthyroidism

GENERAL PRINCIPLES

- Evidence-based recommendations have been developed to guide the treatment of patients with hyperthyroidism and thyrotoxicosis (*Thyroid 2011:21:593*).
- **Graves disease** causes most cases of hyperthyroidism, especially in young patients. This **autoimmune** disorder may also cause **proptosis** (exophthalmos) and pretibial myxedema, neither of which is found in other causes of hyperthyroidism.
- **Toxic multinodular goiter (MNG)** may cause hyperthyroidism in older patients.
- Unusual causes include **iodine-induced hyperthyroidism** (precipitated by drugs such as **amiodarone** or radiographic contrast media), thyroid adenomas, subacute thyroiditis (painful tender goiter with transient hyperthyroidism), painless thyroiditis (nontender goiter with transient hyperthyroidism, most often seen in the postpartum period), and surreptitious ingestion of thyroid hormone. TSH-induced hyperthyroidism is extremely rare.

DIAGNOSIS

Clinical Presentation

History

- Symptoms include heat intolerance, weight loss, weakness, palpitations, oligomenorrhea, and anxiety.

TABLE 24-2 Differential Diagnosis of Hyperthyroidism

Type of Goiter	Diagnosis
Diffuse, nontender goiter	Graves disease or painless thyroiditis
Multiple thyroid nodules	Toxic multinodular goiter
Single thyroid nodule	Thyroid adenoma

Tender painful goiter	Subacute thyroiditis
Normal thyroid gland	Graves disease, painless thyroiditis, or factitious hyperthyroidism

- **In the elderly**, hyperthyroidism may present with only atrial fibrillation, heart failure, weakness, or weight loss, and a high index of suspicion is needed to make the diagnosis.

Physical Examination

- Signs include brisk tendon reflexes, fine tremor, proximal weakness, stare, and eyelid lag. Cardiac abnormalities may be prominent, including sinus tachycardia, atrial fibrillation, and exacerbation of coronary artery disease or heart failure.
- Key differentiating physical exam findings (Table 24-2) include the following:
  - The presence of proptosis or pretibial myxedema, seen only in Graves disease (although many patients with Graves disease lack these signs)
  - A diffuse nontender goiter, consistent with Graves disease or painless thyroiditis
  - Recent pregnancy, neck pain, or recent iodine administration, suggesting causes other than Graves disease

Diagnostic Testing

- In rare cases, **24-hour radioactive iodine uptake (RAIU)** is needed to distinguish Graves disease or toxic MNG (in which RAIU is elevated) from postpartum thyroiditis, iodine-induced hyperthyroidism, or factitious hyperthyroidism (in which RAIU is very low).
- In suspected hyperthyroidism, plasma TSH is the best initial diagnostic test.
  - A TSH level >0.1 microunits/mL excludes clinical hyperthyroidism. If plasma TSH is <0.1 microunits/mL, **plasma free T_4** should be measured to determine the severity of hyperthyroidism and as a baseline for therapy. If plasma free T_4 is elevated, the diagnosis of clinical hyperthyroidism is established.
  - **If plasma TSH is <0.1 microunits/mL but free T_4 is normal**, the patient may have clinical hyperthyroidism due to elevation of plasma T_3 alone; and plasma T_3 should be measured in this case.
  - Very **mild (or subclinical) hyperthyroidism** may suppress TSH to <0.1 microunits/mL, and thus suppression of TSH alone does not confirm that symptoms are due to hyperthyroidism.
  - TSH may also be suppressed by **severe nonthyroidal illness** (see Evaluation of Thyroid Function section).

TREATMENT

- Some forms of hyperthyroidism (subacute or postpartum thyroiditis) are transient and require only **symptomatic therapy**. A **β-adrenergic antagonist** (such as **atenolol** 25-100 mg daily) relieves symptoms of hyperthyroidism, such as palpitations, tremor, and anxiety, until hyperthyroidism is controlled by definitive therapy or until transient

forms of hyperthyroidism subside. The dose is adjusted to alleviate symptoms and tachycardia, then reduced gradually as hyperthyroidism is controlled.

- Three methods are available for definitive therapy (none of which controls hyperthyroidism rapidly): RAI, thionamides, and subtotal thyroidectomy (*Thyroid 2011;21:593*).
  - During treatment, patients are followed by clinical evaluation and measurement of plasma free T_4. Plasma TSH is useless in assessing the initial response to therapy, because it remains suppressed until after the patient becomes euthyroid.
  - Regardless of the therapy used, all patients with Graves disease require lifelong follow-up for recurrent hyperthyroidism or development of hypothyroidism.
- **Choice of definitive therapy**
  - **In Graves disease, RAI therapy is the treatment of choice for almost all patients.** It is simple and highly effective but **cannot be used in pregnancy**. **Propylthiouracil** (**PTU**) **should be used to treat hyperthyroidism in pregnancy.** Thionamides achieve long-term control in fewer than half of patients with Graves disease, and they carry a small risk of life-threatening side effects. Thyroidectomy should be used in patients who refuse RAI therapy and who relapse or develop side effects with thionamide therapy.
  - **Other causes of hyperthyroidism.** Toxic MNG and toxic adenoma should be treated with RAI (except in pregnancy). Transient forms of hyperthyroidism due to thyroiditis should be treated symptomatically with atenolol. Iodine-induced hyperthyroidism is treated with thionamides and atenolol until the patient is euthyroid. Although treatment of some patients with amiodarone-induced hyperthyroidism with glucocorticoids has been advocated, **nearly all patients with amiodarone-induced hyperthyroidism respond well to thionamide therapy** (*Circulation 2002;105:1275*).
- **RAI therapy**
  - A single dose permanently controls hyperthyroidism in 90% of patients, and further doses can be given if necessary.
  - A **pregnancy test** is done immediately before therapy in potentially fertile women.
  - A 24-hour RAIU is usually measured and used to calculate the dose.
  - Thionamides interfere with RAI therapy and should be stopped at least 3 days before treatment. If iodine treatment has been given, it should be stopped at least 2 weeks before RAI therapy.
  - **Follow-up.** Usually, several months are needed to restore euthyroidism. Patients are evaluated at 4- to 6-week intervals, with assessment of clinical findings and plasma free T_4.
    - If thyroid function stabilizes within the normal range, the interval between follow-up visits is gradually increased to annual intervals.
    - If symptomatic hypothyroidism develops, thyroxine therapy is started (see Hypothyroidism section).
    - If symptomatic hyperthyroidism **persists after 6 months, RAI treatment is repeated**.
  - **Side effects**
    - **Hypothyroidism** occurs in most patients within the first year and continues to develop at a rate of approximately 3% per year thereafter.
    - Because of the release of stored hormone, a slight rise in plasma T_4 may occur in the first 2 weeks after therapy. This development is important only in **patients with severe cardiac disease**, which may worsen as a result. Such patients should be treated with thionamides to restore euthyroidism and to deplete stored hormone before treatment with RAI.
    - There is no convincing evidence that RAI has a clinically important effect on the course of Graves eye disease.

- It does not increase the risk of malignancy or cause congenital abnormalities in the offspring of women who conceive after RAI therapy.

- **Thionamides.** Methimazole and PTU inhibit thyroid hormone synthesis. PTU also inhibits extrathyroidal deiodination of T_4 to T_3. Once thyroid hormone stores are depleted (after several weeks to months), T_4 levels decrease. These drugs have no permanent effect on thyroid function. **In the majority of patients with Graves disease, hyperthyroidism recurs within 6 months after therapy is stopped.** Spontaneous remission of Graves disease occurs in approximately one-third of patients during thionamide therapy, and in this minority, no other treatment may be needed. Remission is more likely in mild, recent-onset hyperthyroidism and if the goiter is small. Because of a better safety profile, **methimazole should be used instead of PTU** except in specific situations (see the following text).
  - **Initiation of therapy.** Before starting therapy, patients must be warned of side effects and precautions. Usual starting doses are methimazole, 10-40 mg PO daily, or PTU, 100-200 mg PO tid; higher initial doses can be used in severe hyperthyroidism.
  - **Follow-up.** Restoration of euthyroidism takes up to several months.
    - Patients are evaluated at 4-week intervals with assessment of clinical findings and plasma free T_4. If plasma free T_4 levels do not fall after 4-8 weeks, the dose should be increased. Doses as high as methimazole, 60 mg PO daily, or PTU, 300 mg PO qid, may be required.
    - Once the plasma free T_4 level falls to normal, the dose is adjusted to maintain plasma free T_4 within the normal range.
    - No consensus exists on the optimal duration of therapy, but periods of 6 months to 2 years are usually used. Patients must be monitored carefully for recurrence of hyperthyroidism after the drug is stopped.
- **Side effects** are most likely to occur within the first few months of therapy.
  - Minor side effects include rash, urticaria, fever, arthralgias, and transient leukopenia.
  - **Agranulocytosis** occurs in 0.3% of patients treated with thionamides. Other life-threatening side effects include **hepatitis**, vasculitis, and drug-induced lupus erythematosus. These complications usually resolve if the drug is stopped promptly.
  - **Patients must be warned to stop the drug immediately if jaundice or symptoms suggestive of agranulocytosis develop (e.g., fever, chills, sore throat)** and to contact their physician promptly for evaluation. Routine monitoring of the white blood cell count (WBC) is not useful for detecting agranulocytosis, which develops suddenly.
- **Subtotal thyroidectomy.** This procedure provides long-term control of hyperthyroidism in most patients.
  - Surgery may trigger a perioperative exacerbation of hyperthyroidism, and patients should be prepared for surgery by one of two methods.
    - **A thionamide** is given until the patient is nearly euthyroid. **Supersaturated potassium iodide** (**SSKI**), 40-80 mg (one to two drops) PO bid, is then added 1-2 weeks before surgery. Both drugs are stopped postoperatively.
    - **Atenolol** (50-100 mg daily) is started 1-2 weeks before surgery. The dose of atenolol is increased, if necessary, to reduce the resting heart rate below 90 bpm and is continued for 5-7 days postoperatively. SSKI is given as mentioned earlier.

- **Follow-up.** Clinical findings and plasma free T_4 and TSH should be assessed 4-6 weeks after surgery.
  - If thyroid function is normal, the patient is seen at 3 and 6 months and then annually.
  - If symptomatic hypothyroidism develops, thyroxine therapy is started.
  - Hyperthyroidism persists or recurs in 3-7% of patients.
- **Complications** of thyroidectomy include **hypothyroidism** and **hypoparathyroidism**. Rare complications include permanent vocal cord paralysis, due to recurrent laryngeal nerve injury, and perioperative death. The complication rate appears to depend on the experience of the surgeon.

SPECIAL CONSIDERATIONS

- **Subclinical hyperthyroidism** (*J Clin Endocrinol Metab 2011;96:59*) is present when the plasma TSH is suppressed to <0.1 microunits/mL but the patient has no symptoms that are definitely caused by hyperthyroidism and plasma levels of free T_4 and T_3 are normal.
  - Subclinical hyperthyroidism increases the risk of **atrial fibrillation** in patients older than 60 years and those with heart disease and predisposes to **osteoporosis** in postmenopausal women; it should be treated in these patients.
  - Asymptomatic young patients with mild Graves disease can be observed for spontaneous resolution of hyperthyroidism or the development of symptoms or increasing free T_4 levels that warrant treatment.
- **Urgent therapy** is warranted when hyperthyroidism exacerbates heart failure or acute coronary syndromes and in rare patients with severe hyperthyroidism complicated by fever and delirium (sometimes called thyroid storm). Concomitant diseases should be treated intensively, and confirmatory tests (serum TSH and free T_4) should be obtained before therapy is started.
  - **PTU 300 mg PO q6h or methimazole 60 mg/d PO should be started immediately.**
  - **Iodide** (**SSKI**, two drops PO q12h) should be started to inhibit thyroid hormone secretion rapidly.
  - **Propranolol**, 40 mg PO q6h (or an equivalent dose IV), should be given to patients with angina or myocardial infarction, and the dose should be adjusted to prevent tachycardia. β-Adrenergic antagonists may benefit some patients with heart failure and marked tachycardia but can further impair left ventricular systolic function. In patients with clinical heart failure, it should be given only with careful monitoring of left ventricular function.
  - Plasma free T_4 is measured every 4-6 days. When free T_4 approaches the normal range, the doses of methimazole and iodine are gradually decreased. RAI therapy should be scheduled 2-4 weeks after iodine is stopped.
- **Hyperthyroidism in pregnancy.** If hyperthyroidism is suspected, plasma TSH should be measured. Plasma TSH declines in early pregnancy but rarely to <0.1 microunits/mL (*Endocrinol Metab Clin North Am 2011;40:739*).
  - If TSH is <0.1 microunits/mL, the diagnosis should be confirmed by measurement of plasma free T_4.
  - RAI is contraindicated in pregnancy, and therefore, patients should be treated with PTU. Methimazole is not used in the first trimester because it is associated with certain congenital defects. The dose should be adjusted at 4-week intervals to maintain the plasma free T_4 near the upper limit of the

normal range to avoid fetal hypothyroidism. The dose required often decreases in the later stages of pregnancy.

- Atenolol, 25-50 mg PO daily, can be used to relieve symptoms while awaiting the effects of PTU.
- The fetus and neonate should be monitored for hyperthyroidism. The maternal plasma level of thyroid-stimulating immunoglobulin should be measured in the third trimester to assess this risk.

Euthyroid Goiter and Thyroid Nodules

GENERAL PRINCIPLES

- The diagnosis of euthyroid goiter is based on palpation of the thyroid and evaluation of thyroid function. If the thyroid is enlarged, the examiner should determine whether the enlargement is **diffuse or multinodular or whether a single palpable nodule is present**. All three forms of euthyroid goiter are common, especially in women.

- Thyroid scans and ultrasonography (US) provide no useful additional information about goiters that are diffuse by palpation and should not be performed in these patients.
- Between 30-50% of people have nonpalpable thyroid nodules that are detectable by ultrasound. These nodules rarely have any clinical importance, but their incidental discovery may lead to unnecessary diagnostic testing and treatment.
- **Diffuse goiter**
  - Almost all euthyroid diffuse goiters in the United States are due to **chronic lymphocytic thyroiditis (Hashimoto thyroiditis)**. Because Hashimoto thyroiditis may also cause hypothyroidism, plasma TSH should be measured.
  - Diffuse goiters are usually asymptomatic, and therapy is seldom required. Patients should be monitored regularly for the development of hypothyroidism.
- **MNG**
  - MNG is common in older patients, especially women. Most patients are asymptomatic and require no treatment.
  - In a few patients, **hyperthyroidism** (toxic MNG) develops (see Hyperthyroidism section).
  - In rare patients, the gland compresses the trachea or esophagus, causing dyspnea or dysphagia, and treatment is required. Thyroxine treatment has little, if any, effect on the size of MNGs. RAI therapy reduces gland size and relieves symptoms in most patients. Subtotal thyroidectomy can also be used to relieve compressive symptoms.
  - Evaluation for thyroid carcinoma with needle biopsy is warranted if there is a dominant nodule (a nodule that is disproportionately larger than the rest). Some centers have adopted a policy of performing thyroid US in all patients with MNG and evaluating all nodules larger than 1 cm by needle biopsy. This policy dramatically increases the number of thyroid biopsies and the cost of managing this common condition. There is no evidence that routine thyroid US improves clinical outcomes in patients with MNG.
- **Single thyroid nodules**
  - **Single palpable thyroid nodules** are usually benign, but about 5% are thyroid carcinomas.

- Clinical findings that increase the risk of carcinoma include the presence of cervical lymphadenopathy, a history of radiation to the head or neck, and a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndromes type 2A or 2B. A hard, fixed nodule, recent nodule growth, or hoarseness due to vocal cord paralysis also suggests malignancy.
- Most patients with thyroid carcinomas have none of these risk factors, and all **palpable single thyroid nodules should be evaluated with needle aspiration biopsy**. Patients with thyroid carcinoma should be managed in consultation with an endocrinologist.
- Nodules with benign cytology should be reevaluated periodically by palpation. Thyroxine therapy has little or no effect on the size of single thyroid nodules and is not indicated.
- Some centers routinely use US for thyroids that contain a palpable thyroid nodule and biopsy all nodules that meet size and imaging criteria.

DISORDERS OF ADRENAL FUNCTION

Adrenal Failure

GENERAL PRINCIPLES

- Adrenal failure may be due to disease of the adrenal glands **(primary adrenal failure, Addison disease)**, with deficiency of both cortisol and aldosterone and elevated plasma adrenocorticotropic hormone (ACTH), or due to ACTH deficiency caused by disorders of the pituitary or hypothalamus **(secondary adrenal failure)**, with deficiency of cortisol alone.
- **Primary adrenal failure** is most often due to **autoimmune adrenalitis**, which may be associated with other endocrine deficits (e.g., hypothyroidism).

- Infections of the adrenal gland such as tuberculosis and histoplasmosis may cause adrenal failure.
- **Hemorrhagic adrenal infarction** may occur in the postoperative period, in coagulation disorders and hypercoagulable states, and in sepsis. Adrenal hemorrhage often causes abdominal or flank pain and fever; CT scan of the abdomen reveals high-density bilateral adrenal masses.
- Adrenal failure may develop in patients with AIDS, caused by adrenal lymphoma, disseminated cytomegalovirus, mycobacterial infection, or fungal infection.
- Less common etiologies include adrenoleukodystrophy that causes adrenal failure in young men and drugs such as ketoconazole and etomidate that inhibit steroid hormone synthesis.
- **Secondary adrenal failure** is most often due to **glucocorticoid therapy**; ACTH suppression may persist for a year after therapy is stopped. Any disorder of the pituitary or hypothalamus can cause ACTH deficiency, but other evidence of these disorders is usually obvious.

DIAGNOSIS

Clinical Presentation

- Adrenal failure should be suspected in patients with hypotension, weight loss, persistent nausea, hyponatremia, or hyperkalemia.
- **Clinical findings** in adrenal failure are nonspecific, and without a high index of suspicion, the diagnosis of this potentially lethal but readily treatable disease is easily missed.
  - Symptoms include anorexia, nausea, vomiting, weight loss, weakness, and fatigue. Orthostatic

hypotension and hyponatremia are common.

- Symptoms are usually chronic, but **shock** may develop suddenly and is fatal unless promptly treated. Often, this adrenal crisis is triggered by illness, injury, or surgery. All these symptoms are due to cortisol deficiency and occur in both primary and secondary adrenal failure.

- Hyperpigmentation (due to marked ACTH excess) and hyperkalemia and volume depletion (due to aldosterone deficiency) occur only in primary adrenal failure.

Diagnostic Testing

- **The cosyntropin (Cortrosyn) stimulation test** is used for diagnosis. Cosyntropin, 250 µg, is given IV or IM, and **plasma cortisol is measured 30 minutes later**. The normal response is a stimulated plasma cortisol >18 µg/dL. This test detects primary and secondary adrenal failure, except within a few weeks of onset of pituitary dysfunction (e.g., shortly after pituitary surgery; see Disorders of Anterior Pituitary Function section).
- The distinction between primary and secondary adrenal failure is usually clear.
- Hyperkalemia, hyperpigmentation, or other autoimmune endocrine deficits indicate primary adrenal failure, whereas deficits of other pituitary hormones, symptoms of a pituitary mass (e.g., headache, visual field loss), or known pituitary or hypothalamic disease indicate secondary adrenal failure.
- If the cause is unclear, the **plasma ACTH** level distinguishes primary adrenal failure (in which it is markedly elevated) from secondary adrenal failure.
- Most cases of primary adrenal failure are due to autoimmune adrenalitis, but other causes should be considered. Radiographic evidence of adrenal enlargement or calcification indicates that the cause is infection or hemorrhage.
- Patients with secondary adrenal failure should be tested for other pituitary hormone deficiencies and should be evaluated for a pituitary or hypothalamic tumor (see Disorders of Anterior Pituitary Function section).

TREATMENT

- **Adrenal crisis** with hypotension must be treated immediately. Patients should be evaluated for an underlying illness that precipitated the crisis.
- **If the diagnosis of adrenal failure is known, hydrocortisone, 100 mg IV q8h**, should be given, and **0.9% saline with 5% dextrose** should be infused rapidly until hypotension is corrected. The dose of hydrocortisone is decreased gradually over several days as symptoms and any precipitating illness resolve, then changed to oral maintenance therapy. Mineralocorticoid replacement is not needed until the dose of hydrocortisone is <100 mg/d.
- **If the diagnosis of adrenal failure has not been established**, a single dose of **dexamethasone**, 10 mg IV, should be given, and a rapid infusion of 0.9% saline with 5% dextrose should be started. A **Cortrosyn stimulation test** should be performed, regardless of the time of day. Dexamethasone is used because it does not interfere with measurement of plasma cortisol. After the 30-minute plasma cortisol measurement, hydrocortisone, 100 mg IV q8h, should be given until the test result is known.
- **Maintenance therapy** in all patients requires cortisol replacement with prednisone. Most patients with primary adrenal failure also require replacement of aldosterone with fludrocortisone.
  - **Prednisone**, 5 mg PO every morning, should be started. The dose is then adjusted with the goal

being the lowest dose that relieves the patient's symptoms, to prevent osteoporosis and other signs of Cushing syndrome. Most patients require doses between 4.0-7.5 mg PO daily. Concomitant therapy with rifampin, phenytoin, or phenobarbital accelerates glucocorticoid metabolism and increases the dose requirement.

- **During illness, injury, or the perioperative period, the dose of glucocorticoid must be increased.**
- For minor illnesses, the patient should double the dose of prednisone for 2-3 days. If the illness resolves, the maintenance dose is resumed.
- **Vomiting requires immediate medical attention**, with IV glucocorticoid therapy and IV fluid. Patients can be given a 4-mg vial of dexamethasone to be self-administered IM for vomiting or severe illness if medical care is not immediately available.
- **For severe illness or injury**, hydrocortisone, 50 mg IV q8h, should be given, with the dose tapered as severity of illness wanes. The same regimen is used in **patients undergoing surgery**, with the first dose of hydrocortisone given preoperatively. The dose can be tapered to maintenance therapy by 2-3 days after uncomplicated surgery.

- **In primary adrenal failure, fludrocortisone, 0.1 mg PO daily**, should be given. The dose is adjusted to maintain blood pressure (supine and standing) and serum potassium within the normal range; the usual dosage is 0.05-0.20 mg PO daily.
- **Patients should be educated in management of their disease**, including adjustment of prednisone dose during illness. They should wear a medical identification tag or bracelet.

Cushing Syndrome

GENERAL PRINCIPLES

- Cushing syndrome (*J Clin Endocrinol Metab 2008;93:1526*) is most often **iatrogenic**, due to therapy with glucocorticoid drugs.
- **ACTH-secreting pituitary microadenomas (Cushing disease)** account for 80% of cases of endogenous Cushing syndrome.
- Adrenal tumors and ectopic ACTH secretion account for the remainder.

DIAGNOSIS

Clinical Presentation

- Findings include truncal obesity, rounded face, fat deposits in the supraclavicular fossae and over the posterior neck, hypertension, hirsutism, amenorrhea, and depression. More specific findings include thin skin, easy bruising, reddish striae, proximal muscle weakness, and osteoporosis.
- Hyperpigmentation or hypokalemic alkalosis suggests Cushing syndrome due to ectopic ACTH secretion.
- Diabetes mellitus develops in some patients.

Diagnostic Testing

- **Diagnosis** is based on increased cortisol excretion, lack of normal feedback inhibition of ACTH and cortisol secretion, or loss of the normal diurnal rhythm of cortisol secretion. Three initial tests are available:

- The best initial test is the **24-hour urine cortisol** measurement;
- Alternatively, an **overnight dexamethasone suppression test** may be performed (1 mg dexamethasone given PO at 11:00 p.m.; plasma cortisol measured at 8:00 a.m. the next day; normal range: plasma cortisol <2 µg/dL); or
- Salivary cortisol may be measured at home during the nadir of normal plasma cortisol at 11:00 p.m.

- All these tests are very sensitive, and a normal value virtually excludes the diagnosis. If the overnight dexamethasone suppression test or 11:00 p.m. salivary cortisol is abnormal, 24-hour urine cortisol should be measured.
  - If the 24-hour urine cortisol excretion is more than 3-4 times the upper limit of the reference range in a patient with compatible clinical findings, the diagnosis of Cushing syndrome is established.
  - In patients with milder elevations of urine cortisol, a **low-dose dexamethasone suppression test** should be performed. Dexamethasone, 0.5 mg PO q6h, is given for 48 hours, starting at 8:00 a.m. Urine cortisol is measured during the last 24 hours, and plasma cortisol is measured 6 hours after the last dose of dexamethasone. Failure to suppress plasma cortisol to <2 µg/dL and urine cortisol to less than the normal reference range is diagnostic of Cushing syndrome.
  - Testing should not be done during severe illness or depression, which may cause false-positive results. Phenytoin therapy also causes a false-positive test by accelerating metabolism of dexamethasone.
- After the diagnosis of Cushing syndrome is made, tests to determine the cause are best done in consultation with an endocrinologist.

Incidental Adrenal Nodules

GENERAL PRINCIPLES

- Adrenal nodules are a common incidental finding on abdominal imaging studies.
- Most incidentally discovered nodules are benign adrenocortical tumors that do not secrete excess hormone.

DIAGNOSIS

In patients without a known malignancy elsewhere, the diagnostic issues are whether a syndrome of hormone excess or an adrenocortical carcinoma is present.

Clinical Presentation

Patients should be evaluated for hypertension, symptoms suggestive of pheochromocytoma (episodic headache, palpitations, and sweating), and signs of Cushing syndrome (see Cushing Syndrome section).

Differential Diagnosis

- The differential diagnosis includes adrenal adenomas causing Cushing syndrome or primary hyperaldosteronism, pheochromocytoma, adrenocortical carcinoma, and metastatic cancer.
- The imaging characteristics of the nodule may suggest a diagnosis but are not specific enough to obviate further evaluation.

Diagnostic Testing

- **Plasma potassium, metanephrines, and dehydroepiandrosterone sulfate** should be measured, and an **overnight dexamethasone suppression** test should be performed.
- **Patients who have potentially resectable cancer elsewhere** and in whom an adrenal metastasis must be excluded may require positron emission tomography.
- Patients with hypertension (especially if they have hypokalemia) should be evaluated for primary hyperaldosteronism by measuring the ratio of plasma aldosterone (in nanograms per deciliter [ng/dL]) to plasma renin activity (in ng/mL/h). If the ratio is <20, the diagnosis of primary hyperaldosteronism is excluded, whereas a ratio >50 makes the diagnosis very likely. Patients with an intermediate ratio should be further evaluated in consultation with an endocrinologist.
- An abnormal overnight dexamethasone suppression test should be evaluated further (see Cushing Syndrome section).
- Elevation of plasma dehydroepiandrosterone sulfate or a large nodule suggests adrenocortical carcinoma.

TREATMENT

- Most incidental nodules are <4 cm in diameter, do not produce excess hormone, and do not require therapy. One **repeat imaging procedure** 3-6 months later is recommended to ensure that the nodule is not enlarging rapidly (which would suggest an adrenal carcinoma).
- A policy of resecting all nodules >4 cm in diameter appropriately treats the great majority of adrenal carcinomas while minimizing the number of benign nodules that are removed unnecessarily.
- If clinical or biochemical evidence of a pheochromocytoma is found, the nodule should be resected after appropriate α-adrenergic blockade with phenoxybenzamine.

DISORDERS OF ANTERIOR PITUITARY FUNCTION

GENERAL PRINCIPLES

- The anterior pituitary gland secretes **prolactin**, **growth hormone**, and four **trophic hormones**, including corticotropin (ACTH), thyrotropin (TSH), and the gonadotropins, luteinizing hormone and follicle-stimulating hormone. Each trophic hormone stimulates a specific target gland.
- Anterior pituitary function is regulated by hypothalamic hormones that reach the pituitary via portal veins in the pituitary stalk. The predominant effect of hypothalamic

  regulation is to stimulate secretion of pituitary hormones, except for prolactin, which is inhibited by hypothalamic dopamine secretion.
- Secretion of trophic hormones is also regulated by negative feedback by their target gland hormone, and the normal pituitary response to target hormone deficiency is increased secretion of the appropriate trophic hormone.
- **Anterior pituitary dysfunction** can be caused by disorders of either the pituitary or hypothalamus.

Etiology

- **Pituitary adenomas** are the most common pituitary disorder. They are classified by size and function.

- **Microadenomas** are <10 mm in diameter and cause clinical manifestations only if they produce excess hormone. They are too small to produce hypopituitarism or mass effects.
- **Macroadenomas** are >10 mm in diameter and may produce any combination of pituitary hormone excess, hypopituitarism, and mass effects (headache, visual field loss).
- **Secretory adenomas** produce prolactin, growth hormone, or ACTH.
- **Nonsecretory macroadenomas** may cause hypopituitarism or mass effects.
- **Nonsecretory microadenomas** are common incidental radiographic findings, seen in approximately 10% of the normal population, and do not require therapy.

- **Other pituitary or hypothalamic disorders**, such as head trauma, pituitary surgery or radiation, and postpartum pituitary infarction (Sheehan syndrome) may cause hypopituitarism. Other tumors of the pituitary or hypothalamus (e.g., craniopharyngioma, metastases) and inflammatory disorders (e.g., sarcoidosis, Langerhans cell histiocytosis) may cause hypopituitarism or mass effects.

DIAGNOSIS

Clinical Presentation

- In **hypopituitarism** (deficiency of one or more pituitary hormones), gonadotropin deficiency is most common, causing amenorrhea in women and androgen deficiency in men. Secondary hypothyroidism or adrenal failure rarely occurs alone. Secondary adrenal failure causes deficiency of cortisol but not of aldosterone; hyperkalemia and hyperpigmentation do not occur, although life-threatening adrenal crisis may develop.
- **Hormone excess** most commonly results in **hyperprolactinemia**, which can be due to a secretory adenoma or due to nonsecretory lesions that damage the hypothalamus or pituitary stalk. Growth hormone excess **(acromegaly)** and ACTH and cortisol excess **(Cushing disease)** are caused by secretory adenomas.
- **Mass effects** due to pressure on adjacent structures, such as the optic chiasm, include headaches and loss of visual fields or acuity. Hyperprolactinemia may also be due to mass effect. **Pituitary apoplexy** is sudden enlargement of a pituitary tumor due to hemorrhagic necrosis.
- **Asymptomatic pituitary adenomas incidentally discovered on imaging.**

Diagnostic Testing

- If an incidental microadenoma is found on imaging done for another purpose, the patient should be evaluated for clinical evidence of hyperprolactinemia, Cushing disease, or acromegaly (*J Clin Endocrinol Metab 2011;96:894*).
- Plasma prolactin and **insulin-like growth factor 1** (IGF-1) should be measured, and tests for Cushing syndrome should be performed if symptoms or signs of this disorder are evident.
- If no pituitary hormone excess exists, therapy is not required. Whether such patients need repeat imaging is not established, but the risk of enlargement is clearly small.

- Incidental discovery of a macroadenoma is unusual. Patients should be evaluated for hormone excess and hypopituitarism. Most macroadenomas should be treated because they are likely to grow further.

Hypopituitarism

DIAGNOSIS

Clinical Presentation

Hypopituitarism may be suspected in the presence of clinical signs of target hormone deficiency (e.g., hypothyroidism) or pituitary mass effects.

Diagnostic Testing

Laboratories

- **Laboratory evaluation** for hypopituitarism begins with evaluation of **target hormone function**, including **plasma free T_4** and a **Cortrosyn stimulation test** (see Adrenal Failure section).
  - If recent onset of secondary adrenal failure is suspected (within a few weeks of evaluation), the patient should be treated empirically with glucocorticoids and should be tested 4-8 weeks later because the Cortrosyn stimulation test cannot detect secondary adrenal failure of recent onset.
  - In men, plasma testosterone should be measured. The best evaluation of gonadal function in women is the menstrual history.
- **If a target hormone is deficient**, its trophic hormone is measured to determine whether target gland dysfunction is secondary to hypopituitarism. An elevated trophic hormone level indicates primary target gland dysfunction. In hypopituitarism, trophic hormone levels are not elevated and are usually within (not below) the reference range. Thus, **pituitary trophic hormone levels can be interpreted only with knowledge of target hormone levels**, and **measurement of trophic hormone levels alone is useless in the diagnosis of hypopituitarism**. If pituitary disease is obvious, target hormone deficiencies may be assumed to be secondary, and trophic hormones need not be measured.

Imaging

Anatomic evaluation of the pituitary gland and hypothalamus is best done by MRI. However, hyperprolactinemia and Cushing disease may be caused by microadenomas too small to be seen. The prevalence of incidental microadenomas should be kept in mind when interpreting MRIs. Visual acuity and **visual fields** should be tested when imaging suggests compression of the optic chiasm.

TREATMENT

- Secondary adrenal failure should be treated immediately, especially if patients are to undergo surgery (see Adrenal Failure section).
- Treatment of secondary hypothyroidism should be monitored by measurement of **plasma free T_4** (see Hypothyroidism section).
- Infertility due to gonadotropin deficiency may be correctable, and patients who wish to conceive should be referred to an endocrinologist.
- Treatment of hypogonadism in premenopausal women requires replacement of estrogen and progesterone. This can be conveniently done with combination oral contraceptives.
- Treatment of hypogonadism in men requires testosterone replacement, with either topical testosterone gel, 40-50 mg applied daily, or by injection of testosterone enanthate or testosterone cypionate, 100-200 mg IM every 2 weeks.

- Treatment of growth hormone deficiency in adults has been advocated by some, but the long-term benefits, risks, and cost-effectiveness of this therapy are not established.

- Treatment of pituitary macroadenomas generally requires transsphenoidal surgical resection, except for prolactin-secreting tumors.

Hyperprolactinemia

GENERAL PRINCIPLES

- In women, the most common causes of pathologic hyperprolactinemia are prolactin-secreting pituitary **microadenomas** and **idiopathic hyperprolactinemia** (Table 24-3).
- In men, the most common cause is a prolactin-secreting **macroadenoma**.
- Hypothalamic or pituitary lesions that cause deficiency of other pituitary hormones often cause hyperprolactinemia.
- **Medications** are an important cause in both men and women (*Pituitary 2008;11:209*).

DIAGNOSIS

Clinical Presentation

- In women, hyperprolactinemia causes amenorrhea or irregular menses and infertility. Only approximately half of these women have galactorrhea. Prolonged estrogen deficiency increases the risk of osteoporosis. Plasma prolactin should be measured in women with amenorrhea, whether or not galactorrhea is present. Mild elevations should be confirmed by repeat measurements.
- In men, hyperprolactinemia causes androgen deficiency and infertility but not gynecomastia; mass effects and hypopituitarism are common.
- The history should include medications and symptoms of pituitary mass effects or hypothyroidism.

Diagnostic Testing

Testing for hypopituitarism is needed only in patients with a macroadenoma or hypothalamic lesion. **Pituitary imaging** should be performed in most cases, because large nonfunctional pituitary or hypothalamic tumors may present with hyperprolactinemia.

TABLE 24-3 Major Causes of Hyperprolactinemia

Pregnancy and lactation
Prolactin-secreting pituitary adenoma (prolactinoma)
Idiopathic hyperprolactinemia
Drugs (e.g., phenothiazines, metoclopramide, risperidone, verapamil)
Interference with synthesis or transport of hypothalamic dopamine
Hypothalamic lesions
Nonsecretory pituitary macroadenomas

Primary hypothyroidism

Chronic renal failure

TREATMENT

- For **microadenomas and idiopathic hyperprolactinemia** (*J Clin Endocrinol Metab 2011;96:273*), most patients are treated because of infertility or to prevent estrogen deficiency and osteoporosis.
- Some women may be observed without therapy by periodic follow-up of prolactin levels and symptoms. In most patients, hyperprolactinemia does not worsen, and prolactin levels sometimes return to normal. Enlargement of microadenomas is rare.
- **The dopamine agonists bromocriptine** and **cabergoline** suppress plasma prolactin and restore normal menses and fertility in most women.
  - Initial dosages are bromocriptine, 1.25-2.50 mg PO at bedtime with a snack, or cabergoline, 0.25 mg twice a week.
  - Plasma prolactin levels are initially obtained at 2- to 4-week intervals, and doses are adjusted to the lowest dose required to maintain prolactin in the normal range. In general, the maximally effective doses are bromocriptine 2.5 mg tid and cabergoline 1.5 mg twice a week.
  - **Side effects** include nausea and orthostatic hypotension, which can be minimized by increasing the dose gradually and usually resolve with continued therapy. Side effects are less severe with cabergoline.
  - Initially, women should use barrier contraception, because fertility may be restored quickly.
  - **Women who want to become pregnant** should be managed in consultation with an endocrinologist.
  - **Women who do not want to become pregnant** should be followed with clinical evaluation and plasma prolactin levels every 6-12 months. Every few years, plasma prolactin may be measured after the dopamine agonist has been withdrawn for several weeks, to determine whether the drug is still needed. Follow-up imaging studies are not warranted unless prolactin levels increase substantially.
- **Prolactin-secreting macroadenomas** should be treated with a dopamine agonist, which usually suppresses prolactin levels to normal, reduces tumor size, and improves or corrects abnormal visual fields in 90% of cases.
  - If mass effects are present, the dose should be increased to maximally effective levels over a period of several weeks. Visual field tests, if initially abnormal, should be repeated 4-6 weeks after therapy is started.
  - Pituitary imaging should be repeated 3-6 months after initiation of therapy. If tumor shrinkage and correction of visual abnormalities are satisfactory, therapy can be continued indefinitely, with periodic monitoring of plasma prolactin levels.
  - The full effect on tumor size may take more than 6 months. Further pituitary imaging is probably not warranted unless prolactin levels rise despite therapy.
  - **Transsphenoidal surgery** is indicated to relieve mass effects if the tumor does not shrink or if visual field abnormalities persist during dopamine agonist therapy. However, the likelihood of surgical cure of

a prolactin-secreting macroadenoma is low, and most patients require further therapy with a dopamine agonist.

- **Women with prolactin-secreting macroadenomas should not become pregnant** unless the tumor has been resected surgically or has decreased markedly in size with dopamine agonist therapy, because the risk of symptomatic enlargement during pregnancy is 15-35%. Contraception is essential during dopamine agonist treatment.

Acromegaly

GENERAL PRINCIPLES

Acromegaly is the syndrome caused by growth hormone excess in adults and is due to a growth hormone-secreting pituitary adenoma in the vast majority of cases (*J Clin Endocrinol Metab 2014;99:3933*).

DIAGNOSIS

Clinical Presentation

Clinical findings include thickened skin and enlargement of hands, feet, jaw, and forehead. Arthritis or carpal tunnel syndrome may develop, and the pituitary adenoma may cause headaches and vision loss. Mortality from cardiovascular disease is increased.

Diagnostic Testing

- **Plasma IGF-1**, which mediates most effects of growth hormone, is the best diagnostic test. Marked elevations establish the diagnosis.
- If IGF-1 levels are only moderately elevated, the diagnosis can be confirmed by giving 75 mg glucose orally and measuring serum growth hormone every 30 minutes for 2 hours. Failure to suppress growth hormone to <1 ng/mL confirms the diagnosis of acromegaly. Once the diagnosis is made, the pituitary should be imaged.

TREATMENT

The treatment of choice is transsphenoidal resection of the pituitary adenoma. Most patients have macroadenomas, and complete tumor resection with cure of acromegaly is often impossible. If IGF-1 levels remain elevated after surgery, radiotherapy is used to prevent regrowth of the tumor and to control acromegaly.

Medications

- The somatostatin analog **octreotide** in depot form can be used to suppress growth hormone secretion while awaiting the effect of radiation. A dose of 10-40 mg IM monthly suppresses IGF-1 to normal in about 60% of patients. Side effects include cholelithiasis, diarrhea, and mild abdominal discomfort.
- **Pegvisomant** is a growth hormone antagonist that lowers IGF-1 to normal in almost all patients. The dose is 10-30 mg SC daily. Few side effects have been reported, but patients should be monitored for pituitary adenoma enlargement and transaminase elevation.

METABOLIC BONE DISEASE

Osteomalacia

GENERAL PRINCIPLES

- Osteomalacia is characterized by defective mineralization of osteoid. Bone biopsy reveals increased thickness of osteoid seams and decreased mineralization rate, assessed by tetracycline labeling.
- Suboptimal vitamin D nutrition, indicated by plasma 25-hydroxy vitamin D (25[OH]D) levels <30 ng/mL, is very common and contributes to the development of osteoporosis (*J Clin Endocrinol Metab 2011;96:1911*).

Etiology

- Dietary vitamin D deficiency
- Malabsorption of vitamin D and calcium due to intestinal, hepatic, or biliary disease
- Disorders of vitamin D metabolism (e.g., renal disease, vitamin D-dependent rickets)
- Vitamin D resistance
- Chronic hypophosphatemia
- Renal tubular acidosis
- Hypophosphatasia

DIAGNOSIS

Clinical Presentation

- Clinical findings include diffuse skeletal pain, proximal muscle weakness, waddling gait, and propensity to fractures.
- Osteomalacia should be suspected in a patient with osteopenia, elevated serum alkaline phosphatase, and either hypophosphatemia or hypocalcemia.

Diagnostic Testing

Laboratories

- Serum alkaline phosphatase is elevated. Serum phosphorus, calcium, or both may be low.
- **Serum 25(OH)D** levels may be low, establishing the diagnosis of vitamin D deficiency or malabsorption.

Imaging

Radiographic findings include osteopenia and radiolucent bands perpendicular to bone surfaces (pseudofractures or Looser zones). Bone density is decreased.

TREATMENT

- **Dietary vitamin D deficiency** can initially be treated with ergocalciferol 50,000 international units (IU) PO weekly for 8 weeks to replete body stores, followed by long-term therapy with 2000 IU/d.
- **Malabsorption of vitamin D** may require continued therapy with high doses such as 50,000 IU PO per week. The dose should be adjusted to maintain serum 25(OH)D levels above 30 ng/mL. Calcium supplements, 1 g PO daily-tid, may also be required. Serum 25(OH)D and serum calcium should be monitored every 6-12 months to avoid hypercalcemia.

Paget Disease

GENERAL PRINCIPLES

Paget disease of bone is a focal skeletal disorder characterized by rapid, disorganized bone remodeling. It usually occurs after the age of 40 years and most often affects the pelvis, femur, spine, and skull (*J Clin Endocrinol Metab 2014;99:4408*).

DIAGNOSIS

Clinical Presentation

- Clinical manifestations include bone pain and deformity, degenerative arthritis, pathologic fractures, neurologic deficits due to nerve root or cranial nerve compression (including deafness), and rarely, high-output heart failure and osteogenic sarcoma.
- Most patients are asymptomatic, with disease discovered incidentally because of elevated serum alkaline phosphatase or a radiograph taken for other reasons.

Diagnostic Testing

Laboratories

Serum alkaline phosphatase is elevated, reflecting the activity and extent of disease. Serum and urine calcium are usually normal but may increase with immobilization, as after a fracture.

Imaging

The radiographic appearance is usually diagnostic. A bone scan will reveal areas of skeletal involvement, which can be confirmed by radiography.

TREATMENT

Indications for therapy include (a) bone pain due to Paget disease, (b) nerve compression syndromes, (c) pathologic fracture, (d) elective skeletal surgery, (e) progressive skeletal deformity, (f) immobilization hypercalcemia, and (g) asymptomatic involvement of weight-bearing bones or the skull.

Medications

Bisphosphonates inhibit excessive bone resorption, relieve symptoms, and restore serum alkaline phosphatase to normal in most patients. **Zoledronic acid**, 5 mg IV by a single infusion, is the drug of choice. The effectiveness of therapy is monitored by measuring serum alkaline phosphatase annually. Therapy can be repeated if serum alkaline phosphatase rises above normal. Bisphosphonates are not recommended in patients with renal insufficiency.

25
Arthritis and Rheumatologic Diseases

Zarmeena Ali

María González-Mayda

Tiphanie Vogel

Basic Approach to the Rheumatic Diseases

Arthritis is any medical process affecting a joint or joints, causing pain, swelling, and stiffness. Pain from a true articular process is usually present throughout the complete range of motion of a particular joint, whereas pain from a **periarticular process** is usually evident at a single point in the range of motion, and it is elicited by palpation in a specific area corresponding to a tendon, ligament, or bursa.

Arthritis can be categorized as an inflammatory or noninflammatory process and by the number and type of joints involved.

DIAGNOSIS

Evidence of an inflammatory process includes the presence of morning stiffness lasting more than an hour, worsening of symptoms with inactivity, or constitutional symptoms. Skin rashes, uveitis, scleritis, mouth ulcers, and serositis among others may give clues to an underlying arthropathy or connective tissue disease. Physical exam may reveal swelling, warmth, or erythema. Synovial fluid analysis should be sent for cell count, microscopic examination for crystals, Gram stain, and cultures. Ancillary lab test and imaging are helpful in supporting a diagnosis if their use is directed by the specific findings on the history and physical exam.

TREATMENT

The etiology of most rheumatologic disorders is unknown. Therapeutic approaches involve either local or systemic administration of analgesic, anti-inflammatory, immunomodulatory, or immunosuppressive drugs.

Medications

- **NSAIDs** exert their effects by inhibiting the constitutive (COX-1) and inducible (COX-2) isoforms of cyclooxygenase, producing a mild to moderate anti-inflammatory and analgesic effect. Individual responses to these agents are variable. If one drug is not effective during a 2- to 3-week trial, another should be tried.
  - **Side effects**
    - **Gastrointestinal (GI) toxicity** manifests clinically as dyspepsia, nausea, vomiting, or GI bleeding. Nausea and dyspepsia often respond to the addition of a histamine-2 (H_2)-blocking agent or proton pump inhibitor or to a change in NSAID. Direct GI irritation can be minimized by administration after food, by the use of enteric-coated preparations, and by use of the lowest effective dose. All NSAIDs, however, have a systemic effect on the GI mucosa, resulting in increased permeability to gastric acid. Most serious GI bleeds during NSAID use occur without prior GI symptoms.

      Risk factors for GI bleed include a history of duodenal-gastric ulceration, age >60, smoking, ethanol use, high dose of NSAIDs, and concomitant use of corticosteroids, anticoagulants (i.e.,

aspirin, warfarin, clopidogrel), or selective serotonin reuptake inhibitors. The use of proton pump inhibitors such as **omeprazole** 20 mg PO daily decreases the risk of NSAID-induced gastric or duodenal ulceration. **Misoprostol**, a synthetic prostaglandin E analog, is another alternative but may cause diarrhea and is an abortifacient. Consider *Helicobacter pylori* testing prior to beginning NSAIDs, especially in patients with high risk of duodenal-gastric ulceration. If the test is positive, treat accordingly (see Chapter 18, Gastrointestinal Diseases).

- **Acute renal failure** due to reversible renal ischemia is the most common form of renal toxicity; however, nephrotic syndrome and acute interstitial nephritis may also occur. **Risk factors** for acute renal failure include preexisting renal dysfunction, congestive heart failure (CHF), cirrhosis with ascites, and a concomitant angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Periodic monitoring of renal function is recommended, particularly in elderly patients.
- **Platelet dysfunction** can be caused by all NSAIDs, particularly aspirin, which is a covalent inhibitor of COX. NSAIDs should be used cautiously or avoided in patients with a bleeding diathesis and those taking warfarin. NSAIDs should be discontinued 5-7 days before surgical procedures.
- **Hypersensitivity reactions** are often seen in patients with a history of asthma, nasal polyps, or atopy. NSAIDs may cause a variety of type I hypersensitivity-like reactions, including urticaria, asthma, and anaphylactoid shock, presumably by increasing leukotriene synthesis. Patients with a hypersensitivity reaction to one NSAID should avoid all NSAIDs and selective COX-2 inhibitors.

- **Other side effects: Central nervous system** (CNS) toxicity (headaches, dizziness, dysphoria, confusion, aseptic meningitis) is uncommon. Tinnitus and deafness can complicate NSAID use, particularly with high-dose salicylates. **Blood dyscrasias**, including aplastic anemia, have been observed as isolated case reports with ibuprofen, piroxicam, indomethacin, and phenylbutazone. **Dermatologic reactions** and **elevations in transaminases** have also been described. **A metabolic acidosis and respiratory alkalosis** can be seen with high doses of salicylates. Nonacetylated salicylates have been reported to have less toxicity but also may be less effective. The use of NSAIDs in general may be associated with an increased risk for **cardiovascular thrombotic events** and might diminish the cardioprotective effect of aspirin.

- **Selective COX-2 inhibitors** exhibit selective inhibition of COX-2, thereby reducing inflammation while preserving the homeostatic functions of constitutive COX-1-derived prostaglandins. The anti-inflammatory and analgesic efficacy is similar to that of traditional NSAIDs. Celecoxib is the only selective COX-2 inhibitor approved in the United States.
  - **Side effects**
    - Some data demonstrate that **GI symptoms** and **GI ulcerations are reduced** with these agents in comparison to NSAIDs. The potential gastroduodenal-sparing effect of selective COX-2 inhibitors may be eliminated by concurrent warfarin therapy or the use of low-dose aspirin therapy for primary or secondary prevention of cardiovascular or cerebrovascular disease (*JAMA 2000;284:1247*).
    - Acute kidney injury might be precipitated in patients taking selective COX-2 inhibitors, similar to COX-1 inhibitors.
  - **Platelet function** is not impaired, making selective COX-2 inhibitors a good anti-inflammatory option for patients with thrombocytopenia, hemostatic defects, or chronic anticoagulation. In patients who are taking warfarin, however, the international normalized ratio (INR) should be monitored after the addition of a COX-2 inhibitor (as with any medication change). In addition, there has been controversy as to whether the inhibition of prostacyclin but not thromboxane by these agents may promote clotting.

- Patients with hypersensitivity reactions to NSAIDs should not use a COX-2 inhibitor. Celecoxib should be used with caution in patients with sulfonamide allergy.
- An increase in blood pressure and a dose-related **increase in cardiovascular events** (i.e., CHF exacerbation) have been associated with the use of this medication.

- **Glucocorticoids** exert a pluripotent anti-inflammatory effect via the inhibition of inflammatory mediator gene transcription.
  - **Preparations, dosages, and routes of administration:** The goal of therapy **is to suppress** disease activity with the minimum effective dosage. **Prednisone** (PO) and **methylprednisolone** (IV) are generally the preferred drugs because of cost and half-life considerations. IM absorption is variable and therefore is not advised. The following are **relative anti-inflammatory potencies** of common glucocorticoid preparations: cortisone, 0.8; hydrocortisone, 1.0; prednisone, 4.0; methylprednisolone, 5.0; dexamethasone, 25.0.
  - **Side effects:** Adverse effects are related to dosage and duration of administration and, except for cataracts and osteoporosis, can be minimized by alternate-day administration once the disease is controlled.
    - **Adrenal suppression:** Glucocorticoids suppress the hypothalamic-pituitary-adrenal axis. Assume functional suppression in patients receiving more than 20 mg of prednisone (or the equivalent) daily for more than 3 weeks, patients receiving an evening dose for more than a few weeks, or patients with cushingoid appearance. Adrenal suppression is unlikely if the patient has received any dose of steroids for less than 3 weeks or if using alternate-day therapy. Adrenal suppression is minimized by dosing in the morning and using a single daily low dose of a short-acting preparation, such as prednisone, for a short period. In patients who are receiving chronic glucocorticoid therapy, hypoadrenalism (anorexia, weight loss, lethargy, fever, and postural hypotension) may occur at times of severe stress (e.g., infection, major surgery) and should be treated with stress doses of glucocorticoids.
    - **Immunosuppression:** Glucocorticoid therapy reduces resistance to infections. **Bacterial infections** in particular are related to the dosage of glucocorticoids and are a major cause of morbidity and mortality. Minor infections may become systemic, quiescent infections may be activated, and organisms that usually are nonpathogenic may cause disease. Local and systemic signs of infection may be partially masked, although fever associated with infection generally is not suppressed. A skin test for TB should be performed before glucocorticoid therapy is instituted, and if it is positive, TB should be treated appropriately. For patients on prolonged high-dose therapy, consider prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) and acyclovir to prevent *Pneumocystis jirovecii* and varicella-zoster viral infections.
    - **Endocrine abnormalities:** Endocrine abnormalities include a **cushingoid habitus**, hirsutism, and induced or aggravated hyperglycemia, rarely associated with ketoacidosis. Hyperglycemia is not a contraindication to therapy and may require treatment with insulin therapy. Fluid and electrolyte abnormalities include hypokalemia and sodium retention, which may induce or aggravate hypertension.
    - **Osteoporosis** with vertebral compression fractures is common among patients who are receiving long-term glucocorticoid therapy. **Supplemental calcium**, 1.0-1.5 g/d PO, should be given along with **vitamin D**, 1000 units daily PO, as soon as steroid therapy is begun. Bisphosphonates or teriparatide (recombinant human parathyroid hormone [1-34]) is indicated in postmenopausal women and in premenopausal women or men who are at high risk for osteoporosis (*Nat Rev Rheumatol. 2015;11(2):98-109*). Determination of baseline bone density is appropriate in these

patients. A weight-bearing exercise program and avoidance of alcohol and tobacco are recommended.

- **Steroid myopathy** generally involves the hip and shoulder girdle musculature. Muscles are weak but not tender, and in contrast to inflammatory myositis, serum creatine

kinase, aldolase, and electromyography are normal. The myopathy usually improves with a reduction in glucocorticoid dosage and resolves slowly with discontinuation.

- **Ischemic bone necrosis** (aseptic necrosis, avascular necrosis) caused by glucocorticoid use often is multifocal, most commonly affecting the femoral head, humeral head, and tibial plateau. Early changes can be demonstrated by bone scan or MRI.

- **Other adverse effects:** Changes in **mental status** ranging from mild nervousness, euphoria, and insomnia to severe depression or psychosis may occur. **Ocular effects** include increased intraocular pressure (sometimes precipitating glaucoma) and the formation of posterior subcapsular cataracts. **Hyperlipidemia**, **menstrual irregularities**, increased perspiration with **night sweats**, and **pseudotumor cerebri** also may occur.

- **Immunomodulatory and immunosuppressive drugs**, also known as **disease-modifying antirheumatic drugs (DMARDs)**, include a number of pharmacologically diverse agents that exert anti-inflammatory or immunosuppressive effects. They are characterized by a delayed onset of action and the potential for serious toxicity. Consequently, they should be prescribed with the guidance of a rheumatologist and in cooperative patients who are willing to comply with meticulous follow-up. The specific agents will be discussed in relation to the diseases for which they are indicated. Examples of these agents include methotrexate, azathioprine, hydroxychloroquine, sulfasalazine, cyclosporine, rituximab, and etanercept.

Nonpharmacologic Therapies

- **Joint aspiration should be performed in one of three instances: effusion of unclear etiology**, symptomatic relief in a patient with known arthritis diagnosis, and monitoring treatment response in **infectious arthritis**. Intra-articular glucocorticoid therapy can be used to suppress inflammation when only one or a few peripheral joints are inflamed and infection has been excluded. Intra-articular hyaluronic acid derivatives are used for the treatment of knee osteoarthritis (OA). The joint should be aspirated to remove as much fluid as possible before injection. **Glucocorticoid preparations** include methylprednisolone acetate, triamcinolone acetonide, and triamcinolone hexacetonide. The dose used is arbitrary, but the following guidelines based on volume are useful: large joints (knee, ankle, shoulder), 1-2 mL; medium joints (wrists, elbows), 0.5-1.0 mL; and small joints of the hands and feet, 0.25-0.50 mL. **Lidocaine** (or its equivalent), up to 1 mL of a 1% solution, can be mixed in a single syringe with the glucocorticoid to promote immediate relief but is not generally used in the digits.
- **Contraindications:** Cellulitis overlying the site to be injected is an absolute contraindication. Significant hemostatic defects and bacteremia are relative contraindications to joint aspiration and injection.
- **Complications**
  - **Postinjection synovitis** may develop rarely as a result of phagocytosis of glucocorticoid ester crystals. Reactions usually resolve within 48-72 hours. More persistent symptoms suggest the possibility of iatrogenic infection, which occurs rarely (<0.1% of patients).
  - Localized skin depigmentation and atrophy along with accelerated deterioration of bone and cartilage may occur when frequent injections are administered over an extended period. Therefore, any single joint should be injected no more frequently than every 3-6 months.

Infectious Arthritis and Bursitis

GENERAL PRINCIPLES

- **Infectious arthritis** is generally categorized into gonococcal and nongonococcal disease.
- **Nongonococcal infectious arthritis** in adults tends to occur in patients with previous joint damage or compromised host defenses. It is caused most often by *Staphylococcus*

aureus (60%) and *Streptococcus* spp. Gram-negative organisms are less common and typically seen with IV drug abuse, neutropenia, concomitant urinary tract infection, or postoperative status.

- **Gonococcal arthritis** causes one-half of all septic arthritis in otherwise healthy, sexually active young adults.

DIAGNOSIS

Clinical Presentation

- **Nongonococcal infectious arthritis** usually presents with fever and an acute monoarticular arthritis, although multiple joints may be affected by hematogenous spread of pathogens.
- **Gonococcal arthritis** often includes migratory or additive polyarthralgias, followed by tenosynovitis or arthritis of the wrist, ankle, or knee, and vesicopustular skin lesions on the extremities or trunk (disseminated gonococcal infection).

Diagnostic Testing

- **Joint aspiration should be performed and synovial fluid sent for** Gram stain, cell count with differential, and cultures. Cultures of blood and other possible extra-articular sites of infection also should be obtained.
- Synovial fluid Gram stain may be positive in 50-70% of nongonococcal infectious arthritis cases.
- Gram staining of synovial fluid is positive in **less than 25% of cases** of gonococcal arthritis. Cultures of synovial fluid are positive in 20-50% of cases. Bacteriologic assessment of the throat, cervix, urethra, and rectum may aid in establishing the diagnosis.

TREATMENT

- **Empiric antimicrobial therapy** should be started immediately based on the clinical situation.
  - With a positive Gram stain and culture, antibiotic coverage can be tailored accordingly.
  - With a nondiagnostic Gram stain, antibiotics should be chosen to cover *S. aureus*, *Streptococcus* spp., and *Neisseria gonorrhoeae*. Vancomycin 15 mg/kg IV every 12 hours and ceftriaxone 1 g IV every 24 hours are good initial treatment choices. Cefepime instead of ceftriaxone is preferred if *Pseudomonas* infection is suspected.
  - IV antimicrobials are given for at least 2 weeks, followed by 1-2 weeks of oral antimicrobials, with the course of therapy tailored to the patient's response.
  - Treatment of gonococcal arthritis is with an IV antibiotic, generally ceftriaxone, 1-2 g IV daily. After clinical improvement is noted, usually 48 hours after IV antibiotics, therapy is continued with an oral antibiotic to complete 7-14 days of treatment. Cefixime, 400 mg PO bid, or amoxicillin, 500-850 mg PO bid, may be used. **Treatment of coexisting *Chlamydia* infection** with azithromycin or doxycycline

should also be considered.
    - Oral and intra-articular antimicrobials are not appropriate as initial therapy.
- **Drainage** of the affected joint is needed to decrease the possibility of permanent joint damage. **Surgical drainage** or arthroscopic lavage and drainage are indicated for (a) a septic hip; (b) joints in which the anatomy, large amounts of tissue debris, or loculation of pus prevent adequate needle drainage; (c) septic arthritis with coexistent osteomyelitis; (d) joints that do not respond in 3-5 days to appropriate therapy; and (e) prosthetic joint infection.

- **General supportive measures** include splinting of the joint, which may help to relieve pain. However, prolonged immobilization can result in joint stiffness. An **NSAID** is useful to reduce pain and increase joint mobility but should not be used until response to antimicrobial therapy has been demonstrated by symptomatic and laboratory improvement.

SPECIAL CONSIDERATIONS

Nonbacterial infectious arthritis is common with many viral infections, especially hepatitis B, rubella, mumps, infectious mononucleosis, parvovirus, enterovirus, and adenovirus.

- It is generally self-limiting, lasting for <6 weeks, and responds well to a conservative regimen of rest and NSAIDs.
- Arthralgias (often severe) or a reactive arthritis can also be a manifestation of HIV infection.
- Fungi and mycobacterium can cause septic arthritis and should be considered in patients with chronic monoarticular arthritis.

Septic Bursitis

GENERAL PRINCIPLES

- Usually involves the olecranon or prepatellar bursa and can be differentiated from septic arthritis by localized, fluctuant superficial swelling and by **relatively painless joint motion** (particularly extension).
- Most patients have a history of previous trauma to the area or an occupational predisposition (e.g., “housemaid's knee,” “writer’s elbow”).
- *S. aureus* is the most common pathogen of septic bursitis.

DIAGNOSIS AND TREATMENT

- Aspiration of the joint is performed, with antibiotic therapy guided by Gram stain and culture of bursa fluid. Aspiration can be repeated if fluid reaccumulates. Surgical drainage is indicated only if adequate needle drainage is not possible.
- Oral antibiotics (guided by Gram stain and culture of bursa fluid) and outpatient management are usually appropriate. Preventive measures (e.g., knee pads) should be used in patients with occupational predispositions to septic bursitis.

Lyme Disease

GENERAL PRINCIPLES

Lyme disease is caused by the tick-borne spirochete *Borrelia burgdorferi*.

DIAGNOSIS

- Typical manifestations begin with an erythematous annular rash **(erythema migrans)** and flu-like symptoms.
- Arthralgias, myalgias, meningitis, neuropathy, and cardiac conduction defects may follow in weeks to a few months. Months later, in untreated patients, an intermittent or chronic oligoarticular arthritis, characteristically including the knee, may develop.
- The diagnosis is based on the clinical picture and exposure in an endemic area and **supported by serology**. A two-tiered serologic assay with enzyme-linked immunosorbent assay (ELISA) and IgG western blot for *B. burgdorferi* is uniformly positive by the time frank

arthritis develops. False positives occur, however, and may signify prior infection. *B. burgdorferi* DNA can be detected by polymerase chain reaction in synovial fluid in 85% of cases.

TREATMENT

Antibiotic therapy is required, generally with doxycycline 100 mg PO bid or amoxicillin 500 mg PO tid for 28 days. NSAIDs are a useful adjunct for arthritis.

Crystal-Induced Synovitis

GENERAL PRINCIPLES

Definition

Deposition of microcrystals in joints and periarticular tissues results in **gout**, **pseudogout**, and **apatite disease**.

Classification

- Clinical phases of gout can be divided into asymptomatic hyperuricemia, acute gouty arthritis, and chronic arthritis.
- **Asymptomatic hyperuricemia** is defined as serum uric acid levels >7 mg/dL without arthritis.
- Men are much more commonly affected by gouty arthritis than women. Most premenopausal women with gout have a family history of the disease.

Etiology

- **Primary gouty arthritis** is characterized by hyperuricemia that is usually because of underexcretion of uric acid (90% of cases) rather than its overproduction. Urate crystals may be deposited in the joints, subcutaneous tissues (tophi), and kidneys.
- **Secondary gout**, like primary gout, can be caused by either defective renal excretion or overproduction of uric acid. Intrinsic renal disease, diuretic therapy, low-dose aspirin, cyclosporine, and ethanol all interfere with

renal excretion of uric acid. Starvation, lactic acidosis, dehydration, preeclampsia, and diabetic ketoacidosis also can induce hyperuricemia. Overproduction of uric acid occurs in myeloproliferative and lymphoproliferative disorders, hemolytic anemia, polycythemia, and cyanotic heart disease.

- **Pseudogout** results when calcium pyrophosphate dihydrate crystals deposited in bone and cartilage are released into synovial fluid and induce acute inflammation. **Risk factors** include older age, advanced OA, neuropathic joint, gout, hyperparathyroidism, hemochromatosis, diabetes mellitus, hypothyroidism, and hypomagnesemia.

DIAGNOSIS

Clinical Presentation

- **Acute gouty arthritis** presents as an excruciating attack of pain, usually in a single joint of the foot or ankle. Occasionally, a polyarticular onset can mimic rheumatoid arthritis (RA). Acute gouty arthritis attacks can be precipitated by surgery, dehydration, fasting, binge eating, or heavy ingestion of alcohol.
- **Chronic gouty arthritis:** With time, acute gouty attacks occur more frequently, asymptomatic periods are shorter, and chronic joint deformity may appear.
- **Pseudogout** may present as an **acute monoarthritis or oligoarthritis**, mimicking gout, or as a **chronic polyarthritis** resembling RA or OA. Usually the knee or wrist is affected, although any synovial joint can be involved.

- **Apatite/basic calcium phosphate crystals** may cause periarthritis, tendonitis, or a destructive arthritis.

Diagnostic Testing

Laboratories

- A definitive diagnosis of gout or pseudogout is made by finding **intracellular crystals** in synovial fluid examined with a compensated polarized light microscope. **Urate crystals** are needle shaped and strongly negatively birefringent. **Calcium pyrophosphate dihydrate crystals** are pleomorphic and weakly positively birefringent. Hydroxyapatite complexes and basic calcium phosphate complexes can be identified only by electron microscopy and mass spectroscopy.
- Serum uric acid level is normal in 30% of patients with acute gout.
- **Apatite disease** should be suspected when no crystals are present in the **synovial fluid**.

Imaging

- Erosions with overhanging borders may be seen on imaging with gout.
- If pseudogout is suspected, films of the wrists, knees, and pubic symphysis may be ordered. These are the most common sites for chondrocalcinosis, a finding that is supportive of (but not diagnostic for) pseudogout.
- Hydroxyapatite disease may be suspected by finding poorly defined cloud-like calcific deposits in the periarticular area on imaging.

TREATMENT

- **Asymptomatic hyperuricemia** is not routinely treated. However, patients should be monitored closely for the development of complications if the serum uric acid level is at least 12 mg/dL in men or 10 mg/dL in women. Urate-lowering therapy should then be considered.
- **Management of secondary gout** includes treatment of the underlying disorder and urate-lowering

therapy.

- Treatment of **apatite disease** is similar to that for pseudogout.
- **Acute gout**
  - Although the acute gouty attack will subside spontaneously over several days, prompt treatment can abort the attack within hours.
  - **NSAIDs** are the treatment of choice due to ease of administration and low toxicity. Clinical response may require 12-24 hours, and initial doses should be high, followed by rapid tapering over 2-8 days. One approach is to use indomethacin, 50 mg PO q8h for 2 days, followed by 25 mg PO q8h for 3-7 days. Long-acting NSAIDs are generally not recommended for acute gout.
  - **Glucocorticoids** are useful when NSAIDs are contraindicated. An intra-articular injection of glucocorticoids produces rapid dramatic relief. Alternatively, prednisone, 40-60 mg PO daily, can be given until a response is obtained and then should be tapered rapidly.
  - **Colchicine is most effective if given in the first 12-24 hours** of an acute attack and usually brings relief in 6-12 hours. A dose of 1.2 mg is given at onset of symptoms, and 0.6 mg is taken 1 hour after the initial dose (1.8 mg over 1 hour). This regimen decreases the GI side effects noted with previous higher dose therapies.
  - **Urate-lowering drugs should not be started during an acute gouty attack even if the uric acid is elevated.**
- **Chronic gouty arthritis**
  - **Colchicine**, 0.6 mg PO daily or bid, can be used prophylactically for acute attacks. The dosage needs to be adjusted in patients with renal insufficiency. Colchicine 0.6 mg every other day or every 3 days should be considered in patients with a creatinine

    clearance between 10 and 34 mL/min. Aspirin (uricoretentive), diuretics, high alcohol intake, and foods high in purines (sweetbreads, anchovies, shellfish, sardines, liver, and kidney) should be avoided. Weight loss should be encouraged. Frequent gout attacks, tophi, joint damage, and urate nephropathy are indications for urate-lowering therapy. **Maintenance colchicine, 0.6 mg PO daily or bid, should be given for a few days before manipulation of the uric acid level to prevent precipitation of an acute attack.** In patients without tophi, prophylactic colchicine can be discontinued after 6 months once serum urate levels are <6 mg/dL and no acute attacks have been documented by the patient (*Arthritis Rheum 2004;51(3):321*). In patients with tophi, duration of prophylaxis is uncertain but consider discontinuation 6 months after resolution of tophi.
  - **Allopurinol**, a xanthine oxidase inhibitor, is effective therapy for hyperuricemia in most patients.
    - **Dosage and administration:** Initial dosage varies and should be adjusted for renal and hepatic dysfunction. Daily doses can be increased by 100 mg every 2-4 weeks to achieve the minimum maintenance dosage that will keep the uric acid level below 6 mg/dL, which is below the limit of solubility of monosodium urate in serum. The concomitant use of a uricosuric agent may hasten the mobilization of tophi. **Allopurinol should be continued during an acute gout flare if already started, and use of NSAIDs, colchicine, or steroids to abort the attack be considered.**
    - **Side effects: Hypersensitivity reactions** from a minor skin rash to a diffuse exfoliative dermatitis associated with fever, eosinophilia, and a combination of renal and hepatic injury occur in up to 5% of patients. Patients who have mild renal insufficiency and are receiving diuretics are at greatest risk. Severe cases are potentially fatal and usually require

glucocorticoid therapy. Allopurinol may potentiate the effect of oral anticoagulants and blocks metabolism of azathioprine and 6-mercaptopurine, necessitating a 60-75% reduction in dosage of these cytotoxic drugs.

- **Febuxostat** is a nonpurine selective inhibitor of the xanthine oxidase. It is significantly more expensive than allopurinol. The starting dose is 40 mg/d, with titration to 80 mg/d if needed.
- **Uricase** catabolizes uric acid to the more soluble compound allantoin. It is available in the United States for the treatment of tumor lysis syndrome in a recombinant form **(rasburicase)**. IV **pegloticase** is a recombinant polyethylene glycol-conjugated form of uricase given every 2 weeks that has been shown to provide sustained reductions in plasma uric acid levels to less than the therapeutic target of 6 mg/dL in a substantial proportion of patients with chronic gout who are refractory to, or intolerant of, conventional urate-lowering therapy. The drug is discontinued if serum uric acid levels fail to reach target or are noted to rise above 6 mg/dL on two consecutive times. There is a high risk of anaphylaxis and infusion reactions with this medication, and thus, it is administered in a controlled setting with health care professionals who are familiar with the medication.
- **Uricosuric drugs** lower serum uric acid levels by blocking renal tubular reabsorption of uric acid. A 24-hour measurement of creatinine clearance and urine uric acid should be obtained before therapy is started, because these drugs are **ineffective with glomerular filtration rates of <50 mL/min**. They are also not recommended for patients who already have high levels of urine uric acid (800 mg/24 h) because of the risk of urate stone formation. Risk of urate stone formation can be minimized by maintaining a high fluid intake and by alkalinizing the urine. If these drugs are being used when an acute gouty attack begins, they should be continued while other drugs are used to treat the acute attack.
  - **Probenecid**

    Initial dosage is 500 mg PO daily, which can be raised in 500-mg increments every week until serum uric acid levels normalize or urine uric acid levels exceed 800 mg/24 h. The maximum dose is 3000 mg/d. Most patients require a total of 1.0-1.5 g/d in two to three divided doses.

    Salicylates and probenecid are antagonistic and should not be used together.

    Probenecid decreases renal excretion of penicillin, indomethacin, and sulfonylureas.

    Side effects are minimal.
  - **Sulfinpyrazone** has uricosuric efficacy similar to that of probenecid; however, it also inhibits platelet function. The initial dosage of 50 mg PO bid can be increased in 100-mg increments weekly until serum uric acid levels normalize, to a maximum dose of 800 mg/d. Most patients require 300-400 mg/d in three to four divided doses.

- **Pseudogout**
  - As in gout, the therapy of choice for most patients is a brief high-dose course of an **NSAID**. **Oral corticosteroids, intra-articular corticosteroids**, and **colchicine** may also relieve symptoms promptly.
  - **Maintenance therapy** with colchicine may diminish the number of recurrent attacks. Allopurinol or uricosuric agents have no role in treating pseudogout.
  - Treatment of underlying disease (hyperparathyroidism, hypothyroidism, hemochromatosis) will

also help in disease management.

Rheumatoid Arthritis

GENERAL PRINCIPLES

RA is a systemic disease of unknown etiology that is characterized by a symmetric inflammatory polyarthritis, extra-articular manifestations (rheumatoid nodules, pulmonary fibrosis, serositis, scleritis, vasculitis), and serum rheumatoid factor (RF) in up to 80% of patients. The course of RA is variable but tends to be chronic and progressive.

DIAGNOSIS

Clinical Presentation

- Most patients describe the insidious onset of pain, swelling, and morning stiffness in the hands and/or wrists or feet.
- Synovitis may be evident upon exam of the metacarpophalangeal, proximal interphalangeal, wrist, or other joints. Rheumatoid nodules may be palpated most commonly on extensor surfaces.
- Clinical criteria for the diagnosis of RA are available (*Arthritis Rheum 2010;62:2569*). Suspect the diagnosis in patients presenting with symmetric arthritis in three or more joints especially involving small joints and associated with morning stiffness lasting more than 30 minutes.

Diagnostic Testing

RF may be positive in 80% of patients. Cyclic citrullinated peptide (CCP) antibodies may be detected in 50-60% of patients with early RA.

- CCP antibodies are more specific (>90%) for RA than is the RF, which can also be elevated in the setting of hepatitis C and other chronic infections.
- Hand and wrist radiographs may show early changes of erosions or periarticular osteopenia.
- Musculoskeletal MRI and ultrasonography are more sensitive than plain radiographs and may be used in equivocal cases to demonstrate clinically inapparent synovitis or erosions.

TREATMENT

Most patients can benefit from an early aggressive treatment program that combines medical, rehabilitative, and surgical services designed with three distinct goals: (a) early

suppression of inflammation in the joints and other tissues, (b) maintenance of joint and muscle function and prevention of deformities, and (c) repair of joint damage to relieve pain or improve function.

- **DMARDs** appear to alter the natural history of RA by retarding the progression of bony erosions and cartilage loss. Because RA may lead to substantial long-term disability (and is associated with increased mortality), the standard of care is to initiate therapy with such agents early in the course of RA. Once a clinical response has been achieved, the chosen drug usually is continued indefinitely at the lowest effective dosage to prevent relapse.
  - **An established diagnosis of RA along with any evidence of disease activity is an indication to**

initiate disease-modifying therapy. Initial monotherapy with NSAIDs or steroids is no longer considered appropriate under usual circumstances.

- **Methotrexate** typically is the initial choice for moderate to severe RA. **Leflunomide** is also an alternative. **Hydroxychloroquine** or **sulfasalazine** can be used as the initial choice in very mild RA. If response to the initial agent is unsatisfactory after an adequate trial (or if limiting toxicity supervenes), other DMARDs or a biologic agent can be added or substituted.

- **Methotrexate**, a purine inhibitor and folic acid antagonist, is useful in treating synovitis, regardless of the underlying disease process. RA is its most common indication. It is also useful for myositis and may improve the leukopenia of Felty syndrome.
  - **Dosage and administration:** Typically, methotrexate is administered as a single PO dose once a week starting with 7.5-10.0 mg. Clinical response is usually noted in 4-8 weeks. The dosage can be increased by 2.5- to 5.0-mg increments every 2-4 weeks to a maximum of 25 mg/wk or until improvement is observed. Dosages above 20 mg/wk are generally given by SC injection to promote absorption.
  - **Contraindications and side effects:** Methotrexate is **teratogenic** and should not be used during pregnancy. It should also be avoided in patients with significant hepatic or renal impairment. **Folic acid supplementation** at a dosage of 1-2 mg daily may reduce toxicity without attenuating efficacy. Concomitant use of TMP-SMX should be avoided. Serologic testing for hepatitis B and C should be included before initiation of therapy.
    - **Minor side effects** include GI intolerance, stomatitis, rash, headache, and alopecia.
    - **Bone marrow suppression** may occur, particularly at higher doses. Blood and platelet counts should be obtained before initiation, every 4 weeks during the first 3-4 months or if the dose is changed, and every 8 weeks thereafter. **Macrocytosis** may herald serious hematologic toxicity and is an indication for folate supplementation, dose reduction, or both.
    - **Cirrhosis** occurs rarely with long-term use. Aspartate transaminase (AST), alanine transaminase (ALT), and serum albumin should be obtained initially at 4- to 8-week intervals during the first 3-4 months of therapy or if the dose is changed. Patients on a stable dose should be monitored every 8-12 weeks after 3 months of therapy and every 12 weeks after 6 months of therapy. Liver biopsy should be considered if the liver function tests are persistently abnormal or if the liver function tests are abnormal in 6 of 12 monthly determinations (five of nine determinations if measured every 6 weeks). Alcohol consumption increases the risk of methotrexate hepatotoxicity.
    - **Hypersensitivity pneumonitis** may occur but usually is reversible. Distinction from the interstitial lung disease (ILD) associated with RA may be difficult. Patients with preexisting pulmonary parenchymal disease may be at increased risk. **New or worsening symptoms of dyspnea or cough in a patient on methotrexate should prompt evaluation for pneumonitis.**
    - **Rheumatoid nodules** may develop or worsen, paradoxically, in some patients on methotrexate.

- **Sulfasalazine** is useful for treating synovitis in the setting of RA and seronegative spondyloarthropathies.
  - **Dosage:** Initial dosage is 500 mg PO daily, with increases in 500-mg increments weekly until a total daily dose of 2000-3000 mg (given in evenly divided doses) is reached. Clinical response usually occurs in 6-10 weeks.
  - **Contraindications and side effects: Sulfasalazine should be used with extreme caution in patients with glucose-6-phosphate dehydrogenase deficiency. Sulfasalazine should not be**

used in patients with sulfa allergy. Nausea is the principal adverse effect and can be minimized by the use of the enteric-coated preparation of the drug. Hematologic toxicity, including a reduction in any cell line and aplastic anemia, rarely occurs. Periodic monitoring of blood and platelet counts is recommended.

- **Hydroxychloroquine** is an antimalarial agent that is used to treat dermatitis, alopecia, and synovitis in systemic lupus erythematosus (SLE) and mild synovitis in RA.
  - **Dosage:** Hydroxychloroquine typically is given at a dosage of 4-6 mg/kg PO daily (200-400 mg) after meals to minimize dyspepsia and nausea.
  - **Contraindications and side effects: Hydroxychloroquine should be used with caution in patients with porphyria, glucose-6-phosphate dehydrogenase deficiency, or significant hepatic or renal impairment.** It is safe during pregnancy. The most common side effects are allergic skin eruptions and nausea. Serious ocular toxicity (corneal deposits and retinopathy) occurs, but is rare with currently recommended dosages. Ophthalmologic evaluation should be performed on an annual basis.
- **Leflunomide** is a pyrimidine inhibitor that has been approved for the treatment of RA.
  - **Dosage and administration:** Treatment is begun with 10 or 20 mg PO daily. Clinical response is generally seen within 4-8 weeks.
  - **Contraindications and side effects:** Leflunomide is **teratogenic** and has a very long half-life. Women who plan to become pregnant must discontinue the drug and complete a course of elimination therapy with cholestyramine, 8 g PO tid for 11 days. Plasma levels should then be verified to be <0.02 mg/L on two separate tests at least 14 days apart before pregnancy is considered. Leflunomide is **contraindicated in patients with significant hepatic dysfunction** or in those who are receiving rifampin. **GI side effects** are the most common. **Diarrhea** occurs in up to 20% of patients and may require discontinuation of the drug. Dosage reduction to 10 mg/d may provide relief while maintaining efficacy, and loperamide can be used for symptomatic relief. **Elevations in serum transaminase levels** may occur and should be measured at baseline and then monitored periodically. The dosage should be reduced for confirmed twofold elevations, and greater elevations should be treated with cholestyramine and discontinuation of leflunomide. **Rash** and **alopecia** may occur during therapy.
- **Anticytokine therapies** directed at specific cytokines have been developed. These agents are considered **biologic DMARDs**.
  - **Tumor necrosis factor (TNF) inhibitors** have been approved for treatment of RA and seronegative spondyloarthropathies. These agents are used in patients with moderate to severe RA who have failed a trial of one or more DMARDs. The effect of these agents on synovitis can be dramatic, with responsive patients reporting the onset of symptomatic benefits within 1-2 weeks. In addition to their symptomatic benefits, these agents appear to retard joint damage significantly.
    - **Etanercept is a fusion protein** that consists of the ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG. It binds to TNF, blocking its interaction with cell surface receptors, thus inhibiting the inflammatory and immunoregulatory properties of TNF. It is given in a dosage of 25 mg SC twice a week or 50 mg SC weekly.
    - **Infliximab** is a chimeric monoclonal antibody that binds specifically to human TNF-α, blocking its proinflammatory and immunomodulatory effects. It is given by IV infusion in conjunction with methotrexate to reduce production of neutralizing

antibodies against infliximab. The recommended treatment regimen includes infliximab infusions of 3

mg/kg at initiation, at 2 and 6 weeks, and every 8 weeks thereafter, along with methotrexate at a dose of at least 7.5 mg/wk.

- **Adalimumab** is a recombinant human IgG-1 monoclonal antibody that is specific to human TNF-α. It is given in a dosage of 40 mg SC every other week.
- **Golimumab** is a human monoclonal antibody that binds to human TNF-α. It can be given as a monthly injection or an infusion every 8 weeks after an initial loading dose.
- **Certolizumab pegol** is a pegylated humanized Fab′ fragment of an anti-TNF-α monoclonal antibody. It is given monthly after an initial loading dose.

- **Contraindications and side effects**
  - **Serious infections and sepsis**, including fatalities, have been reported during the use of TNF-blocking agents. These drugs are contraindicated in patients with acute or chronic infections, and if serious infection or sepsis occurs, the drug should be stopped. Those with a history of recurrent infections and those with underlying conditions that may predispose to infection should be treated with caution and counseled to be vigilant for signs and symptoms of infection. Upper respiratory and sinus infections are most common. TB has also been noted, and **a tuberculin skin test and CXR should be obtained before beginning therapy**. These
  - agents are also contraindicated in patients with CHF (usually with a left ventricular ejection fraction <30%). Patients undergoing elective surgical procedures can omit the dose that is scheduled to be given before surgery and the next dose scheduled to follow the surgery as long as their wound has completely healed.
  - **Local injection site reactions** are common with SC administration, particularly during the first month of therapy. Reactions are generally self-limited and do not require discontinuation of therapy. Serious systemic allergic reactions are rare but may occur with infliximab infusions.
  - **Other adverse effects** may include induction of antinuclear antibodies and, rarely, a lupus-like illness. A demyelinating disorder has been described as well as exacerbations of preexisting multiple sclerosis. The risk of nonmelanoma skin cancer is increased in patients who receive TNF blockers. It is unclear whether the frequency of occurrence of lymphoma is increased in patients who receive these agents. A black box warning, however, has been placed on the package insert of these agents.

- **Interleukin inhibitors**
  - **Anakinra** is a recombinant interleukin (IL)-1 receptor antagonist that is approved for use in RA. It blocks binding of IL-1 to its receptor, thus inhibiting the proinflammatory and immunomodulatory actions of IL-1.
    - It is given in a dosage of 100 mg SC daily. Similar to TNF blockers, it should not be prescribed to patients with ongoing or recurrent infections.
    - **Adverse effects** include an increased frequency of bacterial infections and injection site reactions.
  - **Tocilizumab** is an antagonist of soluble and membrane-bound IL-6 receptors. It is given as an IV infusion or as an SC injection at a dose of 162 mg either weekly or every other week depending on the patient's weight. Side effects include increased infections, neutropenia, and elevations in cholesterol.
- **B-cell-directed therapy: Rituximab** is a monoclonal antibody directed against CD20, a cell surface receptor found on B cells. CD20-positive B cells in peripheral blood are rapidly depleted after two infusions of 1 g of rituximab 2 weeks apart. Methotrexate is generally used as background therapy. The infusion can be repeated in 6- to 12-month intervals, based on patient symptoms.

- **Contraindications and side effects:** Rituximab has rarely been reported to cause reactivation of JC virus, leading to the clinical syndrome of progressive multifocal leukoencephalopathy (PML), which is uniformly fatal.

  - **Infusion reactions** are more common with the first dose and rarely fatal. Antihistamines, IV steroids, and acetaminophen are routinely given prior to infusion.
  - **Infectious complications** are a concern, as with all biologics, but appear to be less frequent than in anti-TNF-treated patients.
- **Abatacept** is a fusion protein comprising the CTLA-4 molecule and the Fc portion of IgG-1. It blocks selective co-stimulation of T cells. It is given as an IV infusion of 500-1000 mg every 4 weeks. It is also available as a SC formulation that can be given 125 mg SC weekly with or without an initial loading dose. It is approved in patients with an inadequate response to biologic or nonbiologic DMARDs.
  - **Infections** occur slightly more often than in placebo-treated patients. Opportunistic infections have not been observed. **Infusion reactions** are much less common than with rituximab or infliximab.
  - **Chronic obstructive pulmonary disease exacerbations and respiratory infections** are more common in patients with moderate to severe obstructive lung disease when treated with abatacept.
- **Combinations of DMARDs** can be used if the patient has a partial response to the initial agent.
  - Common combination therapies include methotrexate with hydroxychloroquine, sulfasalazine, or both. Methotrexate is commonly combined with TNF antagonists because there is evidence for additive efficacy and for a decrease in the formation of human antichimeric antibodies against the TNF blocker. Methotrexate is often used in combination with rituximab or abatacept. Methotrexate and leflunomide may have additive hepatotoxicity, and this combination should be used cautiously.
  - **Combination therapy with two biologic agents is contraindicated because of increased infectious complications.**
  - **NSAIDs or selective COX-2 inhibitors** may be used as an adjunct to DMARD therapy. **Glucocorticoids are not curative** but may delay the formation of erosions with other **DMARDs** and are among the most potent anti-inflammatory drugs available.
    - **Indications for glucocorticoids** include (a) symptomatic relief while waiting for a response to a slow-acting immunosuppressive or immunomodulatory agent, (b) persistent synovitis despite adequate trials of DMARDs and NSAIDs, and (c) severe constitutional symptoms (e.g., fever and weight loss) or extra-articular disease (vasculitis, episcleritis, or pleurisy).
    - **Oral administration** of prednisone 5-20 mg daily usually is sufficient for the treatment of synovitis, whereas severe constitutional symptoms or extra-articular disease may require up to 1 mg/kg PO daily. Although alternate-day glucocorticoid therapy reduces the incidence of undesirable side effects, some patients do not tolerate the increase in symptoms that may occur on the off day.
    - **Intra-articular administration** may provide temporary symptomatic relief when only a few joints are inflamed. The beneficial effects of intra-articular steroids may persist for days to months and may delay or negate the need for systemic glucocorticoid therapy.

Nonpharmacologic Therapies

- **Acute care** of inflammatory arthritides involves joint protection and pain relief. Proper joint positioning and splints are important elements in joint protection. Heat is a useful analgesic.
- **Subacute disease** therapy should include a gradual increase in passive and active joint movement.

- **Chronic care** encompasses instruction in joint protection, work simplification, and performance of activities of daily living. Adaptive equipment, splints, orthotics, and mobility

aids may be useful, and specific exercises designed to promote normal joint mechanics and to strengthen affected muscle groups are useful.

Surgical Management

- **Corrective surgical procedures** including synovectomy, total joint replacement, and joint fusion may be indicated in patients with RA to reduce pain and to improve function.
- **Carpal tunnel syndrome** is common, and surgical repair may be curative if local injection therapy is unsuccessful.
- **Synovectomy** may be helpful if major involvement is limited to one or two joints and if a 6-month trial of medical therapy has failed, but usually it is only of temporary benefit.
- **Surgical fusion of joints** usually results in freedom from pain but also in total loss of motion; this is tolerated well in the wrist and thumb.
- **Cervical spine fusion** of C1 and C2 is indicated for significant cervical subluxation (>5 mm) with associated neurologic deficits. Patients with long-standing RA undergoing elective surgical procedures should have a lateral cervical spine radiograph in flexion and extension performed to screen for subluxation.

Immunizations

- Immune response to influenza and pneumococcal vaccinations in patients receiving methotrexate and biologic therapies may be attenuated, although usually adequate. **Influenza** vaccinations should be given to patients prior to starting therapy with all nonbiologic DMARDs, and **pneumococcal** vaccinations should be given to patients starting leflunomide, methotrexate, or sulfasalazine if the patients' vaccinations were not current. In addition, periodic pneumococcal vaccinations and annual influenza vaccinations should be considered for all patients receiving biologic agents, in accordance with the Centers for Disease Control and Prevention (CDC) recommendations for appropriate use and timing of these vaccinations.
- Hepatitis B vaccination is recommended if risk factors for this disease exist and if hepatitis B vaccination has not previously been administered.
- Live vaccines (e.g., varicella-zoster vaccine, oral polio, rabies) are contraindicated during biologic therapy but should be considered before initiation of biologic therapy or high-dose steroids.

COMPLICATIONS

- **Patients with RA and a single joint inflamed out of proportion to the rest of the joints must be evaluated for coexistent septic arthritis.** This complication occurs with increased frequency in RA and carries 20-30% mortality.
- **Sjögren syndrome**, characterized by failure of exocrine glands, occurs in a subset of patients with RA, producing sicca symptoms (dry eyes and mouth), parotid gland enlargement, dental caries, and recurrent tracheobronchitis. **Treatment** is symptomatic with artificial tears and saliva or with pilocarpine up to 5 mg PO qid. Cevimeline, 30 mg tid, can also be considered. Assiduous dental and ophthalmologic care is recommended, and drugs that suppress lacrimal-salivary secretion further should be avoided.
- **Felty syndrome:** The triad of RA, splenomegaly, and granulocytopenia also occurs in a small subset of

patients, and these patients are at risk for recurrent bacterial infections and nonhealing leg ulcers.

- Approximately 70% of patients show irreversible joint damage on radiography within the first 3 years of disease. Work disability is common, and life span may be shortened.

Osteoarthritis

GENERAL PRINCIPLES

OA, or **degenerative joint disease**, is characterized by deterioration of articular cartilage with subsequent formation of reactive new bone at the articular surface. The joints most commonly affected are the distal and proximal interphalangeal joints of the hands and joints of the hips, knees, and cervical and lumbar spine.

Epidemiology

The disease is more common in the elderly but may occur at any age, especially as sequelae to joint trauma, chronic inflammatory arthritis, or congenital malformation. OA of the spine may lead to spinal stenosis (neurogenic claudication), with aching or pain in the legs or buttocks on standing or walking.

TREATMENT

- **Acetaminophen** in a dosage of up to 1000 mg qid is the initial pharmacologic treatment.
- **Low-dose NSAIDs or selective COX-2 inhibitors** are the next step, followed by full-dose treatment (see Treatment under the Basic Approach to Rheumatic Diseases section). Because this patient population is often elderly and may have concomitant renal or cardiopulmonary disease, NSAIDs should be used with caution.
- **The data for glucosamine sulfate and chondroitin sulfate** are contradictory. Some studies suggest it may reduce symptoms as well as the rate of cartilage deterioration, whereas others have shown that these agents have little benefit in patients with OA. Glucosamine should not be administered to patients who are allergic to **shellfish**. Synthetic and naturally occurring hyaluronic acid derivatives can be administered intra-articularly and may reduce pain and improve mobility in select patients. Commercially, hyaluronan preparations currently available in the United States include sodium hyaluronate (**Hyalgan, Supartz, and Euflexxa**) and hylan G-F 20 (**Synvisc**).
- **Intra-articular glucocorticoid injections** often are beneficial but probably should not be given more than every 3-6 months (see General Principles under Basic Approach to the Rheumatic Diseases section). Systemic steroids should be avoided.
- **Tramadol**, a μ-opioid agonist, may be useful as an alternative analgesic agent. Narcotics may be useful for short-term pain relief and in patients in whom other therapeutic modalities are contraindicated, but in general, they should be avoided for long-term use.
- **Topical NSAIDs, lidocaine, or capsaicin** may provide symptomatic relief with minimal toxicity.
- **Gabapentin** has also been used to help with neural pain modification in patients with severe symptoms of arthritis who are unresponsive to the previously mentioned modalities.
- **Duloxetine** has been approved by the US Food and Drug Administration (FDA) for treatment of OA and chronic lower back pain.

Nonpharmacologic Therapies

- Activities that involve excessive use of the joint should be identified and avoided. Poor body mechanics should be corrected, and misalignments such as pronated feet may be aided by orthotics. An exercise

program to prevent or correct muscle atrophy can also provide pain relief. When weight-bearing joints are affected, support in the form of a cane, crutches, or a walker can be helpful. Weight reduction may be of benefit, even for non-weight-bearing joints. Thumb splints may be useful for OA of the first carpometacarpal joint. Consultation with occupational and physical therapists may be helpful.

- **OA of the spine** may cause radicular symptoms from pressure on nerve roots and often produces pain and spasm in the paraspinal soft tissues. Physical supports (cervical collar, lumbar corset), local heat, and exercises to strengthen cervical, paravertebral, and abdominal muscles may provide relief in some patients.
- **Epidural steroid injections** may reduce radicular symptoms.

Surgical Management

- **Surgery** can be considered when patients suffer from disabling pain or deformity. Joint replacement surgery usually relieves pain and increases function in selected patients.
- **Laminectomy and spinal fusion** should be reserved for patients who have severe disease with intractable pain or neurologic complications.

Spondyloarthropathies

The **spondyloarthropathies** are an interrelated group of disorders characterized by one or more of the following features: spondylitis, sacroiliitis, enthesopathy (inflammation at sites of tendon insertion), and asymmetric oligoarthritis. Extra-articular features of this group of disorders may include inflammatory eye disease, urethritis, and mucocutaneous lesions. The spondyloarthropathies aggregate in families, where they are associated with HLA-B27 antigen.

Ankylosing Spondylitis

DIAGNOSIS

- **Ankylosing spondylitis** clinically presents as inflammation and ossification of the joints and ligaments of the spine and sacroiliac joints.
- Patients are usually young men who classically describe low back pain and prolonged morning stiffness, which improve with exercise.
- Hips and shoulders are the peripheral joints that are most commonly involved. Progressive fusion of the apophyseal joints of the spine occurs in many patients and cannot be predicted or prevented.

TREATMENT

Behavioral

- Physical therapy emphasizing extension exercises and posture is recommended to minimize possible late postural defects and respiratory compromise.
- Patients should be instructed to sleep supine on a firm bed without a pillow and to practice postural and deep-breathing exercises regularly.
- Cigarette smoking should be strongly discouraged.

Medications

- **Nonsalicylate NSAIDs**, such as indomethacin, are used to provide symptomatic relief, and **selective COX-2 inhibitors** are also effective (see General Principles under Basic Approach to the Rheumatic Diseases section).
- **Methotrexate and sulfasalazine** provide benefit for peripheral disease in some patients (see Treatment under Rheumatoid Arthritis section).
- **TNF blockade** has been shown to be of benefit even in some patients with apparent fixed deformities.
- **Pamidronate**, a bisphosphonate, may provide modest clinical benefits. Systemic glucocorticoids are not commonly used and can worsen osteopenia.

Surgical Management

Many patients develop osteoporosis in the fused spondylitic spine and are at risk of spinal fracture. Surgical procedures to correct some spine and hip deformities may result in significant rehabilitation in carefully selected patients.

Arthritis of Inflammatory Bowel Disease

GENERAL PRINCIPLES

Arthritis of inflammatory bowel disease occurs in up to 46% of patients with either Crohn disease or ulcerative colitis (*Autoimmun Rev 2014;13(1):20*). It may also occur in some patients with intestinal bypass and diverticular disease.

DIAGNOSIS

Clinical features include **spondylitis**, **sacroiliitis**, and **peripheral arthritis**, particularly in the knee and ankle. Peripheral joint and spinal disease may not always correlate with the activity of the colitis.

TREATMENT

- **NSAIDs** relieve joint pain and inflammation in patients with arthritis due to inflammatory bowel disease (IBD). However, GI intolerance due to NSAIDs may be increased among this group of patients, and NSAIDs may exacerbate underlying IBD.
- **Sulfasalazine, methotrexate, azathioprine, and systemic glucocorticoids** may also be effective (see Treatment under Rheumatoid Arthritis section).
- **TNF antagonists** may benefit both the colitis and arthritis.
- Local **injection of glucocorticoids and physical therapy** are useful adjunctive measures.

Reactive Arthritis

GENERAL PRINCIPLES

- **Reactive arthritis** refers to the inflammatory arthritis that occasionally follows certain GI or genitourinary infections. The triad of arthritis, conjunctivitis, and urethritis was formerly referred to as **Reiter syndrome**.
- *Chlamydia trachomatis* is the most commonly implicated genitourinary infection. *Shigella flexneri*, *Salmonella* spp., *Yersinia enterocolitica*, or *Campylobacter jejuni* are the most commonly implicated GI infections.

Clostridium difficile can also trigger the arthritis.

- Of patients, 50-80% are HLA-B27 positive. Males and females are equally affected after GI infections, although males more commonly develop the above classic triad after a *Chlamydia* infection.

DIAGNOSIS

Clinical Presentation

The clinical syndrome may include **asymmetric oligoarthritis**, **urethritis**, **conjunctivitis**, and characteristic **skin and mucous membrane lesions**. The syndrome is usually transient, lasting from 1 to several months, but chronic arthritis may develop in 4-19% of patients.

Diagnostic Testing

The triggering infection may have been asymptomatic. Testing for stool pathogens is low yield if the diarrheal illness has resolved, but urine testing for *Chlamydia* may be helpful if the clinical syndrome is consistent with reactive arthritis.

TREATMENT

- Conservative therapy is indicated for control of pain and inflammation in these diseases.
- Spontaneous remissions are common, making evaluation of therapy difficult.
- **NSAIDs** (especially indomethacin) are often useful, and **selective COX-2 inhibitors** also provide relief (see General Principles under Basic Approach to the Rheumatic Diseases section).
- **Sulfasalazine** or **methotrexate** may be of benefit for arthritis that does not resolve after several months (see Treatment under Rheumatoid Arthritis section).
- Trial of an **anti-TNF-α** agent might be considered in patients who do not respond to sulfasalazine or methotrexate.
- In unusually severe cases, **glucocorticoid therapy** may be required to prevent rapid joint destruction (see General Principles under Basic Approach to the Rheumatic Diseases section).
- Treatment for chlamydia infection, if detected, is appropriate. Prolonged empiric antibiotic therapy has not been shown to be beneficial.
- **Conjunctivitis** is usually transient and benign, but ophthalmologic referral and treatment with topical or systemic glucocorticoids are indicated for **iritis**.

Psoriatic Arthritis

GENERAL PRINCIPLES

Classification

Five major patterns of joint disease occur: (a) asymmetric oligoarticular arthritis, (b) distal interphalangeal joint involvement in association with nail disease, (c) symmetric rheumatoid-like polyarthritis, (d) spondylitis and sacroiliitis, and (e) arthritis mutilans.

Epidemiology

Prevalence varies; however, it has been reported that as many as 30% of patients with psoriasis have some form

of inflammatory arthritis (*Rheumatology (Oxford) 2015; 54(1):20*).

TREATMENT

- **NSAIDs**, particularly indomethacin, are used to treat the arthritic manifestations of psoriasis, in conjunction with appropriate measures for the skin disease.
- **Intra-articular glucocorticoids** may be useful in the oligoarticular form of the disease, but injection through a psoriatic plaque should be avoided. Severe skin and joint diseases generally respond well to **methotrexate** (see Treatment under Rheumatoid Arthritis section).
- **Sulfasalazine and leflunomide** may also have disease-modifying effects in polyarthritis.
- **TNF-α blockers** may produce dramatic improvement in both skin and joint disease.
- **Ustekinumab** is a human monoclonal antibody to the shared p40 subunit of IL-12 and IL-23 that interferes with receptor binding to immune cells. It is administered subcutaneously. In patients who weigh less than 100 kg, the dose is 45 mg SC at week 0 and 4.

  It is then given every 12 weeks. For patients who weigh more than 100 kg, the dose is 90 mg SC given at the same intervals as the lower dose. It may be administered alone or in combination with methotrexate. Patients should be screened for TB prior to initiating this medication and periodically while on it. Monitor for infections and injection site reactions. Monitor all patients for the development of nonmelanoma skin cancer because this has been reported.
- **Apremilast** is an orally administered phosphodiesterase-4 inhibitor. It suppresses multiple proinflammatory cytokines involved in the innate and adaptive immunity. Initial starting dose is 10 mg daily, which is slowly uptitrated to a maximum dose of 30 mg twice daily. GI upset and headaches have commonly been reported.

COMPLICATIONS

Colonization of psoriatic skin with *S. aureus* increases the risk of wound infection after reconstructive joint surgery.

Systemic Lupus Erythematosus

GENERAL PRINCIPLES

Definition

SLE is a multisystem disease of unknown etiology that primarily affects women of childbearing age. The female-to-male ratio is 9:1. It is most common in the second and third decades of life and in African Americans.

Pathophysiology

Pathophysiology is multifactorial and incompletely understood, with interplay of genetic predisposition and environmental factors.

DIAGNOSIS

- Disease manifestations are protean, ranging in severity from fatigue, malaise, weight loss, and fever, to potentially life-threatening cytopenias, nephritis, cerebritis, vasculitis, pneumonitis, myositis, and myocarditis.
- Current American College of Rheumatology classification criteria are used primarily for research purposes but are helpful to review when suspicion arises. Based on the classification criteria, the presence of 4 or more of the 11 findings are required.
  - Malar rash
  - Discoid rash
  - Photosensitivity
  - Oral or nasopharyngeal ulcers
  - Arthritis
  - Serositis
  - Proteinuria and cellular casts
  - Seizures, psychosis, or other neurologic manifestations
  - Autoimmune hemolytic anemia, leukopenia or lymphopenia, and thrombocytopenia
  - Antinuclear antibodies (ANA)
  - Anti-double-stranded DNA antibodies, anti-Smith (SM) antibodies, or antiphospholipid antibodies
- Commonly associated serology includes anti-SSA (Ro) and anti-SSB (La) antibodies in approximately 30% of patients and anti-RNP in 40% of patients.

- Some classification criteria also include alopecia, low complement, and a positive direct Coombs test (*Arthritis Rheum 2012;64:2677*).

TREATMENT

Medications

- **NSAIDs** usually control SLE-associated arthritis, arthralgias, fever, and mild serositis but not fatigue, malaise, or major organ system involvement. The response to **selective COX-2 inhibitors** is similar. Hepatic and renal toxicities of NSAIDs appear to be increased in SLE.
- **Hydroxychloroquine** 200 mg bid may be effective in the treatment of rash, photosensitivity, arthralgias, arthritis, alopecia, and malaise associated with SLE and in the treatment of **discoid and subacute cutaneous lupus erythematosus**. The drug is not effective for treating fever or major organ manifestations, but long-term usage may decrease incidence of flares and risk of thrombosis, as well as renal and CNS involvement. For the potential ophthalmologic complications, patients need regular eye examination.
- **Glucocorticoid therapy**
  - **Indications** for systemic glucocorticoids include life-threatening manifestations of SLE, such as glomerulonephritis, CNS involvement, thrombocytopenia, hemolytic anemia, and debilitating manifestations of SLE that are unresponsive to conservative therapy.
  - **Dosage:** Patients with severe or potentially life-threatening complications of SLE should be treated

with prednisone, 1-2 mg/kg PO daily, which can be given in divided doses. After disease is controlled, prednisone should be tapered slowly, with the dosage being reduced by no more than 10% every 7-10 days. More rapid reduction may result in relapse. **IV pulse therapy** in the form of methylprednisolone, 500-1000 mg IV daily for 3-5 days, has been used in SLE in such life-threatening situations as rapidly progressive renal failure, active CNS disease, and severe thrombocytopenia. Patients who do not show improvement with this regimen probably are unresponsive to steroids, and other therapeutic alternatives must be considered. A course of oral prednisone should follow completion of pulse therapy.

- **Immunosuppressive therapy**
  - Indications for immunosuppressive therapy in SLE include life-threatening manifestations of SLE such as glomerulonephritis, CNS involvement, thrombocytopenia, hemolytic anemia, and the inability to reduce corticosteroid dosage or severe corticosteroid side effects.
  - Choice of an immunosuppressive therapy is individualized to the clinical situation. Often, **cyclophosphamide** is used for life-threatening manifestations of SLE. High-dose monthly IV pulse cyclophosphamide (0.5-1.0 g/m^2) may be less toxic but is also less immunosuppressive than low-dose daily oral cyclophosphamide (1.0-1.5 mg/kg/d). **Azathioprine** (1-3 mg/kg/d) and **mycophenolate mofetil** (500-1500 mg bid) are also used as steroid-sparing agents for serious lupus manifestations. There is increasing evidence that mycophenolate mofetil may be as effective as cyclophosphamide in certain classes of lupus nephritis with fewer side effects, and it is particularly preferred in the younger population where fertility maintenance is a concern. **Methotrexate** (7.5-20.0 mg weekly) is often used for musculoskeletal and skin manifestations. **Rituximab** has been shown in uncontrolled observational studies to be effective in cases of severe SLE not responding to conventional treatment; however, placebo-controlled studies have been disappointing. **Belimumab** inhibits B-lymphocytic stimulator (BLyS) signaling, thereby decreasing B cell survival, and differentiation into immunoglobulin-producing plasma cells. It was approved by the FDA in 2012 for the treatment of adult autoantibody-positive lupus patients who are receiving standard therapy after it was

shown in trials to reduce SLE disease activity and flares. The efficacy of belimumab has not been evaluated in patients with severe lupus nephritis or CNS lupus, and it has not been studied in combination with other biologics or cyclophosphamide.

Nonpharmacologic Therapies

- **Conservative therapy** alone is warranted if the patient's manifestations are mild.
- **General supportive measures** include adequate sleep and fatigue avoidance.
- All patients, not just those with photosensitive rashes, are advised on use of sunscreens with sun protection factor (SPF) of 30 or greater, protective clothing, and sun avoidance. Isolated skin lesions may respond to **topical steroids**.
- Consider prophylaxis against *Pneumocystis* pneumonia in patients treated with cyclophosphamide. Also consider adding prophylaxis for the prevention of bladder and gonadal toxicity from this agent. Appropriate immunizations should be considered prior to initiation of immunosuppressive therapy, especially against influenza and pneumococcus. Immunization with live vaccines is contraindicated in immunosuppressed patients, but varicella-zoster vaccine may be recommended prior to initiation of therapy.

SPECIAL CONSIDERATIONS

- Patients with lupus have accelerated **coronary and peripheral vascular disease**, especially with high disease activity and chronic steroid use, and cardiovascular risk factors should be managed aggressively.
- **Transplantation and chronic hemodialysis** have been used successfully in SLE patients with renal failure. Clinical and serologic evidence of disease activity often remits when renal failure ensues.
- **Pregnancy in SLE:** An increased incidence of second-trimester spontaneous miscarriages and stillbirths has been reported in women with antibodies to cardiolipin or lupus anticoagulant. SLE patients may experience flares during pregnancy if the lupus is active at the time of conception. Differentiation between active SLE and preeclampsia is often difficult. Women in whom SLE is well controlled are less likely to have a flare of disease during pregnancy.
- **Neonatal lupus** may occur in offspring of anti-SSA- or anti-SSB-positive mothers, with skin rash and heart block as the most common manifestations.
- **Drug-induced lupus** typically has a sudden onset and is associated with serositis and musculoskeletal manifestations. Renal and CNS manifestations are rare. Serology includes positive ANA and **antihistone antibodies**, negative anti-SM and anti-double-stranded DNA antibodies, along with normal complement levels. The disease usually resolves with drug discontinuation. Offending drugs include procainamide, hydralazine, minocycline, diltiazem, isoniazid, chlorpromazine, quinidine, methyldopa, and anti-TNF biologics.

Systemic Sclerosis

GENERAL PRINCIPLES

Definition

Systemic sclerosis (scleroderma) is a systemic illness characterized by progressive fibrosis of the skin and visceral organs. The etiology is unknown, but many manifestations of scleroderma are secondary to vasculopathy.

Classification

- Scleroderma can be subdivided based on anatomic skin distribution into **localized scleroderma** (morphea and linear scleroderma) and **systemic sclerosis** (diffuse

cutaneous, limited cutaneous, and systemic sclerosis sine scleroderma). The limited cutaneous form involves the extremities distal to the knees and elbows as well as the face. Diffuse cutaneous scleroderma involves the skin of the proximal extremities and the trunk. Systemic sclerosis sine scleroderma affects the internal organs without skin involvement. The **CREST syndrome** is **c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasias.
- **Nephrogenic systemic fibrosis** is a potential complication of MRI with gadolinium contrast in patients with renal failure. It is associated with skin thickening and internal organ fibrosis resembling scleroderma, without Raynaud phenomenon or ANA positivity.

DIAGNOSIS

Clinical Presentation

- Nearly all patients with systemic sclerosis have **Raynaud phenomenon**. It is typically the presenting feature. Nail fold capillary changes are also common.
- **Diffuse scleroderma** is associated with scleroderma "renal crisis," and multiple internal organs are affected. Long-term survival is poor.
  - **GI involvement:** Decreased gut motility can occur, leading to bacterial overgrowth, malabsorption, diarrhea, and weight loss. Occasionally, severe constipation and intestinal pseudo-obstruction occur. Classic endoscopic findings include colonic wide mouth diverticula, patulous esophagus, esophageal strictures, and gastric antral vascular ectasia, also known as watermelon stomach.
  - **Renal involvement:** The appearance of sudden hypertension and renal insufficiency indicates potential scleroderma renal crisis. It is associated with a microangiopathic hemolytic anemia and carries a poor prognosis.
  - **Cardiopulmonary involvement:** Patchy myocardial fibrosis can result in heart failure or arrhythmias. Pulmonary involvement includes pleural effusions and inflammatory alveolitis leading to interstitial fibrosis and pulmonary hypertension.
  - **Other organ systems: Skin** involvement appears initially with edematous and erythematous "salt and pepper" pigmentation changes before progressing to skin tightening and thickening. **Musculoskeletal** manifestations range from arthralgias to arthritis with joint contractures due to the regional skin involvement.
- **Limited scleroderma** is more often associated with primary pulmonary hypertension in the absence of ILD or biliary cirrhosis

Diagnostic Testing

More than 95% of scleroderma patients are ANA positive, and 20-40% are anti-Scl-70 positive (associated with diffuse disease). Up to 40% of patients with limited scleroderma have anticentromere antibody. RNA polymerase III antibody has been found to increase the risk of scleroderma renal crisis.

TREATMENT

Therapeutic options for scleroderma are limited. Treatment focuses on organ involvement and symptoms.

- **Skin:** No therapeutic agent is effective for these cutaneous manifestations. **Physical therapy** is important to retard and reduce joint contractures.
- **GI involvement**
  - Reflux esophagitis generally responds to standard therapy (e.g., **H^2-receptor antagonists**, **proton pump inhibitors**, and **promotility agents**).

  - Treatment with broad-spectrum antimicrobials in a rotating sequence including **metronidazole** often improves malabsorption. Metoclopramide may reduce bloating and distention.
  - Occasionally, esophageal strictures require mechanical **esophageal dilation**.
- **Renal involvement:** Aggressive blood pressure control with **ACE inhibitors** may delay, prevent, or even reverse renal failure in patients with suspected scleroderma renal crisis. ARBs do not appear to be

as effective.

- **Cardiopulmonary involvement:** Coronary artery vasospasm can cause angina pectoris and may respond to calcium channel antagonists. Pulmonary involvement, such as pulmonary hypertension, is treated with standard therapies for these conditions (see Chapter 10, Pulmonary Diseases). Patients with pulmonary parenchymal disease may benefit from glucocorticoids and cyclophosphamide.

Raynaud Phenomenon

GENERAL PRINCIPLES

Raynaud phenomenon is a vasospasm of the digital arteries and can result in ischemia of the digits. It manifests as repeated episodes of color changes of the digits after cold exposure or emotional stress. Primary Raynaud disease has no predisposing factors and is milder. Secondary Raynaud disease occurs in individuals with a predisposing factor, usually a collagen vascular disease.

TREATMENT

Medications

- **Calcium channel antagonists** (of the dihydropyridine group) are the preferred initial agents, although they may exacerbate gastroesophageal reflux and constipation.
- Alternative vasodilators such as prazosin are occasionally helpful but can have limiting side effects, including orthostatic hypotension.
- Other agents that might improve vasospasm include **topical nitroglycerin** applied to the dorsum of the hands, phosphodiesterase inhibitor (e.g., **sildenafil**), and endothelin receptor antagonist (e.g., **bosentan**).
- Daily low-dose aspirin therapy is often prescribed for its antiplatelet effects.
- Patients with severe ischemic digits should be hospitalized, and conditions such as macrovascular disease, vasculitis, or a hypercoagulable state should be ruled out. An IV infusion of a prostaglandin or prostaglandin analog may be considered.
- Patients should be instructed to avoid exposure to cold, protect the hands and feet from trauma, limit caffeine intake, and discontinue cigarette smoking.

Surgical Management

- **Sympathetic ganglion blockade** with a long-acting anesthetic agent may be useful when a patient has progressive digital ulceration that fails to improve with medical therapy.
- Surgical digital sympathectomy may be beneficial.

Necrotizing Vasculitis

GENERAL PRINCIPLES

- **Necrotizing vasculitis** is characterized by inflammation of blood vessels, leading to tissue damage and necrosis. This diagnosis includes a broad spectrum of disorders with various

causes that involve vessels of different types, sizes, and locations. The immunopathologic process may involve immune complexes.

- Although in most cases the inciting agent has not been identified, some are associated with chronic hepatitis B and C.
- Vasculitis “mimics” should be considered, including bacterial endocarditis, HIV infection, atrial myxoma, paraneoplastic syndromes, cholesterol emboli, and cocaine and amphetamine use.

DIAGNOSIS

Systemic manifestations including fever and weight loss are common. Table 25-1 summarizes the clinical features and diagnostic and treatment approaches of the most common forms of vasculitis.

TREATMENT

The response to therapy and long-term prognosis of these disorders are highly variable.

- **Glucocorticoids** are the initial therapy. Although vasculitis that is limited to the skin may respond to lower doses of corticosteroids, the initial dosage for visceral involvement should be high (prednisone, 1-2 mg/kg/d). If life-threatening manifestations are present, a brief course of high-dose pulse therapy with methylprednisolone, 500 mg IV q12h for 3-5 days, should be considered.
- Strong immunosuppressives are used in the induction treatment of necrotizing vasculitis when major organ system involvement is present. **Cyclophosphamide** has historically been the initial choice. **Rituximab** is now an approved alternative for remission induction.
- **Methotrexate**, **azathioprine**, and **mycophenolate mofetil** can be used for maintenance therapy and as initial therapy in less severe presentations.

Polymyalgia Rheumatica

DIAGNOSIS

Clinical Presentation

Polymyalgia rheumatica (PMR) presents in elderly patients as proximal limb girdle pain, morning stiffness lasting at least 30 minutes, and constitutional symptoms. It is associated with **temporal arteritis (TA)** in up to 40% of patients (see Table 25-1).

Diagnostic Testing

- There is no established diagnostic criterion. The diagnosis remains clinical.
- The erythrocyte sedimentation rate (ESR) is >50 mm/h.

TREATMENT

- If PMR is present without evidence of TA, **prednisone**, 10-15 mg PO daily, usually produces dramatic clinical improvement within a few days.
- Patients who are suspected of having TA should be treated promptly with high-dose steroids to prevent blindness, and rheumatology should be consulted immediately.
- The ESR should return to normal during initial treatment. Subsequent therapeutic decisions should be based on ESR and clinical status.
- Glucocorticoid therapy can be tapered gradually to a maintenance dosage of 5-10 mg PO daily but

should be continued for at least 1 year to minimize the risk of relapse.

TABLE 25-1 Clinical Features and Diagnostic and Treatment Approaches to Vasculitis

Vasculitic Syndrome	Clinical Features	Diagnostic Approach	Treatment
Large-vessel involvement			
Temporal arteritis	Headache, located temporally in >50% Jaw claudication Commonly associated with PMR	ESR >50 mm/h Temporal artery biopsy	Prednisone, 60-80 mg/d
Takayasu arteritis (affects the aorta and primary branches)	Women more commonly affected Greatest prevalence in Asians Commonly presents between ages 20-30 Constitutional symptoms Finger ischemia Arm claudication	Aortic arch arteriogram	Prednisone, 60-80 mg/d
Medium-vessel involvement			
Polyarteritis nodosa	Skin ulcers Nephritis Mononeuritis Mesenteric ischemia	Skin biopsy Renal biopsy Sural nerve biopsy Mesenteric angiogram Hepatitis B, C testing ANCA negative	Prednisone 60-100 mg/d Cyclophosphamide 1-2 mg/kg/d can be added
Kawasaki disease	Seen in children Fever Conjunctivitis	Clinical Coronary angiogram	IV immunoglobulin Aspirin Anticoagulation

	Lymphadenopathy Mucocutaneous erythema Coronary aneurysms		
Small-vessel involvement			
Granulomatosis with polyangiitis (c-ANCA vasculitis)	Sinusitis Pulmonary infiltrates Nephritis	c-ANCA, sinus biopsy Lung biopsy Renal biopsy	Prednisone 60-100 mg/d *and* cyclophosphamide 1-2 mg/kg/d Rituximab Plasmapheresis
Microscopic polyangiitis	Pulmonary infiltrates Nephritis	p-ANCA Renal biopsy	Prednisone 60-100 mg/d Cyclophosphamide 1-2 mg/kg/d can be added
Churg-Strauss syndrome	Asthma, allergic rhinitis Fleeting pulmonary infiltrates Mononeuritis multiplex	p-ANCA Peripheral eosinophilia Elevated IgE levels Biopsy (sural nerve/skin) with eosinophilic granulomas	Prednisone 60-100 mg/d Cyclophosphamide if renal, GI, CNS, or cardiac involvement
Vasculitis in SLE or RA	Skin ulcers Polyneuropathy	Skin or sural nerve biopsy	Prednisone 60-80 mg/d Cyclophosphamide 1-2 mg/kg/d can be added
Cutaneous leukocytoclastic vasculitis	Palpable purpura	Skin biopsy	NSAIDs, antihistamine, colchicines, dapsone Low-dose prednisone Discontinue inciting drug
Henoch-Schönlein purpura	Palpable purpura Nephritis Mesenteric ischemia	Skin biopsy Renal biopsy IgA immune complex deposition	Supportive treatment Prednisone 20-60 mg/d may be needed

ANCA, antineutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; CNS, central nervous system; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PMR, polymyalgia rheumatica; RA,

rheumatoid arthritis; SLE, systemic lupus erythematosus.

P.805

P.806

Cryoglobulin Syndromes

GENERAL PRINCIPLES

Cryoglobulins are serum immunoglobulins that reversibly precipitate in the cold. Cryoglobulins are categorized as type 1 (monoclonal, no RF activity) or as those with RF activity, the "mixed" types 2 (monoclonal) and 3 (polyclonal).

Etiology

- Patients with **type 1** usually have an underlying hematologic disorder such as myeloma, lymphoma, or Waldenström macroglobulinemia.
- **Types 2 and 3** are associated with small-vessel vasculitis and can be present in patients with chronic inflammatory diseases such as hepatitis B and C virus infection, endocarditis, SLE, and RA. The majority of patients with mixed cryoglobulinemia have hepatitis C, although only 5% of patients with hepatitis C and cryoglobulins develop vasculitis.
- **"Essential"** cryoglobulinemia (cryoglobulinemia without an etiology) has become exceedingly rare since the discovery of hepatitis C.

DIAGNOSIS

- Symptoms in monoclonal cryoglobulinemia are related to hyperviscosity (blurring of vision, digital ischemia, headache, lethargy).
- Clinical manifestations of mixed cryoglobulinemia are mediated by immune complex deposition (arthralgias, palpable purpura, glomerulonephritis, and neuropathy).

TREATMENT

- Secondary cryoglobulinemia responds to **treatment of the underlying disorder**. It may recur when treatment is stopped.
- Patients with progressive renal failure, distal necrosis, advanced neuropathy, or other severe manifestations should be treated aggressively with **prednisone** and immunosuppression.
- **Plasmapheresis** can be used in addition to immunosuppression in severe disease.

Polymyositis and Dermatomyositis

GENERAL PRINCIPLES

- **Polymyositis (PM)** is an inflammatory myopathy that presents as weakness and occasionally tenderness of the proximal musculature.
- **Dermatomyositis (DM)** is an inflammatory myopathy associated with proximal muscle weakness and a

characteristic skin rash. Gottron papules and a heliotrope rash are hallmark features of DM, but other skin manifestations may be seen.

- PM and DM can occur alone or in association with a variety of neoplasms. Patients with rheumatic diseases such as SLE or RA can also have myositis.

DIAGNOSIS

- Elevated muscle enzyme levels (creatine kinase, aldolase, transaminases, lactate dehydrogenase [LDH]).
- Myositis-specific or -associated antibodies such as Jo-1. Anti-Jo-1 antibodies are strongly associated with ILD, Raynaud phenomenon, and arthritis. These antibodies have therapeutic and prognostic implications and should be assessed in all patients.

- Characteristic findings can be seen on electromyogram (EMG), but these changes are not specific and can be seen in infectious or metabolic myopathies.
- A muscle biopsy can establish the diagnosis but may not be required if myositis-related antibodies are present in the right clinical setting. MRI is useful for the detection of inflammation and necrosis and can aid in identifying a biopsy location.
- Screening for common neoplasms, such as colon, lung, breast, and prostate cancer, should be considered in these patients as well as individual risk-based assessment. Risk factors for malignancy in the setting of myositis include the presence of DM, cutaneous vasculitis, male sex, and advanced age.

TREATMENT

- When PM or DM occurs without associated disease, it usually responds well to **prednisone**, 1-2 mg/kg PO daily. Systemic complaints, such as fever and malaise, respond first, followed by muscle enzymes, and finally, muscle strength. Once serum enzyme levels normalize, the prednisone dosage should be reduced slowly to maintenance levels of 10-20 mg PO daily. Appearance of steroid-induced myopathy and hypokalemia may complicate therapeutic assessment.
- Patients who do not respond to glucocorticoids or who need steroid-sparing treatment may respond to **methotrexate**, **mycophenolate mofetil**, or **azathioprine**.
- IV infusion of **immunoglobulin** may hasten improvement of severe dysphagia.
- Severe cases are typically treated with **rituximab**.
- PM or DM associated with neoplasia tends to be less responsive to glucocorticoid therapy but may improve after removal of the malignant tumor.
- **Physical therapy** is essential in the management of myositis.

26
Medical Emergencies

Rebecca Bavolek

Evan S. Schwarz

Jason Wagner

AIRWAY EMERGENCIES

Emergent Airway Management

GENERAL PRINCIPLES

Recognition of the need to manage a patient's airway must be made in a timely and rapid fashion. Respiratory failure can range from immediate to insidious. Increasing evidence shows that inexperienced intubators frequently do more harm than good.

Etiology

The need to emergently manage an airway typically arises for one of three reasons.

- Loss of airway protective reflexes
- Respiratory failure
- Cardiopulmonary arrest

TREATMENT

- If you are not prepared to manage a definitive airway, there are several things that can be done to either temporarily support the airway or help maximize success.
- Inexperienced intubators should maintain the airway with the best device immediately available. Evidence suggests the following order from most effective to least.
  - High-flow nasal cannula oxygen at 15 L/min (apneic oxygenation increases desaturation time)
  - Non-rebreather oxygen mask (NRB) at 15 L/min
  - Bag-valve mask (BVM)
  - Supraglottic airway devices (laryngeal mask airway, Combitube, King Tube)
- While awaiting definitive airway expertise, there are steps that can be taken to improve success during intubation.
  - Place the patient upright to decrease dependent lung volume before intubation.
  - Place the patient on NRB for 3 minutes if possible.
  - If you cannot delay for 3 minutes, then deliver eight vital capacity breaths via BVM.
  - Place a positive end-expiratory pressure valve set to 5-20 cm H_2O on an NRB adding positive pressure to both bagging and passive oxygenation.

Performing the above steps will maximize your chances of success in nearly all airway situations, whether you are the one managing the airway or someone else.

Emergent Airway Adjuncts

- **Gum elastic bougie** is a flexible rubbery stick with a hockey stick tip. The bougie can be used blindly but is better suited for direct laryngoscopy where the intubator cannot visualize the cords. The goal is to obtain the best view possible and for the coude tip of the bougie to be distal and anterior. When the bougie is in the trachea, you can often feel the tracheal rings as you slide the bougie back and forth. Alternatively, you can push the bougie down the oropharynx as deep as possible without losing control of it. If in

the esophagus, the bougie will slide all the way down past the stomach with minimal resistance. If in the trachea, the bougie will quickly hit a bronchus and meet resistance. Once you are in the trachea, you can simply slide an endotracheal tube (ETT) over the bougie and verify placement as you normally would.

- **Laryngeal mask airway (LMA)** is an easy-to-use rescue device for nearly all airway events. It is an ETT with a balloon at the end that is inflated to cup the trachea while occluding the esophagus. Note that it should not be used in patients with upper airway obstruction that cannot be cleared or patients with excessive airway pressures such as with chronic obstructive pulmonary disease (COPD), asthma, or pregnancy. There are models of LMAs (which are preferred) that allow an ETT to be passed through them when a definitive airway is desired. Be cautious with excessive bagging because this can lead to emesis.
- **Supraglottic airway devices** are placed blindly in the oropharynx and inflated with air. An upper balloon obstructs the oropharynx while a lower balloon obstructs the esophagus, allowing ventilation in a similar fashion to an LMA with the same limitations. Note that you cannot intubate through a supraglottic device as you can with intubating LMAs.
- **Fiberoptic/digital airway devices** are considered by many the new standard of care. These devices allow the intubator to get a view of the vocal cords via a camera or fiberoptic scope without having to view it through the mouth, making intubation much easier. Excessive secretions or blood can obstruct the camera, so the person using these devices needs to be capable of direct laryngoscopy as well as indirect fiberoptic laryngoscopy.

Pneumothorax

GENERAL PRINCIPLES

- Pneumothorax may occur spontaneously or as a result of trauma.
- **Primary spontaneous pneumothorax** occurs without obvious underlying lung disease.
- **Secondary spontaneous pneumothorax** results from underlying parenchymal lung disease including COPD and emphysema, interstitial lung disease, necrotizing lung infections, *Pneumocystis jirovecii* pneumonia, TB, and cystic fibrosis.
- **Traumatic pneumothoraces** occur as a result of penetrating or blunt chest wounds.
- **Iatrogenic pneumothorax** occurs after thoracentesis, central line placement, transbronchial biopsy, transthoracic needle biopsy, and barotrauma from mechanical ventilation and resuscitation.
- **Tension pneumothorax** results from continued accumulation of air in the chest that is sufficient to shift mediastinal structures and impede venous return to the heart. This results in hypotension, abnormal gas exchange, and ultimately, cardiovascular collapse.
    - Causes include barotrauma due to mechanical ventilation, a chest wound that allows ingress but not egress of air, or a defect in the visceral pleura that behaves in the same way (“ball-valve” effect).

- Suspect tension pneumothorax when a patient experiences hypotension and respiratory distress on mechanical ventilation or after any procedure in which the thorax is pierced by a needle.

DIAGNOSIS

Clinical Presentation

History

- Patients commonly complain of ipsilateral chest or shoulder pain, usually of acute onset. A history of recent chest trauma or medical procedure can suggest the diagnosis.
- Dyspnea is usually present.

Physical Examination

- Although examination of the patient with a small pneumothorax may be normal, classic findings include decreased breath sounds and a more resonant percussion note on the ipsilateral side.
- With a larger pneumothorax or with underlying lung disease, there may be tachypnea and respiratory distress. The affected hemithorax may be noticeably larger (due to decreased elastic recoil of the collapsed lung) and relatively immobile during respiration.
- If the pneumothorax is very large, and particularly if it is under tension, the patient may exhibit severe distress, diaphoresis, cyanosis, and hypotension. In addition, the patient's trachea may be shifted to the contralateral side.
- If the pneumothorax is the result of penetrating trauma or pneumomediastinum, subcutaneous emphysema may be felt.
- Clinical features alone do not predict the relative size of a pneumothorax, and in a stable patient, further diagnostic studies must be used in order to guide treatment strategy. However, tension pneumothorax remains a clinical diagnosis, and if suspected in the appropriate clinical scenario, immediate intervention should be undertaken prior to further testing.

Diagnostic Testing

Electrocardiography

An **ECG** may reveal diminished anterior QRS amplitude and an anterior axis shift. In extreme cases, tension pneumothorax may cause electromechanical dissociation.

Imaging

- A **CXR** will reveal a separation of the pleural shadow from the chest wall. If the posteroanterior radiograph is normal and pneumothorax is suspected, a lateral or decubitus film may aid in diagnosis (*Thorax 2003;58(suppl II):ii39*). Air travels to the highest point in a body cavity; thus, a pneumothorax in a supine patient may be detected as an unusually deep costophrenic sulcus and excessive lucency over the upper abdomen caused by the anterior thoracic air. This observation is particularly important in the critical care unit, where radiographs of the mechanically ventilated patient are often obtained with the patient in supine position.
- Although tension pneumothorax is a clinical diagnosis, radiographic correlates include mediastinal and tracheal shift toward contralateral side and depression of the ipsilateral diaphragm.
- **Ultrasonography** is a useful tool for bedside diagnosis of pneumothorax, especially on patients who must remain supine or who are too unstable to undergo CT scanning. Placement of the probe in the intercostal spaces provides information regarding the pleura and underlying lung parenchyma. During

normal inspiration, the visceral and parietal pleura move along one another and produce a “sliding sign” phenomenon. In addition, the air-filled lung parenchyma below the pleura produces a ray-like opacity known as “comet tails.” Presence of the sliding sign and comet tails on ultrasound during inspiration rule out a pneumothorax with high reliability at the point of probe placement. Conversely, absence of these signs is a highly reliable predictor for the presence of pneumothorax. Several places on the chest should be evaluated, including places that air is most likely to accumulate such as the anterior and lateral chest (*Chest 2012;141:1099*). Studies have shown that in the hands of an experienced clinician with ultrasound training, chest ultrasound is more sensitive than CXR (*Emerg Radiol 2013;20:131*).

- Chest CT is the gold standard for diagnosis and determining the size of pneumothorax. Although not always necessary, it may be particularly useful for differentiating pneumothorax from bullous disease in patients with underlying lung conditions (*Thorax 2003;58(suppl II):ii42*).

TREATMENT

Treatment depends on cause, size, and degree of physiologic derangement.

- **Primary pneumothorax**
  - A small, primary, spontaneous pneumothorax without a continued pleural air leak may resolve spontaneously. Air is resorbed from the pleural space at roughly 1.5% daily, and therefore, a small (approximately 15%) pneumothorax is expected to resolve without intervention in approximately 10 days.
  - Confirm that the pneumothorax is **not increasing in size** (repeat the CXR in 6 hours if there is no change in symptoms) and send the patient home if he or she is asymptomatic (apart from mild pleurisy). Obtain follow-up radiographs to confirm resolution of the pneumothorax in 7-10 days. Air travel is discouraged during the follow-up period, because a decrease in ambient barometric pressure results in a larger pneumothorax.
  - If the pneumothorax is **small but the patient is mildly symptomatic**, far from home, or unlikely to cooperate with follow-up, admit the patient and administer high-flow oxygen; the resulting nitrogen gradient will speed resorption.
  - If the patient is **more than mildly symptomatic or has a larger pneumothorax**, simple aspiration is a reasonable initial management strategy. However, aspiration may not be successful for very large pneumothoraces. In patients in whom aspiration fails, proceed with thoracostomy tube insertion (*Thorax 2003;58(suppl II):ii39*).
  - **Pleural sclerosis** to prevent recurrence is recommended by some experts but, in most cases, is not used after a first episode unless a persistent air leak is present.
- **Secondary pneumothorax**
  - Individuals with a secondary spontaneous pneumothorax are usually symptomatic and require lung reexpansion.
  - Often, a bronchopleural fistula persists and a larger thoracostomy tube and suction are required.
  - **Consult a pulmonologist** about pleural sclerosis for persistent air leak and to prevent recurrence.
  - **Surgery** may be required for persistent air leak and should be considered for high-risk patients for prevention of recurrence.
- **Iatrogenic pneumothorax**

- Iatrogenic pneumothorax is generally caused either by introducing air into the pleural space through the parietal pleura (e.g., thoracentesis, central line placement) or by allowing intrapulmonary air to escape through breach of the visceral pleura (e.g., transbronchial biopsy). Often, no further air leak occurs after the initial event.
- If the pneumothorax is small and the patient is minimally symptomatic, he or she can be managed conservatively. If the procedure that caused the pneumothorax required sedation, admit the patient, administer oxygen, and repeat the CXR in 6 hours to ensure the patient's stability. If the patient is completely alert and the CXR shows no change, the patient can be discharged.
- If the patient is symptomatic or if the pneumothorax is too large for expectant care, a pneumothorax catheter with aspiration or a one-way valve is usually adequate and can often be removed the following day.
- Iatrogenic pneumothorax due to barotrauma from mechanical ventilation almost always has a persistent air leak and should be managed with a chest tube and suction.
- **Tension pneumothorax**
  - When the clinical situation and physical examination strongly suggest this diagnosis, decompress the affected hemithorax immediately with a 14-gauge needle. Place the needle in the second intercostal space, midclavicular line, just superior to the rib. Release of air with clinical improvement confirms the diagnosis.
  - Recognize that an obese patient or a patient with a large amount of breast tissue may not have resolution of tension with a standard angiocatheter due to inability to reach

    the chest wall or weight of the tissue kinking off the air escape path. These patients may require a longer needle than a standard angiocatheter in order to reach the intrathoracic space for decompression or require insertion of a larger gauge reinforced catheter to stent open the pathway for air release.
  - If long-needle decompression or reinforced catheter insertion is unsuccessful, and the diagnosis is highly probable in an unstable patient, surgical decompression can be performed by incision of the pleura in the fourth to fifth anterior axillary line above the rib in the same space in which thoracostomy tubes are inserted. This technique has been shown to be effective; however, safety and complication rates are not able to be determined due to lack of studies (*Resuscitation 2007;72(1):11*). The full technique for this procedure is beyond the scope of this book.
  - Seal any chest wound with an occlusive dressing and arrange for placement of a thoracostomy tube.

HEAT-INDUCED INJURY

Heat Exhaustion

GENERAL PRINCIPLES

Heat exhaustion occurs through water or sodium depletion but is often a combination of both. Water depletion heat exhaustion often occurs in the elderly or persons working in hot environments with limited water replacement. Salt depletion occurs in unacclimatized individuals who replace fluid losses with large amounts of hypotonic solution.

DIAGNOSIS

- The patient presents with headache, nausea, vomiting, dizziness, weakness, irritability, and/or cramps.
- The patient may have postural hypotension, diaphoresis, and normal or minimally increased core temperature.

TREATMENT

- Treatment consists of resting the patient in a cool environment, accelerating heat loss by fan evaporation, and repleting fluids with salt-containing solutions.
- If the patient is not vomiting and has stable blood pressure, an oral, commercial, balanced salt solution is adequate.
- If the patient is vomiting or hemodynamically unstable, check electrolytes and give 1-2 L of 0.9% saline IV.
- The patient should avoid exercise in a hot environment for 2-3 additional days.

Heat Syncope

GENERAL PRINCIPLES

- Heat syncope is a variant of postural hypotension.
- Exercise in a hot environment results in peripheral vasodilation and pooling of blood, with subsequent loss of consciousness. The affected individual has normal body temperature and regains consciousness promptly when supine. These factors separate this syndrome from heat stroke.

TREATMENT

Treatment consists of resting in a cool environment and fluid repletion.

Heat Stroke

GENERAL PRINCIPLES

- Heat stroke occurs in two varieties, classic and exertional. Both varieties present with high core temperatures that result in direct thermal tissue injury. Secondary effects include acute renal failure from rhabdomyolysis. Even with rapid therapy, mortality rates can be very high for body temperatures above 41.1°C (106°F). The distinction between classic and exertional heat stroke is not important because the therapeutics goals are similar in both and a delay in cooling increases mortality rate.
- The cardinal features of heat stroke are **hyperthermia (>40°C [104°F]) and altered mental status**. Although patients presenting with classic heat stroke may have anhidrosis, this is not considered a diagnostic criterion, because 50% of patients are still diaphoretic at presentation.
- The central nervous system (CNS) is very vulnerable to heat stroke with the cerebellum being highly sensitive. Ataxia may be an early sign. Seizures are common. Neurologic injury is a function of maximum temperature and duration of exposure (*N Engl J Med 2002;346:1978*).

DIAGNOSIS

Diagnosis is based on the history of exposure or exercise, a core temperature usually of 40.6°C (105°F) or higher, and changes in mental status ranging from confusion to delirium and coma.

Differential Diagnosis

- Drug associated
  - Toxicity
    - Anticholinergic
    - Stimulant toxicity
    - Salicylate toxicity
  - Neuroleptic malignant syndrome (NMS) associated with antipsychotic drugs. It is worth noting that NMS and malignant hyperthermia are both accompanied by severe muscle rigidity.
  - Serotonin syndrome
  - Malignant hyperthermia
  - Drug withdrawal syndrome (ethanol withdrawal)
  - Drug fever
- Infections
  - Generalized infections (sepsis, malaria, etc.)
  - CNS infections (meningitis, encephalitis, brain abscess)
- Endocrine
  - Thyroid storm
  - Pheochromocytoma
- Hypothalamic dysfunction due to stroke or hemorrhage
  - Status epilepticus
  - Cerebral hemorrhage (*Emerg Med Clin North Am 2013;31(4):1097*)

Diagnostic Testing

Laboratories

- Laboratory studies should include complete blood count (CBC); partial thromboplastin time; prothrombin time; fibrin degradation products; electrolytes; blood urea nitrogen (BUN); creatinine, glucose, calcium, and creatine kinase levels; liver function tests (LFTs); arterial blood gases (ABGs); urinalysis; and ECG.
- If an infectious etiology is suspected, obtain appropriate cultures.

Imaging

If a CNS etiology is considered likely, CT imaging followed by spinal fluid examination is appropriate.

TREATMENT

- **Immediate cooling** is necessary.

- The best method of cooling is controversial. A systematic review showed that ice water immersion decreases body temperature twice as quickly as passive cooling and is the procedure of choice when exertional heat stroke is anticipated (long-distance races, military training). If that cannot be achieved, continuous water spray accompanied by fanning has been shown to be adequate for most patients with exertional heat stroke (*Int J Sports Med 1998;19(suppl 2):S150*; *Ann Intern Med 2000;132:678*; *J Athl Train 2009;44(1):84*).
- If response is insufficiently rapid, submerge the patient in ice water, recognizing that this may interfere with resuscitative efforts (*Am J Emerg Med 1996;14:355*).
- Most emergency facilities that do not care for large numbers of heat illness cases are not equipped for this treatment. In this case, mist the patient continuously with tepid water (20-25°C [68-77°F]). Cool the patient with a large electric fan with maximum body surface exposure.
- Ice packs should be placed at points of major heat transfer, such as the groin, axillae, and chest, to further speed cooling.
- Antipyretics have no indication.

- **Dantrolene sodium** does not appear to be effective for the treatment of heat stroke (*Crit Care Med 1991;19:176*).
- Monitor core temperatures continuously by rectal probe because oral and tympanic membrane temperature may be inaccurate.
- Discontinue cooling measures when the core temperature reaches 39°C (102.2°F), which should ideally be achieved within 30 minutes. A temperature rebound may occur in 3-6 hours and should be retreated.
- **For hypotension, administer crystalloids:** If refractory, treat with vasopressors and monitor hemodynamics. Avoid pure α-adrenergic agents, because they cause vasoconstriction and impair cooling. Administer crystalloids cautiously to normotensive patients.

COMPLICATIONS

- **Rhabdomyolysis** may occur. Treat as described in Chapter 13, Renal Diseases.
- **Hypoxemia and acute respiratory distress syndrome** may occur. Treat as described in Chapter 8, Critical Care.
- Treat seizures with benzodiazepines and phenytoin.

MONITORING/FOLLOW-UP

Patients should be placed on telemetry.

COLD-INDUCED ILLNESS

Exposure to the cold may result in several different forms of injury. A risk factor is accelerated heat loss, which is promoted by exposure to high wind or by immersion. Extended cold exposure may result from alcohol or drug abuse, injury or immobilization, and mental impairment.

Chilblains

GENERAL PRINCIPLES

- Chilblains are among the mildest form of cold injury and result from exposure of bare skin to a cold, windy environment (0.6-15.6°C [33-60°F]).
- The ears, fingers, and tip of the nose typically are injured, with itchy, painful erythema on rewarming.

TREATMENT

Treatment involves rapid rewarming (see Frostnip section), moisturizing lotions, analgesics, and instructing the patient to avoid reexposure.

Immersion Injury (Trench Foot)

GENERAL PRINCIPLES

Immersion injury is caused by prolonged immersion (longer than 10-12 hours) at a temperature <10°C (<50°F).

TREATMENT

Treat by rewarming followed by dry dressings. Treat secondary infections with antibiotics.

Frostnip (Superficial Frostbite)

GENERAL PRINCIPLES

Superficial frostbite involves the skin and SC tissues.

DIAGNOSIS

Areas with first-degree involvement are white, waxy, and anesthetic; have poor capillary refill; and are painful on thawing. Second-degree involvement is manifested by clear or milky bullae.

TREATMENT

The **treatment of choice** is rapid rewarming. Immerse the affected body part for 15-30 minutes; hexachlorophene or povidone-iodine can be added to the water bath. Narcotic analgesics may be necessary for rewarming pain. Typically, no deep injury ensues and healing occurs in 3-4 weeks.

Deep Frostbite

GENERAL PRINCIPLES

- Deep frostbite involves death of skin, SC tissue, and muscle (third degree) or deep tendons and bones (fourth degree).
- Diabetes mellitus, peripheral vascular disease, an outdoor lifestyle, and high altitude are additional **risk factors**.

DIAGNOSIS

- The tissue appears frozen and hard.

- On rewarming, there is no capillary filling.
- Hemorrhagic blisters form, followed by eschars. Healing is very slow, and demarcation of tissue with autoamputation may occur.
- The majority of deep frostbite occurs at temperatures <6.7°C (44°F) with exposures longer than 7-10 hours.

TREATMENT

- The treatment is rapid rewarming as described earlier. **Rewarming should not be started until there is no chance of refreezing.**
- Administer analgesics (IV opioids) as needed.
- Early surgical intervention is not indicated.
- **Elevate** the affected extremity, prevent weight bearing, separate the affected digits with cotton wool, prevent tissue maceration by using a blanket cradle, and prohibit smoking.
- Update tetanus immunization.
- Intra-arterial vasodilators, heparin, dextran, prostaglandin inhibitors, thrombolytics, and sympathectomy are not routinely justified.
- Role of antibiotics is unclear (*Tintinalli's Emergency Medicine Manual. 7th ed. New York: McGraw-Hill, 2010: Chapter 202: Frostbite and Other Localized Cold Injuries*).
- Amputation is undertaken only after full demarcation has occurred.

Hypothermia

GENERAL PRINCIPLES

Definition

Hypothermia is defined as a core temperature of <35°C (95°F).

Classification

Classification of severity by temperature is not universal. One scheme defines hypothermia as mild at 34-35°C (93.2-95°F), moderate at 30-34°C (86-93.2°F), and severe at <30°C (86°F).

Etiology

- The most common cause of hypothermia in the United States is cold exposure due to alcohol intoxication.
- Another common cause is cold water immersion.

DIAGNOSIS

Clinical Presentation

Presentation varies with the temperature of the patient on arrival. All organ systems can be involved.

- **CNS effects**

- At temperatures **below 32°C (89.6°F)**, mental processes are slowed and the affect is flattened.
- At **32.2°C (90°F)**, the ability to shiver is lost, and deep tendon reflexes are diminished.
- At **28°C (82.4°F)**, coma often supervenes.
- **Below 18°C (64.4°F)**, the electroencephalogram (EEG) is flat. On rewarming from severe hypothermia, central pontine myelinolysis may develop.

- **Cardiovascular effects**
  - After an initial increased release of catecholamines, there is a decrease in cardiac output and heart rate with relatively preserved mean arterial pressure. ECG changes manifest initially as sinus bradycardia with T-wave inversion and QT interval prolongation and may manifest as atrial fibrillation at temperatures of <32°C (<89.6°F).
  - Osborne waves (J-point elevation) may be visible, particularly in leads II and V_6.
  - An increased susceptibility to ventricular arrhythmias occurs at temperatures **below 32°C (89.6°F)**.
  - At temperatures of **30°C (86°F)**, the susceptibility to ventricular fibrillation is increased significantly, and unnecessary manipulation or jostling of the patient should be avoided.
  - A decrease in mean arterial pressure may also occur, and at temperatures of **28°C (82.4°F)**, progressive bradycardia supervenes.
- **Respiratory effects**
  - After an initial increase in minute ventilation, respiratory rate and tidal volume decrease progressively with decreasing temperature.
  - ABGs measured with the machine set at 37°C (98.6°F) should serve as the basis for therapy without correction of pH and carbon dioxide tension (PCO_2) (*Ann Emerg Med 1989;18:72*; *Arch Intern Med 1998;148:1643*).
- **Renal manifestations:** Cold-induced diuresis and tubular concentrating defects may be seen.

Differential Diagnosis

- Cerebrovascular accident
- Drug overdose
- Diabetic ketoacidosis
- Hypoglycemia
- Uremia
- Adrenal insufficiency
- Myxedema

Diagnostic Testing

Laboratories

- Basic laboratory studies should include CBC, coagulation studies, LFTs, BUN, electrolytes, creatinine, glucose, creatine kinase, calcium, magnesium, amylase levels, urinalysis, ABGs, and ECG.
- Obtain toxicology screen if mental status alteration is more profound than expected for temperature decrease.
- Serum potassium is often increased.

- Elevated serum amylase may reflect underlying pancreatitis.

- Hyperglycemia may be noted but should not be treated because rebound hypoglycemia may occur with rewarming.
- Disseminated intravascular coagulation may also occur.

Imaging

Obtain chest, abdominal, and cervical spine radiographs to evaluate all patients with a history of trauma or immersion injury.

TREATMENT

Medications

- Administer supplemental oxygen.
- Give **thiamine** to most patients with cold exposure, because exposure due to alcohol intoxication is common.
- Administration of **antibiotics** is a controversial issue; many authorities recommend antibiotic administration for 72 hours, pending cultures. In general, the patients with hypothermia due to exposure and alcohol intoxication are less likely to have a serious underlying infection than those who are elderly or who have an underlying medical illness.

Other Nonpharmacologic Therapies

- **Rewarming:** The patient should be rewarmed with the goal of increasing the temperature by 0.5-2.0°C/h (32.9-35.6°F/h), although the rate of rewarming has not been shown to be related to the outcome.
- **Passive external rewarming**
  - This method depends on the patient's ability to shiver.
  - It is effective only at core temperatures of **32°C (89.6°F) or higher**.
  - Remove wet clothing, cover patient with blankets in a warm environment, and monitor.
- **Active external rewarming**
  - Application of heating blankets (40-45°C [104-113°F]) or warm bath immersion may cause paradoxical core acidosis, hyperkalemia, and decreased core temperature, as cold stagnant blood returns to the central vasculature (*J R Nav Med Serv 1991;77:139*), although Danish naval research supports arm and leg rewarming as effective and safe (*Aviat Space Environ Med 1999;70:1081*).
  - Pending further investigation, active rewarming is best reserved for young, previously healthy patients with acute hypothermia and minimal pathophysiologic derangement.
- **Active core rewarming is preferred for treatment of severe hypothermia**, although few data are available on outcomes (*Resuscitation 1998;36:101*).
  - **Heated oxygen** is the initial therapy of choice for the patient whose cardiovascular status is stable. This therapeutic maneuver can be expected to raise core temperatures by 0.5-1.2°C/h (32.9-34.2°F/h) (*Ann Emerg Med 1980;9:456*). Administration through an ETT results in more rapid rewarming than delivery via face mask. Administer heated oxygen through a cascade humidifier at a temperature of 45°C (113°F) or lower.
  - **IV fluids** can be heated in a microwave oven or delivered through a blood warmer; give fluids only

through peripheral IV lines.

- **Intravascular heat exchange via catheter** is a recent addition to the options on this list. Less invasive and more familiar to most physicians than the more extreme options, this option can increase body temperature up to 3°C/h. This is simply a central venous catheter placed by the familiar modified Seldinger technique. After placement, warm fluids are run through the catheter (not into the venous system) allowing for cool blood to rewarm as it passes.
- **Heated nasogastric or bladder lavage** is of limited efficacy because of low-exposed surface area and is reserved for the patient with cardiovascular instability.
- **Heated peritoneal lavage** with fluid warmed to 40-45°C (104-113°F) is more effective than heated aerosol inhalation, but it should be reserved for patients with cardiovascular

instability. Only those who are experienced in its use should perform heated peritoneal lavage, in combination with other modes of rewarming.

- **Closed thoracic lavage** with heated fluid by thoracostomy tube has been recommended but is unproved (*Ann Emerg Med 1990;19:204*).
- **Hemodialysis** can be used for the severely hypothermic, particularly when due to an overdose that is amenable to treatment in this way.
- **Extracorporeal circulation** (cardiac bypass) is used only in hypothermic individuals who are in cardiac arrest; in these cases, it may be dramatically effective (*N Engl J Med 1997;337:1500*). Extracorporeal circulation may raise the temperature as rapidly as 10-25°C/h (50-77°F/h) but must be performed in an intensive care unit (ICU) or operating room.

Resuscitation

- Maintain airway and administer oxygen.
- If intubation is required, the most experienced operator should perform it (see Airway Management and Tracheal Intubation section in Chapter 8, Critical Care).
- Conduct **cardiopulmonary resuscitation (CPR)** in standard fashion. Perform simultaneous vigorous core rewarming; as long as the core temperature is severely decreased, it should not be assumed that the patient cannot be resuscitated. Reliable defibrillation requires a core temperature of 32°C (89.6°F) or higher; prolonged efforts (to a core temperature of 35°C [95°F]) may be justified because of the neuroprotective effects of hypothermia. **Do not begin CPR if an organized ECG rhythm is present**, because inability to detect peripheral pulses may be due to vasoconstriction, and CPR may precipitate ventricular fibrillation.
- Do not perform Swan-Ganz catheterization, because it may precipitate ventricular fibrillation.
- If ventricular fibrillation occurs, begin CPR as per the advanced cardiac life support (ACLS) protocol (Appendix C). Amiodarone may be administered as per the protocol, although there is no evidence to support its use or guide dosage; some experts suggest reducing the maximum cumulative dose by half. Avoid procainamide because it may precipitate ventricular fibrillation and increase the temperature that is necessary to defibrillate the patient. Rewarming is key.
- Monitor ECG rhythm, urine output, and, possibly, central venous pressure in all patients with an intact circulation.

Disposition

- Admit patients with an underlying disease, physiologic derangement, or core temperature <32°C (<89.6°F), preferably to an ICU.

- Discharge individuals with mild hypothermia (32-35°C [89.6-95°F]) and no predisposing medical conditions or complications when they are normothermic and an adequate home environment can be ensured.

MONITORING/FOLLOW-UP

- Monitor core temperature.
- A standard oral thermometer registers only to a lower limit of 35°C (95°F). Monitor the patient continuously with a rectal probe with a full range of 20-40°C (68-104°F).

OVERDOSES

Overdose, General

Below is a brief review of three of the most common toxicologic emergencies physicians encounter in the United States. For more information about these exposures and other toxicologic conditions, please refer to Chapter 28, Toxicology, an online chapter.

Acetaminophen

GENERAL PRINCIPLES

N-Acetyl-para-aminophenol (APAP) is available worldwide as an over-the-counter analgesic and antipyretic. It is the most common cause of toxicologic fatalities and liver failure in the United States (*Clin Toxicol (Phila) 2014;52(10):1032*; *Hepatology 2005;42(6):1364*).

DIAGNOSIS

Clinical Presentation

- Patients can initially present with nausea, vomiting, and abdominal pain. However, patients can be asymptomatic, even after potentially toxic ingestions.
- As toxicity progresses, patients develop transaminase elevation, metabolic acidosis, renal failure, and a coagulopathy.
- Patients may eventually develop fulminant hepatic failure, cerebral edema, and sepsis.
- Acetaminophen combination products (such as opioids, antihistamines) can cause additional symptoms such as opioid toxicity and anticholinergic delirium.

History

To predict the risk of hepatotoxicity after acute overdose and use the Rumack-Matthew nomogram, a reliable time of ingestion must be obtained from the patient or family/friends.

Physical Examination

Assess airway, breathing, and circulation (ABCs) and mental status. Especially in patients who are nauseated or vomiting, the assessment of mental status is crucial to prevent aspiration pneumonitis.

Diagnostic Criteria

- Obtain an APAP serum concentration at 4 hours or later after an acute ingestion.
- Plot the APAP concentration on the Rumack-Matthew nomogram (APAP serum concentration vs. time after ingestion) to assess the possibility of hepatic toxicity. Note: The nomogram can only be used for

acute ingestions.

- In general, an APAP dose of 150 mg/kg is the potentially toxic limit that requires therapeutic intervention. This limit includes an added 25% safety margin that was added by the US Food and Drug Administration (*BMJ 1998;316(7146):1724*).
- If the time of ingestion is unknown or the ingestion occurred over multiple days or hours, the Rumack-Matthew nomogram cannot be used. The clinician must use the history and laboratory results to determine if the patient is at risk for hepatic injury.

Diagnostic Testing

- **APAP serum level at 4 hours** after ingestion or later (see above).
- **LFT, international normalized ratio, coagulation tests**—aspartate aminotransferase (AST) is a relatively sensitive nonprognostic marker for hepatic injury.

TREATMENT

- ***N*-Acetylcysteine (NAC):** NAC is the antidote to prevent APAP-related hepatotoxicity (*Toxicol Sci 2004;80(2):343*). It should be administered early (i.e., within 8 hours after ingestion) to prevent liver injury but still offers some protection if its administration is delayed (*N Engl J Med 1988;319(24):1557*).
- NAC can be administered either orally or IV.

- **Oral dosing:** Loading dose of 140 mg/kg PO, then 70 mg/kg PO every 4 hours for a total of 17 doses.
- **IV dosing:** Per the package insert, NAC is administered using a three-bag approach: bag 1: 150 mg/kg over 1 hour; bag 2: 50 mg/kg administered over 4 hours; bag 3: 100 mg/kg over 16 hours. The infusion is then continued if there are signs of toxicity. To simplify the approach, hospitals have developed their own protocols. At Barnes-Jewish Hospital, the protocol is to administer the loading dose over 1 hour followed by a continuous infusion at 14 mg/kg/h for the next 20 hours.
- **NAC indications:** NAC treatment should be started in the following:
  - Any patient after acute poisoning with a toxic APAP level according to the nomogram.
  - Patients who present beyond 8 hours after acute ingestion. Start NAC therapy while awaiting the initial APAP serum concentration and LFTs. Continue treatment if the serum concentration is in the toxic range per nomogram or the LFTs are elevated.
  - Patients who present more than 24 hours after acute ingestion and still have a detectable serum APAP level or elevated AST.
  - Patients with chronic APAP exposure (i.e., >4 g/d in adults, >120 mg/kg/d in children) who present with elevated acetaminophen concentrations and transaminases or a concerning history.
  - Patients with signs of fulminant hepatic failure. NAC treatment should be started immediately and transfer to a transplant center arranged without fail. NAC is shown to improve survival of patients in fulminant hepatic failure (*Lancet 1990;335(8705):1572*; *N Engl J Med 1991;324(26):1852*; *BMJ 1991;303(6809):1026*).

Opioids

DIAGNOSIS

Clinical Presentation

Symptoms of opioid overdose are respiratory depression, a depressed level of consciousness, and **miosis**. However, the pupils may be dilated with acidosis or hypoxia or following an overdose with meperidine, propoxyphene, or dextromethorphan.

Diagnostic Testing

Laboratories

Drug concentrations and other standard laboratory tests are of little use. Urine drug screens are associated with multiple false positives and negatives. Opioid intoxication is a clinical diagnosis.

Imaging

A CXR should be obtained if pulmonary symptoms are present or there is concern for aspiration.

TREATMENT

- Treatment includes airway maintenance, ventilatory support, and naloxone, an opioid antagonist.
- Limit use of whole-bowel irrigation to body packers. Body packers rarely require surgery, except in cases of intestinal obstruction. This should only be done in consultation with a poison center or medical toxicologist.

Medications

- **Naloxone hydrochloride** is indicated for opioid-induced respiratory depression. It should not be used to reverse decreased mental status.

- The lowest effective dose should be used. The goal of treatment is adequate spontaneous respiration and not necessarily alertness. The initial dose is 0.04-2 mg IV, although the lowest effective dose should be used.
- Larger doses (up to 10 mg IV) may be required to reverse the effects of methadone.
- If multiple doses of naloxone are required, an IV infusion should be initiated. The infusion should be started at two-thirds of the dose required to reverse respiratory depression.
- In the absence of an IV line, naloxone can be administered sublingually (*Ann Emerg Med 1987;16:572*), intranasally (*Emerg Med J 2006;23:221*), or IM. Isolated opioid overdose is unlikely if there is no response to a total of 10 mg of naloxone.
- **Disposition**
  - Patients should be observed for at least an hour following naloxone administration.
  - Patients requiring a naloxone infusion should be admitted to an ICU.
  - Body packers should be admitted to an ICU for close monitoring of the respiratory rate and level of consciousness and remain in the ICU until all packets have passed, as documented by CT.

Salicylates

GENERAL PRINCIPLES

Definition

- Salicylate toxicity may result from **acute or chronic** ingestion of acetylsalicylic acid (aspirin is a generic

name in the United States, but a brand name in the rest of the world).

- Toxicity from chronic ingestion typically occurs in elderly patients with chronic underlying medical conditions. They can present similarly to patients with sepsis.

DIAGNOSIS

Clinical Presentation

- Nausea, vomiting, tinnitus or hearing changes, tachypnea, tachycardia, diaphoresis, hyperpnea, and malaise are common in acute toxicity.
- Severe intoxications may include lethargy, noncardiogenic pulmonary edema, seizures, and coma, which may result from cerebral edema and energy depletion in the CNS.

Diagnostic Testing

- Obtain electrolytes, BUN, creatinine, and glucose.
- Obtain either ABGs or venous blood gases.
- Obtain a serum salicylate concentration. Patients generally require treatment for concentrations >30 mg/dL. **Note: Units may be different at other institutions. For the purposes of this chapter, salicylate concentrations are in mg/dL.**
- Salicylate concentrations >100 mg/dL are very serious and often fatal.
- Salicylate concentrations of 10-30 mg/dL often do not require treatment. However, patients should receive serial evaluations to make sure that the concentration is appropriately decreasing.
- Chronic ingestion can cause toxicity at lower salicylate concentrations than acute ingestions.

TREATMENT

Medications

- **Multidose charcoal** may be useful in severe overdose (*Pediatrics 1990;85:594*) or in cases in which salicylate concentrations fail to decline as absorption tends to be delayed due to bezoar formation and pylorospasm.

- Patients are often volume depleted and require 1-2 L of normal saline.
- **Urine alkalinization** is indicated for patients with salicylate concentrations >30 mg/dL.
- Administer 150 mEq (three ampules) sodium bicarbonate in 1000 mL 5% dextrose in water (D5W) at 1.5-2 times maintenance.
- Maintain alkalinization and titrate to a goal urine pH of 7.5-8. Patients with hypokalemia cannot effectively have their urine alkalinized.
- **Use caution in patients who cannot handle large volumes of fluid such as the elderly, patients with renal failure, patients with heart failure, or patients with cerebral or pulmonary edema.**
- Alkalinization can be stopped once the serum concentration is <30 mg/dL. The patient should have a repeat salicylate concentration drawn 4-6 hours after all treatment is stopped. If it is declining appropriately (approximately half of previous concentration), the patient does not require further treatment.
- **Hyperventilate any patient requiring endotracheal intubation.** Intubation should be avoided if at all

possible in these patients, because they require complex ventilatory settings. The ventilator should be set at their maximal respiratory rate. Any worsening of their acidosis due to improper ventilator settings can result in rapid deterioration and death.

- **Treat altered mental status with IV dextrose** even with a normal blood glucose.
- Treat **seizures** with a **benzodiazepine**. Standard antiepileptics will not be effective.

Hemodialysis

Indications include:

- Salicylate concentrations >100 mg/dL in acute toxicity
- Salicylate concentrations >80 mg/dL or rising despite treatment
- Salicylate concentrations >60 mg/dL in chronic toxicity
- Patients with pulmonary edema, cerebral edema, or seizures
- Patients requiring intubation
- Patients who cannot receive large amounts of fluid and have potentially toxic ingestions

27
Neurologic Disorders

Robert C. Bucelli

Beau M. Ances

Alterations in Consciousness

GENERAL PRINCIPLES

Definition

- **Coma** is a state of complete behavioral unresponsiveness to external stimulation. Because multiple etiologies can lead to irreversible brain damage, evaluation and treatment should be performed concurrently and expeditiously. The need for neurosurgical intervention must be determined promptly.
- **Delirium** is an acute state of confusion that can result from diffuse or multifocal cerebral dysfunction and is characterized by relatively rapid reduction in the ability to focus, sustain, or shift attention. Changes in cognition, fluctuations in consciousness, disorientation, and even hallucinations are common.

Epidemiology

- About 30% of older patients (>60 years old) experience delirium during hospitalization.
- Delirious patients often have prolonged hospitalizations and are at greater risk for subsequent cognitive decline.

Etiology

- Coma results from diffuse or multifocal dysfunction that involves both cerebral hemispheres or the reticular activating system in the brainstem.
- Etiologies of altered mental status are listed in Table 27-1.
- Mild systemic illness (e.g., urinary tract infections [UTIs]), introduction of new medications, fever, and/or sleep deprivation are common causes of delirium in the elderly and in patients with chronic central nervous system (CNS) dysfunction of any etiology.

DIAGNOSIS

- Initial assessment should focus on recognizing the development and progression of altered consciousness. The examiner should query for history of trauma, seizures, stroke, medication changes, and alcohol or drug use as possible etiologies. A collateral source can be extremely helpful and is often necessary.
- The AWOL tool is a useful, quick bedside measure that can be used to assess patients' risk of delirium at the time of admission (*J Hosp Med 2013;9:493*). The AWOL score is derived from assigning one point for each of the following variables (**a**ge ≥80, inability to spell the word "**w**orld" backward, dis**o**rientation to location, and nurse-rated i**l**lness severity [with a point given for patients considered to be at least moderately ill]). In the pilot study describing this tool, 2% of patients with a score of 0 went on to develop delirium, whereas 64% of patients with a score of 4 went on to develop delirium.

- If trauma has or may have occurred, **immobilize the spine immediately** and then proceed with imaging to identify or exclude fracture or instability. Consultation with additional services (e.g., neurosurgery) may be needed.

TABLE 27-1 Causes of Altered Mental Status

Metabolic derangements/diffuse etiologies

- Hypernatremia/hyponatremia
- Hypercalcemia
- Hyperglycemia/hypoglycemia
- Hyperthyroidism/hypothyroidism
- Acute intermittent porphyria
- Hypertensive encephalopathy/reversible posterior leukoencephalopathy
- Hypoxia/hypercapnia
- Global cerebral ischemia from hypotension

Infections

- Meningitis/encephalitis
- Sepsis
- Systemic infectious with spread to CNS

Drugs/toxins/poisons

- Prescription medications and side effects of medications
- Drugs of abuse
- Withdrawal situations
- Medication side effects
- Inhaled toxins

Inborn errors of metabolism

Nutritional deficiency (i.e., thiamine)

Seizures

- Subclinical seizures
- Postictal state

Head trauma

Vascular

- Ischemic stroke (only certain stroke locations cause altered mental status)
- Hemorrhage

Structural

- Hydrocephalus
- Tumor

Systemic organ failure

- Hepatic failure
- Renal failure

Psychiatric

Autoimmune/inflammatory

- Vasculitis (primary CNS or systemic)
- Encephalitis
- Autoantibody-mediated encephalopathies (e.g., anti-voltage-gated potassium channel

antibodies)

CNS, central nervous system.

Clinical Presentation

- Search for signs of systemic illness associated with coma (e.g., cirrhosis, hemodialysis shunt, rash of meningococcemia) or signs of head trauma (e.g., lacerations, periorbital or mastoid ecchymosis, hemotympanum). The physical and neurologic examination may reveal systemic illness (e.g., pneumonia or elevated temperature) or neurologic signs (meningismus or paralysis) that can help narrow the differential diagnosis.

- **Herniation** occurs when mass lesions or edema cause shifts in brain tissue. The diagnosis of brain herniation **requires immediate recognition and treatment**. If a risk of herniation is present, the patient should be monitored in a neurosurgical/neurologic critical care unit, and frequent "neuro checks" should be performed to evaluate for signs of impending herniation.
  - **Nonspecific signs and symptoms of increased intracranial pressure** include headache, nausea, vomiting, hypertension, bradycardia, papilledema, sixth nerve palsy, transient visual obscurations, and alterations in consciousness.
  - **Uncal herniation** is caused by unilateral supratentorial lesions. The earliest sign is a dilated pupil ipsilateral to the mass, diminished consciousness, and hemiparesis, first contralateral to the mass and later ipsilateral to the mass (Kernohan notch syndrome).
  - **Central herniation** is caused by medial or bilateral supratentorial lesions. Signs include progressive alteration of consciousness, Cheyne-Stokes or normal respirations followed by central hyperventilation, midposition and unreactive pupils, loss of upward gaze, and posturing of the extremities.
  - **Tonsillar herniation** occurs when pressure in the posterior fossa forces the cerebellar tonsils through the foramen magnum, compressing the medulla. Signs include altered level of consciousness and respiratory irregularity or apnea.
- In general, the neurologic assessment should ascertain the patient's ability to focus, sustain, and shift attention appropriately. Due to fluctuations, repeated exams are often necessary.
- **Level of consciousness** can be semiquantitatively assessed and followed by using the Glasgow coma scale (GCS). Scores range from 3 (unresponsive) to 15 (normal).
- **Respiratory rate and pattern**
  - Cheyne-Stokes respirations (rhythmic crescendo-decrescendo hyperapnea alternating with periods of apnea) occur in metabolic coma and supratentorial lesions, as well as in chronic pulmonary disease and congestive heart failure (CHF).
  - Hyperventilation is commonly seen in the setting of metabolic acidosis, hypoxemia, pneumonia, or other pulmonary disease but can also occur with an upper brainstem injury.
  - Apneustic breathing (long pauses after inspiration), cluster breathing (breathing in short bursts), and ataxic breathing (irregular breaths without pattern) are signs of brainstem injury and are commonly associated with impending respiratory arrest.
- **Pupil size and light reactivity**

- Anisocoria (asymmetric pupils) in a patient with altered mental status requires immediate diagnosis (i.e., stat head CT) or exclusion and treatment of possible herniation. Anisocoria may be physiologic or produced by mydriatics (e.g., scopolamine, atropine), and therefore requires well-documented serial examinations.
- Small but reactive pupils are seen in narcotic overdose, metabolic encephalopathy, and pontine lesions.
- Fixed midposition pupils imply midbrain lesions or transtentorial herniation.
- Bilaterally fixed and dilated pupils occur with severe anoxic encephalopathy or drug intoxication (scopolamine, atropine, glutethimide, or methanol).

- **Eye movements**
  - To test the oculocephalic reflex ("doll's eyes" maneuver, assuming no cervical injury is present), the examiner quickly turns the head laterally or vertically (head impulse test). Intact brainstem oculomotor function, in the setting of coma, will result in conjugate eye movements opposite to the direction of head movement.
  - Another means of testing the vestibulo-ocular reflex is via cold caloric testing. This can be used if cervical trauma is suspected or if eye movements are absent with the

    head impulse test described above. Brainstem oculomotor function is intact if there are conjugate eye movements toward the ear lavaged with ice cold water. Vertical gaze can be assessed with simultaneous lavage of both ears (cold water → eyes depress, warm water → eyes elevate).
  - In the absence of a history to suggest a drug-induced cause (e.g., barbiturates, phenytoin, paralytics) or a preexisting disorder such as progressive external ophthalmoplegia, absence of all eye movements indicates a bilateral pontine lesion.
  - Dysconjugate gaze suggests a brainstem lesion.
  - A conjugate gaze preference to one side suggests a unilateral pontine or frontal lobe lesion. Oculocephalic and oculovestibular tests can help localize the lesion in the setting of a concurrent hemiparesis. In pontine lesions, gaze preference is toward the paretic side, and eyes may move toward but do not cross midline. In frontal lobe lesions, gaze preference is away from the paresis, and eye movements are conjugate and move to both sides of midline.
  - Impaired vertical eye movement occurs in midbrain lesions and central herniation. Conjugate depression and impaired elevation suggest a tectal lesion (e.g., pinealoma) or hydrocephalus.
- **Motor responses** also help with localization. Asymmetric motor responses (spontaneous or stimulus induced, including noxious stimuli if necessary) also have localizing value.

Diagnostic Testing

Laboratories

Obtain serum electrolytes, creatinine, glucose, calcium, complete blood count (CBC), and urinalysis. Drug levels should be ordered if appropriate. An accurate medication list and any history to suggest intoxication are critical features of the evaluation. Toxicology screen of blood and urine should be considered.

Imaging

A head CT should be obtained to evaluate for structural abnormalities. Brain MRI can be useful if head CT is nondiagnostic and there is suspicion for an ischemic or parenchymal lesion (especially of the posterior fossa).

Diagnostic Procedures

- Lumbar puncture (LP) should be considered in patients with fever and/or new headache or those with high risk of infection. A funduscopic examination and/or head imaging should be performed prior to performing the LP to assess risk of herniation. Basic cerebrospinal fluid (CSF) studies (e.g., protein, glucose, cell count, Gram stain, and aerobic culture) should be obtained with additional studies depending on the possible etiology.
- Electroencephalography (EEG) can be considered to rule out seizures. Nonconvulsive status epilepticus is a common cause of unexplained encephalopathy in the critically ill population. Interictal abnormalities can be suggestive of specific etiologies (e.g., periodic lateralized epileptiform discharges in herpes simplex virus [HSV] encephalitis, triphasic waves in hepatic or uremic encephalopathy, and β activity or voltage suppression in barbiturate or other sedative intoxications).

TREATMENT

Coma

- Ensure adequate airway and ventilation, administer oxygen as needed, and maintain normal body temperature.

- Establish secure IV access and adequate circulation.
- Neurosurgical consult may need to be obtained for intracranial pressure monitoring and treatment, if applicable.

Delirium

- Repeated attempts should be made to reorient the patient and possibly have a sitter present if necessary.
- A quiet room with close observation is necessary. Patients should have a well-lit environment with familiar objects during the day and dark, quiet (minimize stimulation if possible) environments at night.
- Physical and pharmacologic restraints should be used only as a last resort and with appropriate documentation in the medical record. If restraints are needed, they should be carefully adjusted and checked periodically to prevent excessive constriction.

Medications

- IV thiamine (100 mg), followed by dextrose (50 mL of 50% dextrose in water = 25 g dextrose), should be administered. Thiamine is administered first because dextrose administration in thiamine-deficient patients may precipitate Wernicke encephalopathy.
- IV naloxone (opiate antagonist), 0.01 mg/kg, should be administered if opiate intoxication is suspected (coma, respiratory depression, small reactive pupils). Naloxone may provoke opiate withdrawal syndrome in patients on opioids chronically.
- Flumazenil (benzodiazepine antagonist), 0.2 mg IV, may reverse benzodiazepine intoxication, but its duration of action is short, and additional doses may be needed. Flumazenil should be used with caution in certain patient populations (e.g., epileptics) because it reduces the seizure threshold.
- In delirious patients, sedatives should be avoided if possible. If necessary, low doses of quetiapine (12.5-25.0 mg), lorazepam (1 mg), or chlordiazepoxide (25 mg) can be used. Remember to always consider

comorbidities before administering these medications.

Other Nonpharmacologic Therapies

If herniation is identified or suspected, treatment consists of measures to lower intracranial pressure while surgically treatable etiologies are identified or excluded. All of the listed measures are only **temporizing methods**. Consultation with neurosurgery should be performed concurrently.

- Elevate the head of the bed to at least 30 degrees.
- Endotracheal intubation is usually performed to enable hyperventilation to a partial pressure of carbon dioxide (PCO_2) of 25-30 mm Hg. This reduces intracranial pressure within minutes by cerebral vasoconstriction. Bag-mask ventilation can be performed if manipulation of the neck is precluded by possible or established spinal instability. Reduction of PCO2 below 25 mm Hg is not recommended because it may reduce cerebral blood flow.
- Administration of IV mannitol (1-2 g/kg over 10-20 minutes) osmotically reduces free water in the brain via elimination by the kidneys and does not require a central line for administration. This effect peaks at 90 minutes. Remember that, given its potent diuretic effect, mannitol can precipitate renal failure if volume is not adequately replaced. Hypertonic saline (23.4% saline) is an alternative option but also has side effects and requires central venous access.
- Dexamethasone, 10 mg IV, followed by 4 mg IV q6h, reduces the edema surrounding a tumor or an abscess but is not indicated for diffuse cerebral edema or the mass effect associated with malignant cerebral infarcts.

- Coagulopathy should be corrected if intracranial hemorrhage is diagnosed and before surgical treatment or invasive procedures (e.g., LP) are performed. Each patient's circumstances should be carefully assessed before therapeutic anticoagulation is reversed.

Surgical Management

Surgical evacuation of epidural, subdural, or intraparenchymal (e.g., cerebellar) hemorrhage and shunting for acute hydrocephalus should be considered in the appropriate clinical circumstances. However, some structural lesions are not amenable to surgical treatment.

SPECIAL CONSIDERATIONS

- **Brain death** occurs from irreversible brain injury sufficient to permanently eliminate all cortical and brainstem functions. Because the vital centers in the brainstem sustain cardiovascular and respiratory functions, brain death is incompatible with survival despite mechanical ventilation and cardiovascular and nutritional supportive measures. Brain death is distinguished from persistent vegetative state (PVS) in which the absence of higher cortical function is accompanied by intact brainstem function. Patients in a PVS are unable to think, speak, understand, or meaningfully respond to visual, verbal, or auditory stimuli, yet with nutritional and supportive care, their cardiovascular and respiratory functions can sustain viability for many years. Research using functional MRI (fMRI) has broadened our understanding of the marked variability in function present across PVS patients and even demonstrated instances of misdiagnosis. However, the role of fMRI in the assessment of comatose patients remains to be determined.
- Brain death criteria vary somewhat by institution. Refer to your institution's policy for details.
- **Alcohol withdrawal** typically occurs when illness or hospitalization interrupts continued alcohol intake.
  - Tremulousness, irritability, anorexia, and nausea characterize minor alcohol withdrawal. Symptoms

usually appear within a few hours after reduction or cessation of alcohol consumption and resolve within 48 hours. Treatment includes a well-lit room, reassurance, and the presence of family or friends. **Thiamine**, 100 mg IM/IV, followed by 100 mg PO daily; multivitamins containing **folic acid**; and a balanced diet as tolerated should be administered. Serial evaluation for signs of major alcohol withdrawal is essential.

- Alcohol withdrawal seizures, typically one or a few brief generalized convulsions, occur 12-48 hours after cessation of ethanol intake. **Antiepileptic drugs (AEDs) are not indicated for typical alcohol withdrawal seizures.** Other causes for seizures (see Seizures section) must be excluded. If hypoglycemia is present, thiamine should be administered before glucose.
- Severe withdrawal or delirium tremens consists of tremulousness, hallucinations, agitation, confusion, disorientation, and autonomic hyperactivity (fever, tachycardia, diaphoresis), typically occurring 72-96 hours after cessation of drinking. Symptoms generally resolve within 3-5 days. Delirium tremens complicates 5-10% of cases of alcohol withdrawal, with mortality up to 15%. Other causes of delirium must be considered in the differential diagnosis (see Table 27-1). One should administer supportive management as follows:
  - Chlordiazepoxide is an effective sedative for delirium tremens, 100 mg IV or PO q2-6h as needed (maximum dose, 500 mg in the first 24 hours). One-half the initial 24-hour dose can be administered over the next 24 hours; the dosage can be reduced by 25-50 mg/d each day thereafter. Longer lasting benzodiazepines facilitate smoother tapering, but shorter acting agents (i.e., lorazepam, 1-2 mg

    PO or IV q6-8h as needed) may be desirable in older patients and those with reduced drug clearance. In patients with severe hepatic failure, oxazepam (15-30 mg PO, q6-8h as needed), which is excreted by the kidney, can be used instead of chlordiazepoxide.
  - Maintenance of fluid and electrolyte balance is important. Alcoholic patients are susceptible to hypomagnesemia, hypokalemia, hypoglycemia, and fluid losses, which may be considerable due to fever, diaphoresis, and vomiting.

Alzheimer Disease

GENERAL PRINCIPLES

Alzheimer disease (AD) is the most common neurodegenerative disorder in older individuals (>60 years old), typically characterized by memory problems and inability to independently perform activities of daily living.

Epidemiology

- Prevalence is <1% before age 65, 5-10% at age 65, and approximately 45% by age 85. Approximately five millions Americans have AD.
- Inherited forms of AD manifest typically before age 65 years and are associated with mutations in amyloid precursor protein (*APP*) gene on chromosome 21, presenilin-1 gene on chromosome 14, and presenilin-2 gene on chromosome 1.
- The greatest risk factor for late-onset/sporadic AD is the presence of the apolipoprotein ε4 variant.
- Lifetime risk doubles if a sibling or parent is diagnosed with AD.
- It is common for AD patients to present at late stages of the disease after an unrelated medical illness

unmasks signs and symptoms of the disease that had previously gone unrecognized by the family.

- Pseudodementia (cognitive impairment related to comorbid depression) should be considered in the appropriate clinical context.

Pathophysiology

Pathologic diagnosis requires presence of both neurofibrillary tangles due to tau and neuritic plaques composed of amyloid.

DIAGNOSIS

Clinical Presentation

- Memory impairment is required for diagnosis of AD.
- Episodic memory for newly acquired information is impaired, whereas memory for more remote events is not affected.
- Declarative memory for facts and events is affected, whereas procedural memory and motor learning are spared at earlier stages of the disease.
- With progression of disease, language, visuospatial skills, abstract reasoning, and executive function deteriorate. Some patients will also develop apraxia, alexia, and delusions.

Differential Diagnosis

See Table 27-2.

Diagnostic Testing

Progression of disease can be assessed by the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Clinical Dementia Rating Scale (CDR).

TABLE 27-2 Differential Diagnosis of Alzheimer Dementia

Frontotemporal dementia	
	Changes in personality, behavior, and executive functioning
Vascular dementia	
	Stepwise course due to repeated strokes or stroke-like events
Dementia with Lewy bodies	
	Visual hallucinations, dream enactment behavior (i.e., REM behavior disorder), cognitive fluctuations, parkinsonism, sensitivity to neuroleptics

Normal pressure hydrocephalus
Triad of dementia, urinary incontinence, and gait instability (“wacky, wet, and wobbly”)
Vitamin B_{12} deficiency
Neurosyphilis
Thyroid dysfunction
HIV
Creutzfeldt-Jakob disease
Autoimmune encephalopathies (e.g., paraneoplastic syndromes)

REM, rapid eye movement.

Laboratories

- Definitive diagnosis of AD requires histopathologic confirmation (i.e., autopsy).
- Reversible causes of dementia such as B_{12} deficiency, neurosyphilis, and thyroid abnormalities should be ruled out.

Imaging

- Brain MRI can suggest potential alternative diagnoses.
- MRI may show diffuse atrophy with hippocampal atrophy that is seen with AD.
- [^{18}F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) or perfusion singlephoton emission computed tomography (SPECT) may demonstrate hypometabolism and hypoperfusion, respectively, within the parietotemporal cortex.
- Amyloid PET tracers (florbetapir) can measure amyloid deposition in the brain and are approved for clinical use but are quite expensive. New PET tracers for tau are being actively developed.

Diagnostic Procedures

- Neuropsychological testing can establish a baseline cognitive status. This testing can sometimes differentiate dementia from depression (i.e., pseudodementia).
- Both structural MRI and PET imaging may assist in early diagnosis.
- CSF measures of reduced AB_{42} and increased tau can be obtained and may assist in the diagnosis.

TREATMENT

- Cholinesterase inhibitors including donepezil, rivastigmine, and galantamine can be considered for early

AD.

- Memantine, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, can be considered for moderate to severe dementia.
- A combination of the above medications is sometimes used in more advanced AD patients. Additional therapies (including anti-amyloid agents) are being investigated.

Seizures

GENERAL PRINCIPLES

Definition

- Seizure: stereotyped spells caused by abnormal electrical brain activity. A more complex definition is uncontrolled excessive electrical discharges in the brain that may produce a sudden change in brain function causing physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms.
- Epilepsy is defined as a state of recurrent seizures.
- Status epilepticus is defined by >30 minutes of continuous seizure activity or recurrent seizures without full recovery between episodes. However, in practice, a seizure lasting >5 minutes in adults (>10 minutes in children) should be treated as status epilepticus. Generalized convulsive status epilepticus (GCSE) is a medical emergency.
- Nonconvulsive status epilepticus (NCSE) is defined by electrographic seizures with clinically absent or subtle motor activity and impairment or loss of consciousness. NCSE should be treated promptly to avoid irreversible cerebral injury.
- An aura is a simple partial seizure manifesting as sensory, autonomic, or psychic symptoms.
- A prodrome is a sensation or feeling that a seizure will soon occur. Distinguishing a prodrome from an aura can be clinically challenging.

Classification

- Partial seizures begin focally. Provided are both the classic nomenclature and, in parentheses, the 2010 updated nomenclature from the International League Against Epilepsy.
  - **Simple partial (focal seizure without impairment of consciousness):** Consciousness is not impaired. The symptoms can be motor (hand jerking), sensory (focal tingling, visual, auditory), autonomic (sensation of epigastric rising), or psychic (déjà vu).
  - **Complex partial (focal seizure with impairment of consciousness, or "dyscognitive" focal seizures):** Consciousness is impaired. The symptoms vary based on whether they involve the temporal (automatisms such as lip smacking or picking at clothes, staring, behavior arrest), frontal (hypermotor behaviors, bicycling, pelvic thrusting, and automatisms), or occipital lobes (unformed images, visual hallucinations). Frontal seizures are often misdiagnosed as nonepileptic seizures (i.e., pseudoseizures) due to their often complex, sometimes bizarre semiology and the frequent absence of electrographic seizure activity on standard EEG.
- Generalized seizures originate from bilateral hemispheres, and by definition, consciousness is lost.

- May begin as generalized or as partial seizures with secondary generalization.
- Include tonic, clonic, tonic-clonic, atonic, myoclonic, and absence.

Epidemiology

- Epilepsy is estimated to affect approximately 70 million people worldwide with the prevalence being twice as high in low-income countries relative to high-income countries.
- The median worldwide incidence of epilepsy is approximately 50 per 100,000 per year (*Neurology 2011;77(10):1005*).

Etiology

Etiologies for seizures include those listed in Table 27-3. For patients with a known seizure disorder presenting with an increase in seizure frequency, the most common causes are anticonvulsive medication noncompliance, subtherapeutic anticonvulsant levels, or infection.

TABLE 27-3 Etiologies of Seizures

- CNS infections
- Fever
- Hypoxic brain injury
- Stroke (ischemic or hemorrhagic)
- Cerebral venous thrombosis
- Vascular malformations
- Tumors/carcinomatous meningitis
- Head injury
- Eclampsia
- Hypertensive encephalopathy/reversible posterior leukoencephalopathy
- Hyperthyroidism
- Congenital brain malformations
- Hereditary (Sturge-Weber, tuberous sclerosis, Dravet syndrome, and other channelopathies)
- Toxic metabolic (porphyria, uremia, liver failure)
- Drug withdrawal (alcohol, barbiturates, benzodiazepine, AEDs)
- Drug intoxication (TCAs, bupropion, clozapine, tramadol, cocaine, amphetamine)
- Electrolyte abnormalities/metabolic
  - Hyponatremia or hypernatremia
  - Hypocalcemia
  - Hypomagnesemia
  - Hypophosphatemia
  - Hypoglycemia/hyperglycemia

AEDs, antiepileptic drugs; CNS, central nervous system; TCAs, tricyclic antidepressants.

DIAGNOSIS

Clinical Presentation

History

- Query for family history of epilepsy, developmental delay, trauma, medical historical information including preexisting medical conditions, current and recently discontinued medications, drug allergies, recreational drug use, and possible precipitating events.
- Ask the patient about any prodrome/aura. An eyewitness account of the event is critical, and a video of the event can be extremely helpful. Inquire about the temporal features (i.e., seizures are typically acute onset with a rapid crescendo), **incontinence**, **tongue biting**, and how the patient behaved after the event ended (e.g., confused?, somnolent? if so, for how long?).

Physical Examination

- Vital signs and blood sugar should be obtained immediately on all patients. As discussed previously, empiric thiamine should be given when treating hypoglycemia. Ictal and/or postictal fever can occur.
- Look for nuchal rigidity, rash, asterixis, or signs of trauma.
- Convulsive seizures are usually easily identified.
- Features of the seizure can aid in identifying the ictal focus (e.g., complex automatisms in frontal lobe seizures, lip smacking and postictal nose wiping in temporal lobe seizures, ictal laughter in hypothalamic seizures).
- Carefully observe for subtle signs of nonconvulsive seizures, such as automatisms, facial or extremity twitching, eye deviation, and periods of relatively preserved mental status alternating with periods of impaired consciousness.

- Patients may present during the postictal period, defined as the time between the end of the seizure and the return to baseline mental status. During this time, patients may act confused, obtunded, and have amnesia for events since the seizure. This period can typically last from minutes to hours or, rarely, days in the elderly and those with prior CNS injury.
- Postictal paresis (also called Todd paralysis) is a transient neurologic deficit that lasts for hours or, rarely, days after an epileptic seizure.

Differential Diagnosis

Alternate diagnoses that may mimic seizures include:

- Syncope, especially convulsive syncope in which seizure-like motor activity is observed. The Calgary Seizure Syncope score is a useful and reliable clinical tool in distinguishing these two entities (*J Am Coll Cardiol 2002;40(1):142*).
- Nonepileptic seizures (“pseudoseizures”) (see the following text).
- Transient ischemic attack.
- Complicated migraine.
- Toxic-metabolic encephalopathy.
- Tremors, dyskinesias (episodic movement disorders).
- Nonepileptic myoclonus following a hypoxic event.
- Sleep disorders.
- Rigors.

Diagnostic Testing

Laboratories

Initial laboratory studies should include blood glucose, electrolytes (sodium, calcium, magnesium, and phosphorus), CBC, urinalysis, urine drug screen, and AED levels if indicated.

Imaging

Neuroimaging is usually indicated to identify structural etiologies.

- Start with a head CT in the acute setting. The administration of contrast can assist in diagnosis of possible tumors.
- Brain MRI with and without contrast, protocolled to evaluate for an ictal focus, is almost always indicated in the evaluation of new-onset seizures and is certainly indicated in patients with recurrent unprovoked seizures.

Diagnostic Procedures

- LP should be done if there is concern for CNS infection. Send for routine CSF studies as well as HSV polymerase chain reaction (HSV-PCR). Save extra CSF for any additional testing, if later indicated.
- EEG is not required for initial diagnosis and management of GCSE. If mental status is not improving as expected after convulsive seizures stop, EEG may be necessary to exclude conversion to NCSE. Unless the patient is known to typically have an extraordinarily prolonged postictal period, NCSE should be considered in any patient who fails to return to baseline within an hour of a seizure. Approximately 50% of patients who present with GCSE will go on to develop NCSE within 24 hours of cessation of clinical seizure activity.
- Routine EEG is indicated for all new-onset seizures (*Neurology 2007;69(18):1772*).
- Video EEG is the gold standard test for the evaluation of suspected nonepileptic seizures. A significant (30-50% in some studies) number of patients with nonepileptic seizures ("pseudoseizures") will also have epileptic seizures.

TREATMENT

- **Initiation of AED therapy is usually not indicated after a single unprovoked seizure** because about two-thirds of patients who had a single seizure will not have seizure recurrence (*N Engl J Med 1998;338(7):429*). However, patients with a single unprovoked seizure and either an abnormal EEG or evidence of an ictal focus on head CT or brain MRI warrant initiation of AED therapy given a much higher likelihood of seizure recurrence.
- In general, AEDs should not be started in patients with provoked seizures.
- A diagnosis of epilepsy is made after two or more unprovoked seizures. AED treatment is generally started after the second seizure because the patient has a substantially increased risk (approximately 75%) for repeated seizures after two events.
- Treatment of status epilepticus must be prompt because efficacy of treatment decreases with increased seizure duration (*Semin Neurol 2008;28(3):342*) and GCSE carries an all-cause mortality of 30%. (See Figure 27-1 for treatment of status epilepticus.) Within 5-30 minutes of GCSE onset, the body's homeostatic mechanisms begin to fail and patients' risk of permanent brain injury increases, as does risk

of systemic complications including hyperthermia, pulmonary embolism, cardiovascular and respiratory insufficiency, and other life-threatening complications. Prolonged NCSE will also result in brain injury but on a timescale of days as opposed to minutes (see Figure 27-2).

Medications

- The selection of a specific AED for a patient must be individualized according to the drug effectiveness for seizure type(s), potential adverse effects of the drug, interactions with other possible medications, cost, and mechanism of drug action (*Epilepsia 2006;47:1094*).
- About half of all patients with a new diagnosis of epilepsy will be seizure free with the first AED prescribed (*Epilepsia 2001;42:1255*).
- Treatment should be started with a single drug that can be titrated until adequate control or until side effects are experienced.
- **Combination therapy (polytherapy) should be attempted only after at least two adequate sequential trials of single agents have failed.** Failure to control epilepsy with adequate trials of two drugs meets criteria for treatment-resistant epilepsy, and a referral for presurgical evaluation should be considered (*Epilepsia 2010;51(6):1069*).

Lifestyle Modifications

- Patients should not start other medications (e.g., over-the-counter medications or herbal remedies) without contacting their physician because there may be drug interactions.
- Patients should keep a seizure calendar to identify possible seizure triggers. Screen patients for poor sleep hygiene. Females may have catamenial (perimenstrual) seizures.
- Women should ideally inform their physicians well in advance of any plans for pregnancy or at the very least immediately upon finding out they are pregnant given the teratogenicity associated with certain AEDs, the increased risk of teratogenicity with polytherapy versus monotherapy, and the potential need for medication adjustment during pregnancy.
- Patients should reduce alcohol intake because heavy consumption (three or more drinks per day) is associated with an increased risk of seizures.

REFERRAL

Neurologic consultation may be helpful for managing status epilepticus and for evaluation and management of new-onset seizures.

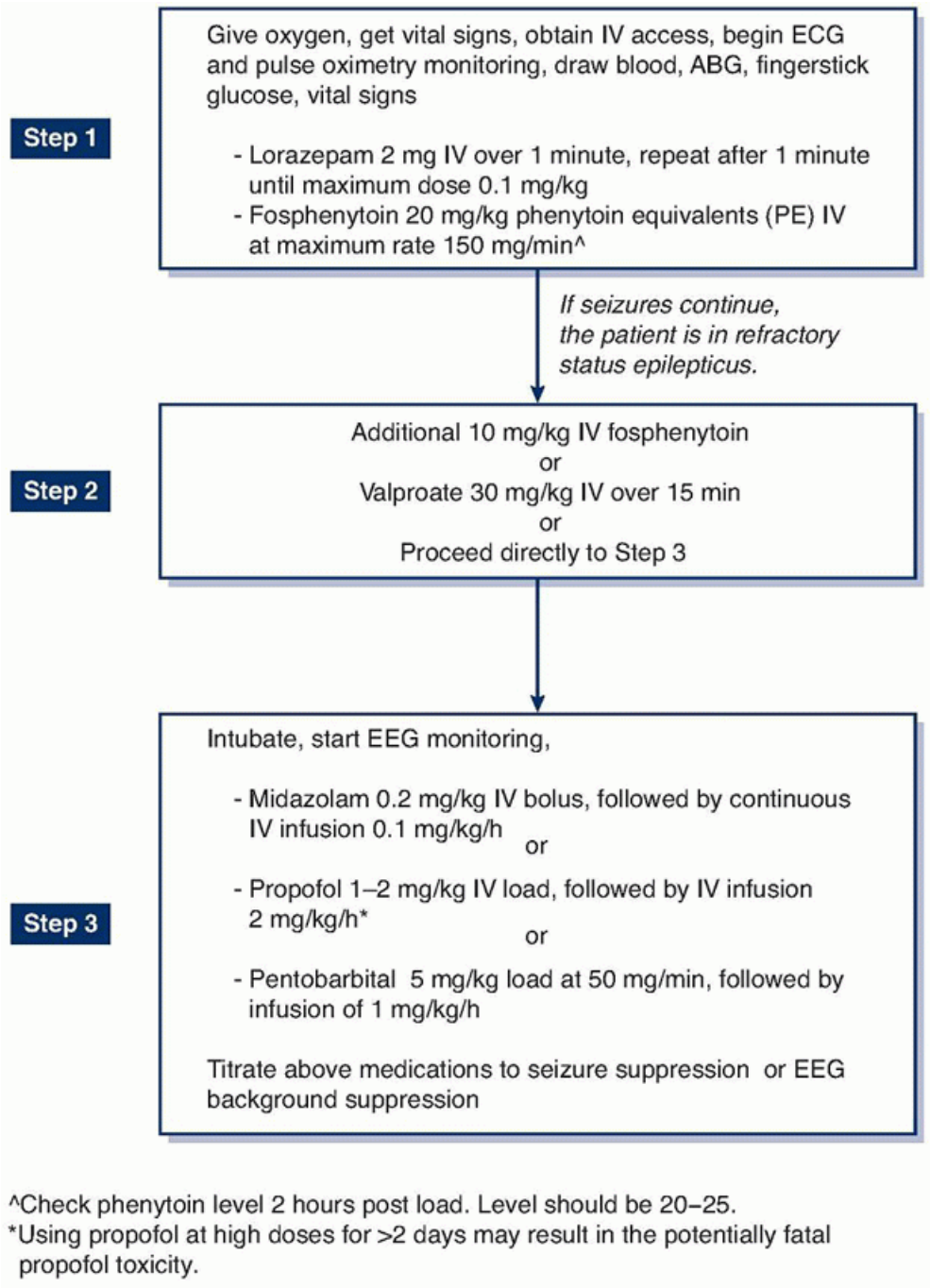


Figure 27-1. Treatment of status epilepticus. ABG, arterial blood gas; EEG, electroencephalogram. (Modified from Arif H, Hirsch LJ. Treatment of status epilepticus. *Semin Neurol* 2008;28(3):342.)

PATIENT EDUCATION

Patients with epilepsy, especially those left untreated, have a small risk of sudden death in epilepsy (*Lancet Neurol 2011;10(11):961*). Patients with epilepsy should not swim unsupervised, bathe in a bathtub of standing water, use motorized tools, or be in position to fall from heights during a seizure (i.e., patients should avoid situations in which they could harm themselves or others if they were to have a seizure). Driver licensing requirements for

patients with epilepsy vary from state to state. A complete listing of state laws can be found at *https://www.epilepsy.com/driving-laws*.

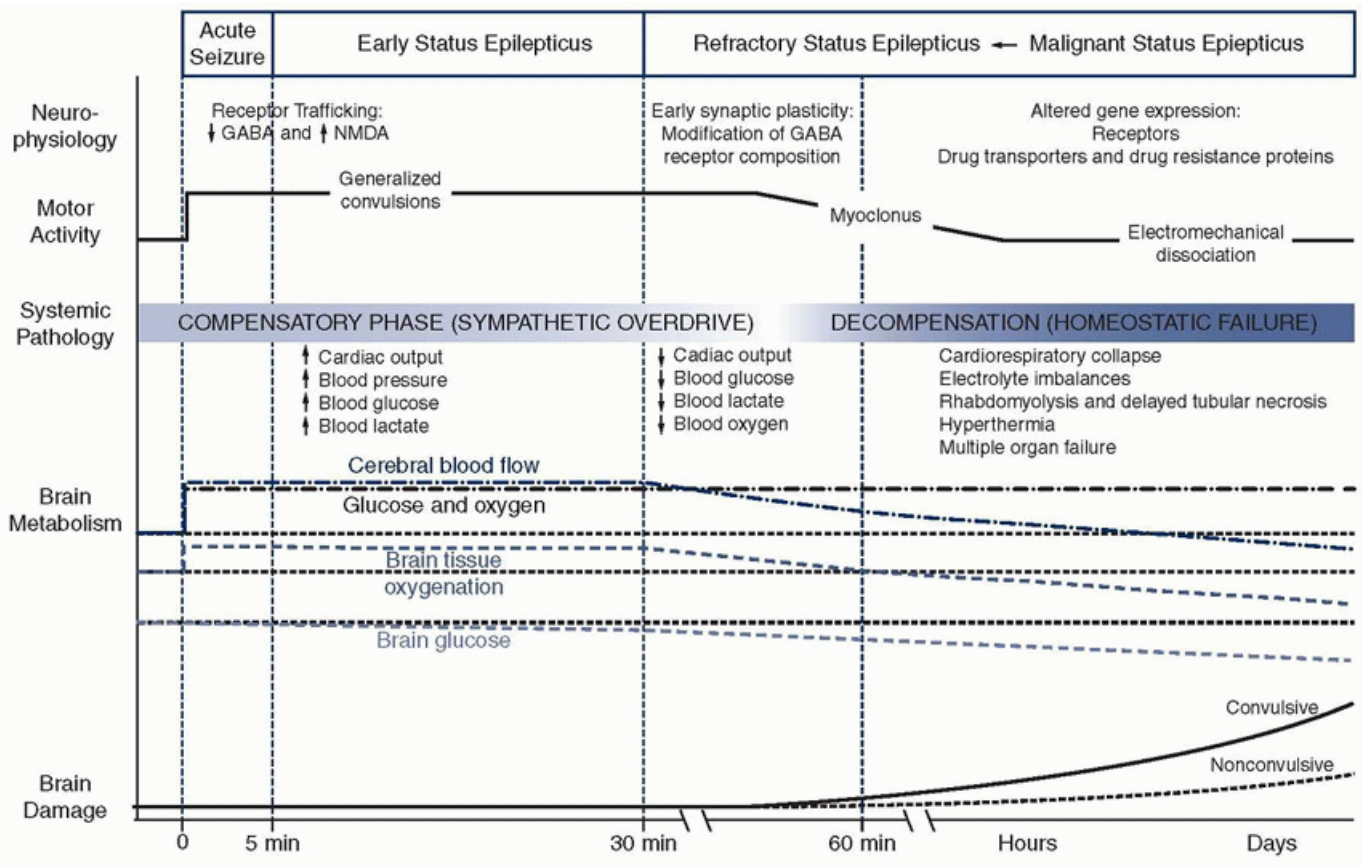


Figure 27-2. Brain and systemic pathology in prolonged convulsive and nonconvulsive status epilepticus. (From Hirsch LJ, Gaspard N. Status epilepticus. *Continuum* 2013;19(3):767.)

MONITORING/FOLLOW-UP

- Regular follow-up visits should be scheduled to check drug concentrations, blood counts, and hepatic and renal function. Side effects after initiating AED should be monitored.
- Again, correctable causes for seizures (e.g., hyponatremia, drug toxicity, alcohol withdrawal) do not require long-term anticonvulsant therapy.

Multiple Sclerosis

GENERAL PRINCIPLES

Definition

- Multiple sclerosis (MS) is a chronic, progressive, immune-mediated disorder of the CNS, initially characterized by inflammatory demyelination followed later in its course by neurodegeneration.
- Although the disorder is presumed to be autoimmune in nature, the antigen(s) driving the immune response remains unknown.

Classification

- Forms of MS include the most common form, relapsing-remitting MS (RRMS), associated with episodic neurologic dysfunction followed by a complete or partial recovery in between episodes. The majority of patients are initially diagnosed with RRMS.

- A less common variant is primary progressive MS (PPMS), a form of the disease characterized by progressive neurologic dysfunction from onset without relapses or remissions.
- Secondary progressive MS (SPMS) is also characterized by a course of progressive neurologic dysfunction but follows an initial relapsing remitting course.
- The least common form is one of a progressive relapsing course in which patients have a steady, progressive decline from the time of onset with superimposed exacerbations (i.e., worsening).
- Classification is important in that progressive forms of the disease, in general, do not respond to the disease-modifying therapies (DMTs) effective in RRMS.

Epidemiology

- Approximately 400,000 patients carry a diagnosis of MS in the United States.
- The worldwide prevalence is estimated at over 1.25 million and growing.

Etiology

The exact etiology of MS remains unknown. The pathophysiologic pattern of MS is characterized by inflammatory cell infiltration, demyelination, axonal damage, and gliosis culminating in neurodegeneration.

DIAGNOSIS

Clinical Presentation

- At disease onset, symptoms are variable and can include visual dysfunction (i.e., optic neuritis), sensory abnormalities, motor dysfunction, ataxia, fatigue, and bowel/bladder dysfunction.

- For the majority of patients, remission occurs after the initial episode, but repeated flares lead to RRMS.
- Eventually, patients can progress to SPMS (see above).

Differential Diagnosis

- The differential diagnosis of MS is too extensive to be covered here but is reviewed in great detail by Sand and Lublin (*Continuum 2013;19(4):922*).
- An important differential diagnosis to mention is neuromyelitis optica (NMO), another immune-mediated demyelinating disorder of the CNS. NMO, in the majority of cases, is associated with antibodies against the aquaporin-4 antigen.

Diagnostic Testing

- A cornerstone of diagnostic testing and monitoring/follow-up is MRI of the brain and spinal cord (in many cases).
- CSF analysis is second to MRI in its value as a diagnostic marker of MS. Ninety-five percent of patients with MS will have oligoclonal bands specific to the CSF (on comparison to serum).

TREATMENT

- Acute relapses are often treated with corticosteroids.
- There is no cure for MS. DMTs remain the cornerstone of treatment, but no treatment definitively halts

the disease.

- Approved injectable DMTs for the treatment of RRMS include interferon-β (IFN-β) preparations (Betaseron, Extavia, Avonex, and Rebif), glatiramer acetate (Copaxone), mitoxantrone (Ralenova), and natalizumab (Tysabri).
- Currently approved oral agents include fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera).
- There has been a substantial growth in the number of DMTs available to treat MS in recent years. See Table 27-4 for more details.

REFERRAL

In general, all patients with suspected MS or MS should be referred to a neurologist for formal diagnostic testing and initiation of DMT if indicated.

Cerebrovascular Disease

GENERAL PRINCIPLES

- Stroke is a medical emergency that requires rapid diagnosis and treatment. Remember that "TIME IS BRAIN."
- The hallmark of stroke is the abrupt interruption of cerebral blood flow to a specific brain region, resulting in neurologic deficits.
- Fluctuation of functional deficits after stroke onset or a brief deficit known as transient ischemic attack (TIA) suggests tissue at risk for infarction that may be rescued by reestablishing perfusion.

Epidemiology

More than 750,000 strokes occur per year in the United States (one stroke every 40 seconds in the US population), and it is the fourth leading cause of death in the United States (one death every 4 minutes).

TABLE 27-4 Disease-Modifying Therapies Approved for Use in Relapsing-Remitting Multiple Sclerosis

Drug	Mechanism of Action	Efficacy	Side Effects
Injectables			
Interferon-β preparations—IM or SC (Betaseron, Extavia, Avonex, and Rebif)	Modulates B- and T-cell function Reverses blood-brain barrier disruption Modulation of cytokine expression	30% reduction in relapses Reduction in disability Reduction in MRI lesions	Flu-like symptoms Injection site reactions Transaminitis
Glatiramer	Stimulates regulatory T cells	30%	Injection site

acetate (Copaxone)—SC	Neuroprotection and repair (?)	reduction in relapses Reduction in disability Reduction in MRI lesions	reactions
Natalizumab (Tysabri)—IV	Humanized monoclonal antibody that blocks the interaction of α4β1-integrin on leukocytes with vascular cell adhesion molecules to prevent migration of leukocytes from the blood to the CNS	68% reduction in relapses Reduction in disability Reduction in MRI lesions by 92% relative to placebo	Infusion reactions including anaphylaxis Progressive multifocal leukoencephalopathy
Alemtuzumab (Lemtrada)—IV	Humanized monoclonal antibody against CD52 Depletes circulating lymphocytes and monocytes	50% reduction in relapses relative to interferon-β Reduction in MRI lesions relative to interferon-β	Infusion reactions Infections (URI, UTI, oral herpes) Secondary autoimmune disorders
Orals			
Fingolimod (Gilenya)	Sphingosine-1-phosphate receptor modulator Inhibits egress of lymphocytes from lymph nodes toward CNS	Reduces annual number of relapses and MRI lesions Reduces the risk of disability progression	First-dose bradycardia Skin malignancies Herpes infection Cardiac arrhythmia Macular edema Lymphopenia
Teriflunomide (Aubagio)	Downregulation of T- and B-cell proliferation via de novo synthesis of pyrimidines (drug derived directly from leflunomide)	Reduces annual number of relapses and MRI	Lymphopenia UTIs Elevated liver enzymes Teratogenicity

		lesions Reduces the risk of disability progression	(washout necessary)
Dimethyl fumarate (Tecfidera)	Shifts dendritic cell differentiation Suppresses inflammatory cytokine production	Reduces annual number of relapses and MRI lesions Reduces the risk of disability progression	Lymphopenia Abdominal pain Diarrhea

CNS, central nervous system; URI, upper respiratory tract infection; UTI, urinary tract infection.

Etiology

- **Ischemic stroke** can be subclassified into atherothrombotic, embolic, hypoperfusion, or hypercoagulable state (the latter being relatively rare).
  - **Atherothrombosis** results from reduced flow within an artery or embolism of thrombus into the distal segment of an artery.
    - Atherosclerosis is the most common etiology of thrombus formation in large vessels.
    - Less common etiologies include dissection, fibromuscular dysplasia, Moyamoya, and giant cell arteritis.
    - Lipohyalinosis, usually due to hypertension, is the most common etiology of small-vessel disease.
  - **Cardioembolic** strokes account for about 20% of all ischemic strokes. High-risk cardiac sources include atrial fibrillation, sustained atrial flutter, rheumatic valve disease, atrial or ventricular thrombus, dilated cardiomyopathy, prosthetic valve, bacterial endocarditis, nonbacterial endocarditis (antiphospholipid antibody syndrome, marantic endocarditis, Libman-Sachs endocarditis), sick sinus syndrome, and coronary artery bypass graft (CABG) surgery.
  - **Hypoperfusion** occurs due to general circulatory problems and often results in bilateral symptoms. Infarction commonly occurs in border zones between large vessels, resulting in watershed infarcts.
  - Hypercoagulable states may predispose to arterial thrombosis. These include sickle cell disease, polycythemia vera, essential thrombocythemia, thrombotic thrombocytopenic purpura (TTP), antiphospholipid antibody syndrome, hyperhomocysteinemia, etc.
  - Factor V Leiden, protein C and S deficiency, and antithrombin (AT)-III deficiency typically result in venous, not arterial, infarcts.
- **Hemorrhagic stroke** occurs in about 20% of all cases.
  - The location of an **intraparenchymal hemorrhage (IPH)** may suggest its etiology.

- Hemorrhage in basal ganglia, thalamus, or pons is often due to chronic systemic hypertension.

- Amyloid angiopathy typically causes lobar hemorrhages and is a common etiology in the elderly.
- Head trauma, anticoagulants, drugs (cocaine or amphetamines), arteriovenous malformation (AVM), tumor, blood dyscrasia, hemorrhagic conversion of an ischemic stroke, and vasculitis are other possible hemorrhagic stroke etiologies.

- **Aneurysmal subarachnoid hemorrhage** (for this section, SAH will refer to aneurysmal subarachnoid hemorrhage unless designated otherwise) is caused by the rupture of an arterial aneurysm resulting in bleeding into the subarachnoid space (which contains CSF). Hypertension, cigarette smoking, genetic factors, and septic emboli (resulting in mycotic aneurysms) can all contribute to aneurysm formation.

- **Cerebral venous sinus thrombosis** is the occlusion of a venous sinus(es) by a thrombus. It occurs in hypercoagulable states such as late pregnancy or postpartum, cancer, and thrombophilias, as well as with trauma and adjacent inflammation/infection. It may manifest with ischemic infarcts and/or hemorrhage.

Risk Factors

Major significant risk factors for ischemic stroke include hypertension, TIA, prior stroke, carotid stenosis, diabetes mellitus, dyslipidemia, heart failure, cigarette smoking, alcohol consumption, oral contraceptive use, obesity, genetics, and age.

DIAGNOSIS

Clinical Presentation

History

- Time of onset is critical if thrombolytic therapy is to be administered. Time of onset is when the patient was last seen normal and **not** when the patient was found with their deficit.
- Onset of symptoms is typically sudden. Ask about progression or fluctuation of symptoms and when the patient was **last normal**.
- Prior TIA symptoms (e.g., transient monocular loss of vision, aphasia, dysarthria, paresis, or sensory disturbance) suggest atherosclerotic vascular disease, the most common cause for stroke.
- Inquire about cardiac arrhythmias and atherosclerotic risk factors.
- A history of neck trauma or recent chiropractic maneuvers warrants evaluation for arterial dissection.
- SAH commonly presents with sudden onset of a severe headache (i.e., the “worst headache of my life”). Lethargy or coma, fever, vomiting, seizures, and low back pain may also be present.
- IPH presents with neurologic deficits accompanied by headache, vomiting, and possibly lethargy.
- Cerebral venous sinus thrombosis (CVST) often presents with signs and symptoms of elevated intracranial pressure, such as a positional headache with diurnal variability (waking from sleep, worse in the morning), bilateral sixth nerve palsies, blurred vision (typically peripheral with sparing of central vision initially), and papilledema.

Physical Examination

- A careful neurologic examination can reliably establish the anatomic location of a stroke in most cases.
- In general, carotid artery distribution (anterior circulation) strokes produce combinations of functional deficits (hemiparesis, hemianopsia, cortical sensory loss, often with aphasias or agnosias) contralateral

to the affected hemisphere.

- Vertebrobasilar strokes (posterior circulation) produce unilateral or bilateral motor/sensory deficits, usually accompanied by cranial nerve and brainstem signs (vertigo, diplopia, ataxia).
- Horner syndrome (ptosis, miosis, anhidrosis) contralateral to an acute hemiparesis suggests carotid dissection. A Horner syndrome with nystagmus and ipsilateral loss of facial pain and temperature sensation with contralateral loss of body pain and temperature sensation is diagnostic of a lateral medullary stroke (posterior inferior cerebellar artery [PICA]) infarct (i.e., Wallenberg syndrome).
- General physical exam should be focused on possible etiologic factors. Examine for abnormal pulses, arrhythmias, murmurs, carotid bruits, and embolic phenomena.

Differential Diagnosis

Mimics of stroke include postseizure paralysis (Todd paralysis), migraine with neurologic deficit (i.e., complicated migraine), and hypoglycemia or hyperglycemia.

Diagnostic Testing

Laboratories

- In the acute setting (e.g., acute evaluation for thrombolytic therapy), these should include CBC with platelets, prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and blood glucose.
- The following are indicated but not emergent: basic metabolic panel, troponin, lipid profile, and hemoglobin A1C. Tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and blood cultures (if suspect endocarditis), rapid plasma reagin, antinuclear antibody, anticardiolipin antibody, drug toxicology screen, and HIV are not part of a “standard screen” but may be indicated in certain clinical contexts.

Electrocardiography

ECG should be done to look for atrial fibrillation or ischemic changes.

Imaging

- **Noncontrast head CT** scan should be obtained acutely to rapidly differentiate hemorrhagic from ischemic strokes. It can identify acute hemorrhages in most cases. It is insensitive for acute ischemic strokes. It is often the rate-limiting step in making decisions on thrombolytic therapy. Head CT scan is diagnostic of SAH in 90% of SAH patients in the first 24 hours.
- At centers with the necessary infrastructure in place, emergent vascular imaging (typically CT angiography) is now performed in all patients presenting with suspected proximal intracranial arterial occlusion in order to screen for lesions amenable to endovascular therapy.
- **MRI** scan is the most sensitive imaging study for stroke diagnosis. Diffusion-weighted images detect stroke the earliest. If a diagnosis of stroke is clear from clinical exam, MRI is not always necessary because it is unlikely to affect management in a great majority of cases.
- Magnetic resonance angiography (MRA) and venograms are useful noninvasive tests to evaluate large arteries and veins, respectively. MRA of the neck with contrast can serve as a screen for carotid stenosis.
- **Carotid Doppler** studies enable noninvasive estimation of carotid stenosis and should be done for anterior circulation strokes unless some form of angiography has already been performed for another

indication.

- **Two-dimensional transthoracic echocardiography** is helpful to demonstrate intracardiac thrombi, valve vegetations, valvular stenosis or insufficiency, and right-to-left shunt (bubble study). In some patients, transesophageal echocardiography may be necessary to evaluate the left atrium for thrombi.

Diagnostic Procedures

- **Cerebral angiography** is the definitive study for vascular malformations but may miss small aneurysms. Some surgeons prefer having this procedure performed before proceeding with carotid endarterectomy (CEA).
- If suspicion for SAH is high and head CT is negative, an **LP** should be performed.
  - Tubes 1 and 4 should be sent for cell count. If the number of red blood cells (RBCs) decreases dramatically from tube 1 to tube 4, a traumatic LP is more likely than SAH.
  - Bloody CSF should be centrifuged and examined for xanthochromia (yellow color). Xanthochromia results from RBC lysis and takes several hours to develop, indicating SAH rather than a traumatic LP.

TREATMENT

- Vital signs, including oximetry and continuous telemetry, should be monitored.
- Hypertension management after ischemic stroke:
  - Perfusion pressure in areas of the brain distal to the arterial occlusion may be low. Cerebral perfusion depends in part on mean systemic arterial pressure. Thus, a degree of hypertension may be necessary to maintain adequate perfusion pressure to injured areas.
  - Aggressive lowering of blood pressure (BP) has been associated with neurologic deterioration (*Neurology 2003;61(8):1047*), although there exists an ongoing debate in the field on this topic (see the following text).
  - Patients with acute stroke often present hypertensive. BP tends to fall on its own over several days following a stroke.
  - Although management of hypertension in the setting of acute stroke remains controversial, BP should not be lowered acutely unless necessary for treatment of acute coronary syndrome, CHF, hypertensive crisis with end-organ involvement, or systolic BP >220 mm Hg or diastolic BP >120 mm Hg (*Stroke 2007;38(5):1655*). BP lowering should proceed cautiously, with 15% during the first 24 hours being a reasonable goal.
- Treatment of intracranial hemorrhage consists of supportive care, gradual reduction in BP, and elevation of head of bed by 15 degrees.
- Treatment of SAH depends on etiology (surgical clipping vs. intravascular coiling).
  - Supportive measures include bed rest, sedation, analgesia, and laxatives to prevent sudden increases in intracranial pressure.
  - Patients with SAH tend toward volume contraction, and although there is insufficient evidence to support a benefit for volume expansion, guidelines do emphasize the importance of maintaining

euvolemia to avoid delayed cerebral ischemia (DCI).

- Induced hypertension (unless contraindicated by cardiac comorbidities or in patients with baseline elevated BP) is still recommended in patients with vasospasm/DCI because it has been shown to improve cerebral blood flow in these patients.
- Endovascular angioplasty is recommended in patients with symptomatic vasospasm of proximal cerebral arteries that fail to respond to induced hypertension. In many instances, endovascular therapies are combined with intra-arterial vasodilator therapies (e.g., calcium channel blockers).
- Other nonpharmacologic (hemodilution) and pharmacologic (statins, endothelin receptor antagonists, magnesium) therapies have failed to demonstrate a definitive benefit in patients with SAH.
- Future therapies for preventing and treating cerebral vasospasm hinge on gaining a better understanding of the mechanisms underlying cerebral vasospasm and DCI.

Medications

- Recombinant tissue plasminogen activator (rt-PA) remains the only US Food and Drug Administration (FDA)-approved pharmacologic therapy for acute ischemic stroke.
  - Administration of rt-PA must commence within 4.5 hours of stroke onset (*N Engl J Med 2008;359(13):1317*) but should be started as close to onset as possible (i.e., do not delay to see if the patient "gets better" on his or her own if the patient presents early on in the window).
  - rt-PA treatment increases risk for symptomatic brain hemorrhage, compared to placebo, but without any significant impact on 3- and 12-month mortality rates.
  - Exclusion criteria for the 0- to 3-hour and 3- to 4.5-hour windows are available in Tables 27-5 and 27-6. However, the acute stroke team should be contacted emergently to evaluate **all** acute strokes, because some patients with exclusion for IV t-PA may be eligible for other interventions, such as intra-arterial t-PA or intra-arterial catheter-based interventions. Given the results of a number of recent clinical trials (discussed in more detail below), select patients with large-vessel occlusions can benefit from a combination of IV t-PA and endovascular therapy.
  - Aspirin, heparin, and warfarin should be held for the first 24 hours after rt-PA.
- Aspirin reduces atherosclerotic stroke morbidity and mortality and is typically given at an initial dose of 325 mg within 24-48 hours of stroke onset. The dose may be reduced to 81 mg in the post-acute stroke period.
- Other antiplatelet-aggregating drugs (clopidogrel, aspirin/dipyridamole) are available and may be of benefit for certain patients. Both of these drugs have a significant advantage over aspirin in secondary stroke prevention. However, there is no evidence to suggest any benefit to dual antiplatelet therapy for secondary stroke prevention.
- Heparin, low-molecular-weight heparin (LMWH), and warfarin anticoagulation are **not** recommended for acute ischemic stroke.
- Anticoagulation with warfarin, dabigatran, rivaroxaban, or apixaban is indicated to prevent recurrent embolic strokes due to atrial fibrillation. Target INR for warfarin therapy is 2-3 (*Stroke 2007;38(5):1655*).
- Nimodipine, a calcium channel blocker, improves outcome in SAH patients and may reduce the incidence of associated cerebral infarction with few side effects. However, the mechanism by which nimodipine offers neuroprotection remains unclear (i.e., no evidence that it prevents vasospasm). Anticoagulation with heparin/LMWH followed by warfarin is indicated for venous sinus thrombosis both with and without hemorrhagic infarcts. Boluses of heparin to correct the aPTT should be avoided in the setting of

hemorrhage. aPTTs should be closely monitored and maintained between 60-80 seconds.

Other Nonpharmacologic Therapies

- Four recently published trials (MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME) have demonstrated a clear benefit to endovascular therapy in select patients with acute ischemic stroke, typically in combination with IV rt-PA (*N Engl J Med 2015;372(1):11*; *N Engl J Med February 11, 2015*; *N Engl J Med 2015 Mar 12;372(11):1019-30*; *N Engl J Med 2015 Jun 11;372(24):2365-6*; *N Engl J Med 2015 Jun 11;372(24):2285-95 [Epub]*).
- These four studies represent the first major breakthrough in acute ischemic stroke therapy since the introduction of IV rt-PA in 1996. The next major challenge in the field lies in determining how best to make these therapies accessible to the stroke population at large.
- Physical, occupational, and speech therapy are extremely important in stroke rehabilitation and have a clear beneficial impact on poststroke outcomes.
- Stroke patients with obvious dysphagia, dysarthria, or a facial droop should be kept nothing by mouth (NPO) until an experienced individual can assess their swallowing abilities.

TABLE 27-5 Inclusion and Exclusion Criteria for 0- to 3-Hour IV t-PA for Acute Stroke

t-PA Eligibility

1. Age ≥18 yr
2. Clinical diagnosis of ischemic stroke causing measurable neurologic deficit and noncontrast head CT showing no hemorrhage
3. Onset of stroke symptoms well established to be <180 min (3 h) before treatment would begin

Contraindications

1. Symptoms minor or rapidly improving.
2. Other stroke or serious head trauma within past 3 mo.
3. Major surgery within last 14 d.
4. Known history of intracranial hemorrhage.
5. Sustained systolic blood pressure >185 mm Hg.
6. Sustained diastolic blood pressure >110 mm Hg.
7. Aggressive treatment necessary to lower blood pressure.

8. Symptoms suggestive of subarachnoid hemorrhage.

9. Received heparin within 48 h and has elevated PTT.[a]

10. Patient has received treatment (not prophylactic) doses of injectable anticoagulants (e.g., enoxaparin) in the past 48 h.[a]

11. The safety of t-PA use in patients taking newer oral anticoagulants (dabigatran, rivaroxaban, apixaban) has not been established. Refer to your institution's established protocols on blood tests (anti-factor Xa assay, thrombin time, PT) used in evaluating eligibility for IV t-PA.[b]

12. Arterial puncture at noncompressible site within 7 d.

13. GI or GU hemorrhage within 21 d.

14. International normalized ratio (INR) >1.7.[a]

15. Platelet count <100,000/μL.

16. Seizure at onset of stroke (with deficits thought to be related to ictal or postictal state and not new stroke).

17. Serum glucose <50 mg/dL. (If glucose is >400 mg/dL, consider other etiology such as unmasking of old deficits vs. new stroke.)

GI, gastrointestinal; GU, genitourinary; PT, prothrombin time; PTT, partial thromboplastin time; t-PA, tissue plasminogen activator.

[a]Because time is critical, thrombolytic therapy should not be delayed while waiting for the results of the PT, PTT, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected; the patient has been taking warfarin, heparin, dabigatran, rivaroxaban, or apixaban; or anticoagulation use is uncertain.

[b]Given that the safety of IV t-PA administration in patients taking oral anticoagulants beyond warfarin has not been formally assessed, many institutions (including our own) require informed consent before administering IV t-PA in this population.

Data from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007;38(5):1655.

TABLE 27-6 Inclusion and Exclusion Criteria for 3.0- to 4.5-Hour IV t-PA for Acute Stroke

t-PA Eligibility

1. Age 18-80 yr
2. Clinical diagnosis of ischemic stroke causing measurable neurologic deficit and noncontrast head CT showing no hemorrhage
3. Onset of stroke symptoms well established to be between 3.0-4.5 h before treatment would begin

Contraindications

1. Symptoms minor or rapidly improving.
2. Seizure at onset of stroke.
3. Major surgery or significant trauma in past 3 mo.
4. Blood glucose <50 or >400 mg/dL.
5. Prior stroke within the last 3 mo.
6. Known history of or suspected ICH.
7. Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg, or aggressive management (more than a single dose of IV medication) necessary to reduce BP to these limits.
8. Symptoms suggestive of SAH.
9. Recent (<10 d) puncture of a noncompressible blood vessel, external heart massage, or obstetrical delivery.
10. Received heparin within previous 48 h and an elevated PTT.
11. Patients receiving warfarin even with normal PT/INR.
12. History of CNS damage (e.g., neoplasm, aneurysm, intracranial or spinal surgery).
13. Patient has received treatment (not prophylactic) doses of injectable anticoagulants (e.g.,

enoxaparin) in the past 48 h.

14. The safety of t-PA use in patients taking newer oral anticoagulants (dabigatran, rivaroxaban, apixaban) has not been established. Refer to your institution's established protocols on blood tests (anti-factor Xa assay, thrombin time, PT) used in evaluating eligibility for IV tPA.[a]

15. Platelet count <100,000/μL.

16. Severe stroke assessed clinically (NIHSS >25) or by imaging (>1/3 involvement MCA).

17. History of prior disabling stroke (MRS ≥2) and diabetes requiring treatment.

18. Known hemorrhagic diathesis.

19. Recent severe/dangerous bleeding.

20. Hemorrhagic retinopathy (e.g., in diabetes, vision disturbance may indicate hemorrhagic retinopathy).

21. Acute pancreatitis, documented ulcerative GI disease during last 3 mo, esophageal varices, arterial aneurysm, or AVM.

22. Other major disorders associated with a risk of bleeding, such as known bacterial endocarditis, pericarditis, or severe liver disease.

AVM, arteriovenous malformation; BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; ICH, intracranial hemorrhage; MCA, middle cerebral artery; MRS, Modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; PT/INR, prothrombin time/international normalized ratio; PTT, partial thromboplastin time; SAH, subarachnoid hemorrhage; t-PA, tissue plasminogen activator.

Bold text is different from 0- to 3-hour criteria (see Table 27-5).

[a]Given that the safety of IV t-PA administration in patients taking oral anticoagulants beyond warfarin has not been formally assessed, many institutions (including our own), require informed consent before administering IV t-PA in this population.

Surgical Management

- CEA decreases the risk of stroke and death in patients with recent TIAs or nondisabling strokes and ipsilateral high-grade (70-99%) carotid stenosis (*N Engl J Med 1991;325(7):445*).
  - The CREST (Carotid Revascularization Endarterectomy Versus Stenting) trial provides evidence to suggest that carotid stenting is of equal efficacy to CEA (*N Engl J Med 2010;363:11*).
  - Recommendations from a neurologist should be solicited before deciding on which of the two

approaches is indicated.

- CEA for asymptomatic high-grade carotid stenosis (≥60%) reduces the 5-year risk of ipsilateral stroke in men, provided that the operator's surgical/angiography complication rate is <3% (*JAMA 1995;273(18):1421*; *Stroke 2004;35(10):2425*).
- See the earlier section on nonpharmacologic therapies for information on endovascular therapies in acute ischemic stroke.
- Hemicraniectomy increases survival and can improve functional outcomes in select patients with large hemispheric infarcts and severe edema (e.g., "malignant" middle cerebral artery infarcts). Neurosurgical consultation should be obtained early in these cases.
- Cerebellar infarction or hematomas may result in brainstem compression or obstructive hydrocephalus and may also warrant urgent neurosurgical intervention.

Lifestyle/Risk Modification

Modifiable risk factors (Table 27-7) include the following.

- BP reduction even in normotensive stroke patients is beneficial (*Lancet 2001;358 (9287):1033*).
- Diabetes control is important with care taken to avoid hypoglycemia and hyperglycemia.
- Smoking cessation.
- Patients under age 75 with no concerns for safety of statin therapy should be placed on "high-intensity" statin therapy (e.g., 40-80 mg of atorvastatin or 20-40 mg of rosuvastatin), whereas patients over 75 or patients for whom there is concern for safety of statin therapy should be placed on "moderate-intensity" statin therapy (e.g., 10-20 mg of atorvastatin, 5-10 mg of rosuvastatin, 20-40 mg of simvastatin, 40-80 mg of pravastatin) (*J Am Coll Cardiol 2014;64(6):601*).
- Treat obstructive sleep apnea.
- Oral contraceptives may need to be discontinued in women with stroke.

TABLE 27-7 Secondary Stroke Prevention ("BLASTED")

- Blood pressure
- LDL
- ASA (antiplatelet), A1C
- Stroke management and rehabilitation team (varies from facility to facility)
  - PT, OT, ST, stroke educator, diabetes educator, smoking cessation counseling
- Telemetry
- Echocardiography
- Doppler, diabetes (A1C, educator, etc.)

ASA, acetylsalicylic acid; LDL, low-density lipoprotein; OT, occupational therapy; PT, physical therapy; ST, speech therapy.

COMPLICATIONS

- Cerebral edema following ischemic stroke peaks at 48-96 hours after stroke, and patients need to be watched closely during this time.
- Hemorrhagic conversion of an ischemic stroke is more likely in patients who are receiving anticoagulation or in patients with large strokes, particularly those with embolic ischemic infarcts.

Headache

GENERAL PRINCIPLES

Classification

- **Primary headache syndromes** include migraines with (classic) or without (common) aura, the hemicranias and indomethacin-responsive headaches, tension headaches, chronic daily headaches, and cluster headaches.
- **Secondary headaches** have specific etiologies, and symptomatic features vary depending on the underlying pathology (i.e., SAH, tumor, hypertension, posterior reversible encephalopathy syndrome or reversible posterior leukoencephalopathy, reversible cerebral vasoconstriction syndrome [RCVS], analgesic overuse, iatrogenic).
- **Migraine without aura (common):** At least five attacks that last 4-72 hours. Symptoms should include at least two of the following: unilateral location, pulsating or throbbing, moderate to severe in intensity, aggravated by activity, and at least one of these associated features: nausea/vomiting, photophobia, and/or phonophobia.
- **Migraine with aura (classic):** Same as the aforementioned, except at least two attacks with an associated aura that lasts from 4 minutes to 1 hour (longer than 60 minutes is a red flag). The aura should have a gradual onset, should be fully reversible, and can occur before, with, or after headache onset.
- **Cluster headache:** Unilateral orbital or temporal pain with lacrimation, conjunctival injection, nasal congestion, rhinorrhea, facial swelling, miosis, ptosis, and eyelid edema.
- **Rebound headache** (analgesic overuse headache) occurs in the setting of chronic use of analgesics or narcotics.
- **Trigeminal neuralgia** presents as episodic sharp stabbing pain that is unilateral. Rule out MS or an alternative etiology with MRI.
- **Temporal arteritis** presents as a dull unilateral headache with a thick tortuous artery over temporal region. The disease is almost exclusively limited to individuals over 60 years of age with jaw claudication, low-grade fever, and an elevated ESR and CRP.

Etiology

Secondary headache etiologies include:

- Subdural hematoma (SDH), intracerebral hemorrhage, SAH, AVM, brain abscess, meningitis, encephalitis, vasculitis, obstructive hydrocephalus, and cerebral ischemia or infarction.
- Idiopathic intracranial hypertension (commonly known as pseudotumor cerebri) presents with headache, papilledema, diplopia, and elevated CSF pressure (>20 cm H_2O in relaxed lateral decubitus position). CVST should be ruled out in all patients presenting with suspected idiopathic intracranial hypertension.
- Extracranial causes include giant cell arteritis, sinusitis, glaucoma, optic neuritis, dental disease (including

temporomandibular joint syndrome), and disorders of the cervical spine ("cervicogenic" headache).

- Systemic causes include fever, viremia, hypoxia, carbon monoxide poisoning, hypercapnia, systemic hypertension, allergy, anemia, caffeine withdrawal, and vasoactive or toxic chemicals (nitrites).
- Depression is a common cause of long-standing, treatment-resistant headaches. Specific inquiry about vegetative signs of depression and exclusion of other causes help support this diagnosis.

DIAGNOSIS

Clinical Presentation

History

- The sudden onset of severe headache ("**the worst headache of my life**," also known as a "thunderclap headache") or a severe persistent headache that reaches maximal intensity within a few seconds/minutes warrants immediate investigation for possible SAH.
- Other headache syndromes that can present with a thunderclap headache include RCVS, posterior cerebral artery infarcts, CVST, arterial dissections, CNS vasculitis, pituitary apoplexy, intracerebral hemorrhage, and some of the indomethacin-responsive headache syndromes.
- History should focus on:
  - Age at onset
  - Frequency, intensity, and duration of attacks
  - Triggers, associations (menstrual cycle), associated symptoms (e.g., photophobia, phonophobia, nausea, vomiting), and alleviating factors
  - Location and quality of pain (e.g., sharp, dull)
  - Number of headaches per month, including number of disabling headaches
  - Family history of migraines
  - Sleep and diet hygiene (caffeine intake)
  - Use of pain medications, including over-the-counter medications

Physical Examination

- On general examination, check BP and pulse, listen for possible bruits, palpate head and neck muscles, and check temporal arteries.
- If neck stiffness and meningismus (resistance to passive neck flexion) are present on exam, then consider meningitis.
- If papilledema is observed on exam, then consider an intracranial mass, meningitis, CVST, or idiopathic intracranial hypertension.

Diagnostic Testing

Imaging

Neuroimaging is generally not indicated for known primary headache syndromes but may be required to exclude secondary etiologies (listed earlier) in cases that have not been previously diagnosed or in patients presenting with new headaches, especially those who present with atypical features or abnormal exam findings.

Diagnostic Procedures

LP is indicated in a patient with severe headache with suspicion of SAH even if the head CT scan is negative. However, head CT is over 99% sensitive for detecting SAH if obtained within 6 hours of headache onset.

TREATMENT

- **Acute treatment of migraine**, the most common primary headache syndrome, is directed at aborting the headache. This is easier at onset and often very difficult when the attack is well established. Accordingly, the threshold for treating at the first sign of a

headache should be low. Patients have often used nonprescription analgesics (acetylsalicylic acid [ASA], acetaminophen, NSAIDs) and oral prescription medications (butalbital with aspirin or acetaminophen), which are the first-line treatments and are most effective early in the course of an attack. Emergent treatments include serotonin agonists and other parenteral medications.

- Scheduled IV NSAID (e.g., ketorolac) in combination with antiemetics (typically prochlorperazine) and IV fluids is an effective first-line regimen in many cases.
- Antidopaminergic therapies including haloperidol and droperidol are also effective first-line therapies. A baseline ECG should be obtained to evaluate for a prolonged QT_c.
- **Triptans** (serotonin receptor $5HT_{1B}$ and $5HT_{1D}$ agonists) are effective abortive medications available in multiple formulations and may be effective even in a protracted attack. Triptans should not be used in patients with coronary artery disease, cerebrovascular disease, uncontrolled hypertension, hemiplegic migraine, or vertebrobasilar migraine.
- **Dihydroergotamine** is a potent venoconstrictor with minimal peripheral arterial constriction. Cardiac precautions and a baseline ECG are indicated in all patients. This medication is contraindicated when there is a history of angina, myocardial infarction, or peripheral vascular disease. Alternative therapies should also be considered in elderly patients.
- **Ergotamine** is a vasoconstrictive agent effective for aborting migraine headaches, particularly if administered during the prodromal phase. Ergotamine should be taken at symptom onset in the maximum dose tolerated by the patient; nausea often limits the dose. Rectal preparations are better absorbed than oral agents. This medication is also contraindicated in patients with a history of angina, myocardial infarction, or peripheral vascular disease.
- Additional abortive therapies with less evidence supporting their use include IV valproic acid, IV methylprednisolone, IM ziprasidone, and IV magnesium.
- Chronic daily headaches should not be treated with narcotic analgesics so as to prevent addiction, rebound headaches, and tachyphylaxis.
- Treatment of secondary headaches is directed at the primary etiology, such as surgical treatment of cerebral aneurysm causing SAH, evacuation of SDH, calcium channel blockers in RCVS, or shunting in obstructive hydrocephalus.
- **Prophylactic medications** should be considered if a patient has at least three disabling migraines per month.
    - It is important to review a patient's use of all medications and comorbidities because they may influence choice of medication and offer additional factors contributing to the headache syndrome.

- Possible prophylactic medications include propranolol, topiramate, tricyclic antidepressants (TCAs) (amitriptyline, nortriptyline), and now less commonly, valproic acid. Second-line agents include verapamil, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Weaker evidence exists for other AEDs and for calcium channel blockers.
- Alternative (nonprescription) therapies for migraine prophylaxis include butterbur, riboflavin, magnesium, and acupuncture.
- Botulinum toxin (onabotulinumtoxinA) is FDA approved for migraine prophylaxis in adult patients with chronic migraine (defined as ≥15 headache days per month).

Lifestyle Modifications

- Patients should keep a headache calendar to identify possible triggers.
- Patients should reduce alcohol, caffeine, and other triggers that may increase risk of migraines.

REFERRAL

Neurosurgical consultation is indicated for managing SAH, SDH, vascular malformations, tumors, and other space-occupying lesions resulting in mass effect. Neurologic consultation is indicated if a patient is not well controlled on a first-line prophylactic agent with appropriate use of an abortive therapy.

Head Trauma

GENERAL PRINCIPLES

Definition

- **Traumatic brain injury (TBI)** can occur with head injury due to contact and/or acceleration/deceleration forces.
- **Concussion:** Trauma-induced alteration in mental status with normal radiographic studies that may or may not involve loss of consciousness.
- **Contusion:** Trauma-induced lesion consisting of punctate hemorrhages and surrounding edema.

Classification

- Closed head injuries may produce axonal injury.
- Contusion or hemorrhage can occur at site of initial impact, “coup injury,” or opposite to the side of impact, “countercoup injury.”
- Penetrating injuries (including depressed skull fracture) or foreign objects cause brain injury directly.
- Secondary increases in intracranial pressure may compromise cerebral perfusion.

Epidemiology

- Head injury is the most common cause of neurologic illness in young people.
- The overall incidence of TBI in the US population is estimated at approximately 550 per 100,000 (i.e., approximately 2 million per year with approximately one-quarter requiring hospitalization).
- Two-thirds of TBIs are considered “mild,” whereas 20% are severe and 10% are fatal. Note that although

designated as “mild,” mild TBI can still translate into significant disability (permanent in 15%).

- Rates of TBI are highest in the very young, adolescents, and the elderly.

DIAGNOSIS

Clinical Presentation

- Patients will often present with confusion and amnesia, including loss of memory for the traumatic event as well as inability to recall events both immediately before and after trauma.
- Patients may complain of nonspecific signs including headache, vertigo, nausea, vomiting, and personality changes.
- Intracerebral hematomas may be present initially or develop after a contusion.
- Epidural hematoma is usually associated with skull fractures across a meningeal artery and may cause precipitous deterioration after a **lucid interval**.
- SDH is most common in aged, debilitated alcoholics and/or in anticoagulated patients. Antecedent trauma may be minimal or absent.

Physical Examination

- Careful examination for penetrating wounds and other injuries.
- Hemotympanum, mastoid ecchymosis (Battle sign), periorbital ecchymosis (“raccoon eyes”), and CSF otorrhea/rhinorrhea are indicative of a basilar skull fracture.
- Neurologic examination should focus on the level of consciousness, focal deficits, and signs of herniation. The GCS should be used for an assessment. Serial examinations must be performed and documented to identify neurologic deterioration.
- Degree of impairment due to trauma can be classified using injury severity scores, with GCS being the most common.
- Treatment and diagnostic assessment of patients with severe head injury at admission are done according to the Advanced Trauma Life Support (ATLS) protocol.
- The Standardized Assessment of Concussion (SAC) is a standardized tool for the sideline evaluation of athletes who suffer a head injury.

Diagnostic Testing

- Head CT should be considered for patients with GCS <15 2 hours after trauma, suspected skull fracture, repeated episodes of vomiting after trauma, age >65 years, dangerous mechanism (e.g., pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from ≥3 ft or ≥five stairs), drug or alcohol intoxication, or persistent anterograde amnesia.
- Noncontrast head CT scan in the emergency room can rapidly identify intracranial hemorrhage and contusion.
  - A lenticular-shaped extra-axial hematoma is characteristic of epidural hematoma.
  - Bone window views may help to locate fractures, if present.
- Cervical radiographs ± CT of the neck must be performed to exclude fracture or dislocation.
- MRI can assist in evaluation of TBI patients with persistent sequelae because it is more sensitive for demonstrating small areas of contusion or petechial hemorrhage, axonal injury, and small extra-axial hematomas.

TREATMENT

- Hospital admission is recommended for patients at risk for immediate complications from head injury. These include patients with GCS <15, abnormal CT scan, intracranial bleeding, cerebral edema, seizures, or abnormal bleeding parameters.
- When admitted, continuously monitor vital signs and oximetry. ECG should be performed. Arterial pressure monitoring in conjunction with intracranial monitoring may be indicated.
- Immobilize the neck in a hard cervical collar to avoid spinal cord injury from manipulating an unstable or fractured cervical spine.
- **Avoid hypotonic fluids** to limit cerebral edema.
- Steroids are not indicated for head injury.
- Avoid hypoventilation and systemic hypotension because they may reduce cerebral perfusion.
- Anticipate and conservatively treat increased intracranial pressure:
  - Head midline and elevated 30 degrees.
  - In the mechanically ventilated patient, modest hyperventilation (PCO_2 approximately 35 mm Hg) reduces intracranial pressure by cerebral vasoconstriction; excessive hyperventilation may reduce cerebral perfusion. Remember that these are merely temporizing measures and neurosurgical consultation is always warranted if there is concern for increased intracranial pressure due to head injury.

- Neurologic deterioration after head injury of any severity requires an immediate repeat head CT scan to differentiate an expanding hematoma that necessitates surgery from diffuse cerebral edema that requires monitoring and reduction of intracranial pressure.
- The use of AEDs in the acute management of TBI can reduce the incidence of early seizures but does not prevent development of epilepsy at a later time. Furthermore, certain AEDs can have adverse effects on cognition, and so these agents should only be used when clinically indicated, with careful consideration of the specific agent chosen. There is no evidence to support AED use for seizure prophylaxis.
- Because a second injury, referred to as the “second impact syndrome,” may lead to severe complications including death, guidelines have been proposed for when individuals can return to play (*J Athl Train 2013;48:554*).

Surgical Management

- Neurosurgical consultation is indicated for patients with contusion, intracranial hematoma, cervical fracture, skull fractures, penetrating injuries, or focal neurologic deficits.
- In cases of closed head injury complicated by increased intracranial pressure, intracranial pressure monitoring assists medical management.
- Evacuation of chronic SDH is determined by the symptoms and degree of mass effect.

Acute Spinal Cord Dysfunction

GENERAL PRINCIPLES

- Spinal cord dysfunction is demonstrated by a level below which motor, sensory, and autonomic functions are interrupted.
- **Traumatic spinal cord injury** (TSCI) may be obvious from history or exam but should also be considered in unconscious, confused, or inebriated patients with trauma.
- **Spinal cord concussion** refers to posttraumatic spinal cord symptoms and signs that resolve rapidly (hours to days).

Etiology

See Table 27-8.

DIAGNOSIS

Clinical Presentation

- **Spinal cord compression** often presents with back pain at the level of compression, progressive walking difficulties, sensory impairment, urinary retention with overflow incontinence, and diminished rectal tone. Rapid deterioration may occur.
- **Transverse myelitis or myelopathy** can present with symptoms and signs similar to cord compression.
- **Spinal shock** with hypotonia and areflexia may be present soon after traumatic event.
- Acute presentations suggest traumatic or vascular insults, whereas a subacute course suggests an enlarging mass lesion or infectious process. Autoimmune/inflammatory disorders can present in both ways.
- **Radicular signs** (lancinating pain, paresthesias, and numbness in the dermatomal distribution of a nerve root, with weakness and decreased tone and reflexes in muscles supplied by the root) suggest concurrent inflammation or compression of the corresponding nerve root. Tenderness to spinal percussion over the lesion may be present.

TABLE 27-8 Causes of Acute Spinal Cord Dysfunction

Structural
- Tumor (primary or metastatic)
- Herniated disk
- Epidural abscess or hematoma
- Osteomyelitis
- Trauma ± fracture of bony elements
- Atlantoaxial instability (e.g., rheumatoid arthritis)
- Fibrocartilaginous

Ischemia/infarction (particularly after aortic surgery)
- Aortic dissection or surgery
- Embolic (cardiogenic, gaseous embolus)
- Prolonged hypotension with underlying vascular disease
- Intravascular lymphoma

Toxic
- Nitrous oxide (typically in the setting of vitamin B_{12} deficiency)
- Heroin

Vascular malformations (e.g., AVM)
Inflammatory/infectious (transverse myelitis)

- Multiple sclerosis
- Neuromyelitis optica (classically longitudinally extensive, >3 spinal segments)
- Acute disseminated encephalomyelitis
- Parainfectious processes (e.g., after *Mycoplasma pneumoniae*)
- Sarcoidosis
- Paraneoplastic (amphiphysin and CRMP-5)
- Systemic lupus erythematosus
- Sjögren syndrome
- Behçet disease
- Viruses (e.g., enterovirus, HSV, HIV, VZV, CMV, WNV)
- Fungal (extremely rare)
- Lyme disease
- TB
- Syphilis

AVM, arteriovenous malformation; CMV, cytomegalovirus; CRMP-5, collapsing response mediator protein 5; HSV, herpes simplex virus; VZV, varicella-zoster virus; WNV, West Nile virus.

- **Spinal cord syndromes**
  - **Complete cord syndrome:** Bilateral flaccid paralysis (quadriplegia or paraplegia) and loss of all sensation (anesthesia) below a dermatomal level, initially with areflexia and sphincter dysfunction (urinary retention/loss of rectal tone). With time, patients develop spasticity and hyperreflexia caudal to the lesion with possible lower motor neuron signs (areflexia and flaccid paralysis) at the level of the lesion and extensor plantar responses (Babinski signs).
  - **Brown-Séquard syndrome:** Unilateral cord lesion resulting in contralateral pain and temperature loss, with ipsilateral weakness and proprioceptive loss.
  - **Anterior cord syndrome** often results from anterior spinal artery lesion and produces bilateral pain and temperature loss and weakness below the site of the lesion with preserved proprioception and vibratory sensation.

  - **Cauda equina syndrome** from compression of the lower lumbar and sacral roots produces sensory loss in a saddle distribution, asymmetric flaccid leg weakness, decreased reflexes, and urinary/bowel incontinence due to an areflexic bladder and loss of rectal tone.
  - **Conus medullaris syndrome** has similar features to cauda equina syndrome with one important difference being the presence of mixed upper and lower motor neuron signs due to involvement of the caudal spinal cord.
  - **Central cord syndrome** is often characterized by motor impairment in upper extremities more than lower extremities, bladder dysfunction, and variable degree of sensory loss at the site of the lesion. Trauma is a common cause.

Diagnostic Testing

Imaging

- The presence and extent of spinal cord injuries should be confirmed with neuroimaging.

- Plain radiographs of the spine may reveal metastatic disease, osteomyelitis, discitis, fractures, or dislocation.
- Emergent MRI scan of the entire cord can confirm the exact level and extent of the lesion(s). CT myelography may be necessary in individuals unable to undergo MRI.
- CT of the spine with and without contrast can also be used to evaluate for epidural abscess, osteomyelitis, and/or discitis in patients unable to undergo MRI.

Diagnostic Procedures

- LP: Inflammatory and infectious etiologies often require CSF analysis for pleocytosis, malignant cells, abnormal protein/glucose, oligoclonal bands, and IgG index; if indicated, tests for specific pathogens and cytology/flow cytometry can be considered. If possible, imaging should be performed prior to performing an LP to rule out abscess, tumor, or other structural contraindication to LP. Remember to always check an opening pressure when possible and save CSF for additional studies that may be deemed indicated once additional clinical data have been gathered.
- Spinal angiogram is the gold standard diagnostic test to evaluate for a spinal AVM. However, a normal spine MRI with and without contrast, of adequate quality, makes the likelihood of finding an abnormality on spinal angiography extremely low.

TREATMENT

- Vital signs should be continuously monitored, and adequate oxygenation and perfusion should be ensured.
- Respiratory insufficiency from high cervical cord injuries requires immediate airway control and ventilatory assistance, without manipulation of the neck.
- Immobilization, especially of the neck, is essential to prevent further injury while the patient's condition is stabilized and radiographic and neurosurgical assessment of the injuries is performed.
- Autonomic dysfunction is common and can lead to fluctuating vital signs and BP. Bladder distension can cause sympathetic overactivity (headache, tachycardia, diaphoresis, and hypertension) as a result of autonomic dysreflexia.
  - Management of autonomic dysreflexia should incorporate the help of a spinal cord rehabilitation specialist. These patients require strict attention to bowel and bladder functions (e.g., manual disimpaction, promotility agents, straight catheterization) as a means to prevent an autonomic crisis.
  - Do not treat fluctuations in vital signs blindly, because changes can occur precipitously with potential for iatrogenic injury. Always look first for a cause and treat fluctuations in heart rate or BP with caution.

Medications

- Treatable infections require appropriate antimicrobial therapies (e.g., acyclovir for varicella-zoster myelitis).
- **Dexamethasone**, 10-20 mg IV bolus followed by 2-4 mg IV q6-8h, is often administered for compressive lesions, tumors, or spinal cord infarction, although benefit has not been proven for all etiologies.
- For TSCI, **methylprednisolone**, 30 mg/kg IV bolus, followed by an infusion of 5.4 mg/kg/h for 24 hours when initiated within 3 hours of injury, and infusion for 48 hours when initiated within 3-8 hours of injury,

may improve neurologic recovery.

- Pharmacologic deep venous thrombosis prophylaxis is extremely important. LMWH is superior to unfractionated heparin for prevention of venous thromboembolism and pulmonary embolism. Inferior vena cava filters should be considered in bedbound patients.

Surgical Management

Neurosurgical consultation should be obtained because in many cases, spinal cord compression can be decompressed and stabilized. Penetrating injury, foreign bodies, comminuted fractures, misalignment, and hematoma may require surgical treatment.

SPECIAL CONSIDERATIONS

Emergent radiation therapy combined with high-dose steroids is usually indicated for cord compression due to malignancy and generally requires a histologic diagnosis.

MONITORING/FOLLOW-UP

Long-term supportive care is important for patients with spinal cord dysfunction. Pulmonary and urinary infections, skin breakdown, joint contractures, spasticity, and irregular bowel and bladder elimination are common long-term problems.

Parkinson Disease

GENERAL PRINCIPLES

- Parkinson disease (PD) is a chronic, progressive neurodegenerative disease characterized by at least two of three cardinal features: resting tremor, bradykinesia, and rigidity. Often, postural instability is seen later in the disease.
- The neurologic exam remains the gold standard diagnostic test for PD.
- Cognitive dysfunction and dementia are common in PD (one-third of patients in most studies; six times higher than age-matched controls). Considerable overlap can occur between AD and PD.
  - One-third of PD patients are depressed.
  - Olfactory dysfunction, autonomic dysfunction, and sleep disorders are also common in PD and have a significant impact on quality of life.

Epidemiology

Between 0.5-1.5 million people in the United States have been diagnosed with PD. Usually, the age at diagnosis is >50 years old. Approximately 1% of the population >50 years old has the disorder.

DIAGNOSIS

Clinical Presentation

- The parkinsonian tremor is a resting pill rolling tremor (3-7 Hz) that is often asymmetric (*Lancet Neurol 2006;5(1):75*).
- Bradykinesia is characterized by generalized slowness of movement, especially in finger movement

dexterity and gait (often shuffling).

- Cogwheel rigidity is often observed with a ratchety pattern of resistance and relaxation as examiner moves limbs ("cog wheeling" is due to the rigidity with a superimposed tremor).
- Postural instability can be assessed by the "pull" test, where the examiner pulls the patient by the shoulders while standing behind the patient.
- Other signs that are often associated but not required for diagnosis include masked-like facies, decreased eye blink, increased salivation, hypokinetic dysarthria, micrographia, and sleep disorders (rapid eye movement [REM] sleep behavior disorder).
- Dementia seen with PD is typically subcortical with psychomotor retardation, memory difficulty, and altered personality. Accordingly, a brief cognitive assessment (e.g., MoCA) could be considered as a screening test for cognitive dysfunction.

Differential Diagnosis

See Table 27-9.

Diagnostic Testing

MRI of the brain (or head CT with contrast in patients unable to undergo MRI) should be performed to exclude specific structural abnormalities.

TREATMENT

Medications

- **PD patients should not be given neuroleptics or any dopamine-blocking medications under any circumstances** (prochlorperazine, metoclopramide) because this can have devastating consequences ranging from worsening and prolongation of PD symptoms to death (*Expert Opin Drug Saf 2006;5(6):759*). If a neuroleptic is absolutely necessary, quetiapine and clozapine are the safest, but the risk/benefit profile needs to be considered.

TABLE 27-9 Differential Diagnosis of Parkinson Disease

- Essential tremor
  - Action tremor
- Dementia with Lewy bodies
  - Visual hallucinations, fluctuating cognition, sensitivity to neuroleptics
- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Alzheimer disease
- Frontotemporal dementia
  - Changes in personality
- Huntington disease
- Wilson disease and other neurodegenerative disorders with metal accumulation
- Toxic/iatrogenic
  - Carbon monoxide, manganese, neuroleptics, other dopamine receptor antagonists

- Treatment of PD can be divided into neuroprotective and symptomatic therapy.
- Initiation of symptomatic treatment for a PD patient is determined by the degree to which the patient is functionally impaired.

First Line

- Carbidopa-levodopa (CL) is the most effective symptomatic therapy for PD and is often considered when both the patient and the physician decide that quality of life of the patient is being affected by PD.
- Dopamine agonists (pramipexole, ropinirole) can be used as monotherapy or in combination with other PD medications. They are ineffective in patients who show no response to levodopa. They are often used in patients who develop significant dyskinesias or motor fluctuations on CL, but these drugs are less efficacious and have more adverse effects.
- Many patients can be managed with CL alone without need for agonist therapy.

Second Line

- Amantadine and catechol-*O*-methyl transferase (COMT) inhibitors can help supplement the effects of dopamine replacement therapy and are beneficial with regard to the dyskinesias and fluctuations, respectively, commonly experienced by patients.
- Anticholinergic drugs are used only in younger patients in whom tremor is the predominant symptom.

Third Line

Deep brain stimulation (DBS) has had a remarkable benefit in PD patients who eventually develop motor fluctuations and dyskinesias unresponsive to oral medications. It is important to note that DBS is not a cure for PD and patients will continue to progress.

COMPLICATIONS

- Patients can develop neuroleptic malignant syndrome (NMS) after sudden withdrawal of levodopa or dopamine agonists and following exposure to neuroleptics or other antidopaminergic drugs.
- Serotonin syndrome can occur when monoamine oxidase inhibitors (MAOIs) are combined with TCAs or SSRIs.

NEUROMUSCULAR DISEASE

Guillain-Barré Syndrome

GENERAL PRINCIPLES

Definition

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy syndrome and a common cause of acute flaccid paralysis. There are many GBS subtypes with marked geographic variability in their prevalence. The clinical syndrome is classically characterized by ascending weakness, distal paresthesias, and areflexia. Classically, GBS follows a viral infection, vaccination, or surgery, but in many instances, no prodrome is identified.

Classification

- The acute immune/inflammatory demyelinating polyneuropathy (AIDP) variant is the most common GBS variant in North America. It is an acute immune-mediated polyneuropathy/radiculopathy with presumed autoantibodies (as of yet identified) directed against myelin antigens.

- Axonal variants of GBS include acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), acute motor conduction block neuropathy (AMCBN), Miller Fisher syndrome (MFS), and pharyngeal-cervical-brachial (PCB) weakness. Many of these syndromes are associated with antiganglioside antibodies directed against gangliosides located in the axolemma near the nodes of Ranvier. These axonal variants are much more common in Japan, China, and third-world countries than they are in the United States. Antibody associations include:
  - IgG anti-GM1 antibodies in AMAN and AMCBN
  - IgG anti-GQ1b and less commonly IgG anti-GT1a in MFS, a syndrome consisting of ophthalmoparesis, ataxia, and areflexia
  - IgG anti-GT1a and less commonly IgG anti-GQ1b in PCB weakness syndrome

Pathophysiology

- GBS results from an attack of peripheral myelin or axons mediated by autoantibodies originally generated in response to an infection that typically precedes the onset of neuropathy symptoms by days to weeks. These antibodies cross-react with the myelin or nodal axolemma antigens via molecular mimicry.
- This concept is well established in the axonal variants where there is definitive evidence of molecular mimicry between *Campylobacter jejuni* lipo-oligosaccharides and the ganglioside antigens listed above. In fact, GBS was the first disease to illustrate the concept of molecular mimicry and fulfills all four criteria ("Witebsky postulates") for designation as an autoimmune disease.
- This concept is less well established in AIDP, given the absence of a known autoantibody/myelin antigen. Prodromal infections commonly associated with AIDP include cytomegalovirus and Epstein-Barr virus.

DIAGNOSIS

Clinical Presentation

- AIDP typically presents with progressive, symmetric ascending paralysis.
- Mild asymmetries are common, but major asymmetries are a red flag suggestive of an alternative diagnosis.
- Reflexes are almost always hypoactive or absent. Exceptions exist, especially with the axonal variants (in particular with Fisher-Bickerstaff syndrome, which has elements of MFS along with hypersomnolence in the setting of concurrent brainstem encephalitis).
- Sensory symptoms, such as paresthesias in the hands and feet, are often present, but objective sensory loss is uncommon.
- Facial and/or oropharyngeal weakness occurs in about 70% of AIDP patients.
- Respiratory failure, necessitating intubation, occurs in 25-30% of patients (*Lancet Neurol 2008;7(10):939*).
- Pain in the back, hips, and thighs is common. Pain is one of the most common presenting symptoms of

GBS in the pediatric population.

- Autonomic instability is common (approximately 60%) and potentially life threatening. Common manifestations include tachycardia/bradycardia, hypotension alternating with hypertension, and ileus.

Differential Diagnosis

See Table 27-10.

TABLE 27-10 Differential Diagnosis of Acute Immune Demyelinating Polyneuropathy

- Acute/initial presentation of chronic inflammatory demyelinating polyneuropathy
- Paraproteinemic/paraneoplastic polyradiculopathy/polyneuropathy
- Diabetic/nondiabetic lumbosacral radiculoplexopathies
- Sarcoidosis
- Mononeuritis multiplex (confluent)
- West Nile and polioviruses (usually has fever, CSF pleocytosis, and often asymmetric paralysis)
- HIV
- Lyme disease (if in endemic area)
- Postdiphtheric paralysis
- Tick paralysis and other neurotoxins
- Myasthenia gravis (MFS variant)
- Critical illness myopathy
- Prolonged neuromuscular junction blockade
- Periodic paralysis
- Thiamine deficiency (MFS variant in particular)
- Botulism
- Arsenic
- Lead
- Chemotherapy
- Acute intermittent porphyria
- Carcinomatous or lymphomatous meningitis with root involvement
- Functional weakness/conversion disorder

See *http://neuromuscular.wustl.edu/time/nmacute.htm* for further information.

CSF, cerebral spinal fluid; MFS, Miller Fisher syndrome variant of Guillain-Barré Syndrome (associated with ataxia, areflexia, and ophthalmoparesis).

Diagnostic Testing

Imaging

MRI of the spine is indicated in atypical cases or in those with concern for one of the differentials listed earlier that could result in a myeloradiculopathy. Nerve root gadolinium enhancement and/or thickening can be seen with GBS.

Diagnostic Procedures

- **LP should be performed to narrow the differential and evaluate for cytoalbuminologic dissociation.**
- CSF protein is usually elevated about 1 week after symptom onset. It may be normal if checked earlier (e.g., 85% of patients with normal CSF within first 2 days).
- CSF leukocytosis is uncommon, and if present (especially >25 cells/μL), an alternative diagnosis should be considered.
- Nerve conduction studies (NCS) and electromyography (EMG) are a very important part of the evaluation but should not delay initiation of treatment, particularly in severe cases. NCS should include evaluation of the proximal nerve segments. EMG-NCS performed early in the disease course may have very few abnormalities and can even be normal. A repeat study after a few weeks can be extremely useful for classification and prognostication.

TREATMENT

- Follow **respiratory function closely**, including oximetry and frequent bedside measurements of vital capacity (VC) and negative inspiratory force (NIF).
- We use the "20/30" rule in identifying patients who will likely require ventilatory support: <20 mL/kg of forced VC (FVC) (approximately 1.5 L for an average-size adult) and an NIF >-30 cm H_2O. These parameters provide a more sensitive measure for impending respiratory failure than do the presence of hypoxia, dyspnea, and acidosis. The threshold for elective intubation should be low.
- If NIF/FVC testing is not available at the bedside, a quick and indirect measure is to ask the patient to count to as high a number as possible on one breath. Each number equals 100 mL of VC (e.g., a count to 10 = 1 L).
- Paroxysmal hypertension should not be treated with antihypertensive medications unless absolutely necessary (e.g., signs of end-organ injury or comorbid coronary artery disease). If necessary, extremely low doses of titratable short-acting agents are preferred.
- Hypotension is usually caused by decreased venous return and peripheral vasodilation. Mechanically ventilated patients are particularly prone to hypotension. Treatment consists of intravascular volume expansion; occasionally, vasopressors may be required (see Chapter 8, Critical Care).
- Continuous telemetry monitoring is necessary to monitor for cardiac arrhythmias.
- Prevention of exposure keratitis of the eye, venous thrombosis, and vigilance for hyponatremia (including syndrome of inappropriate diuretic hormone [SIADH]) should be priorities.

Medications

- **Plasma exchange (PLEX) and IV immunoglobulin (IVIG)** are comparably effective in improving outcomes and shortening duration of disease when administered early to patients who cannot walk or have respiratory failure (*Brain 2007;130(pt 9):2245*). The decision between the two depends on the individual patient's comorbidities and medical history.
- Corticosteroids are not indicated and may actually delay recovery.
- Neuropathic pain medications may be needed.

Other Nonpharmacologic Therapies

Physical therapy to prevent contractures and improve strength and function should be started early.

COMPLICATIONS

Complications from prolonged hospitalization and ventilation may occur. These include aspiration pneumonia, sepsis, pressure ulcers, and pulmonary embolism.

PROGNOSIS

- The disease typically progresses over 2-4 weeks, with all patients, by definition, reaching their nadir by 4 weeks.
- This is followed by a plateau of several weeks in duration.
- Recovery takes place over months.
  - Overall, about 80% of patients recover completely or have only minor deficits (*Lancet 2005;366(9497):1653*).
  - A total of 5-10% of patients (usually elderly patients and those with more severe disease) have significant permanent residual disability, and 3% remain wheelchair bound.

- Of course, there are many exceptions, and many patients have a shorter course and/or a quicker recovery.
- About 5% of the patients die due to respiratory or autonomic complications despite optimal medical therapy.
- By definition, GBS is a monophasic disease, and a recurrence of symptoms should lead you to revisit the original diagnosis (e.g., consider chronic inflammatory demyelinating polyneuropathy). Repeat electrodiagnostic studies are critical in determining the etiology of an apparent “recurrent GBS.”

Myasthenia Gravis

GENERAL PRINCIPLES

Definition

Myasthenia gravis (MG) is an autoimmune disorder that involves antibody-mediated postsynaptic dysfunction of the neuromuscular junction of skeletal muscle resulting in fatigable weakness.

Classification

- Generalized disease is most common and affects a variable combination of ocular, bulbar, respiratory, and appendicular muscles.
- Ocular MG is confined to eyelid and oculomotor function. It accounts for 10-40% of all MG cases. The longer a patient with ocular MG goes without evidence of generalization, the less likely he or she is to develop generalized MG (<5% will advance to generalized MG if there are no symptoms of generalization by 2 years).

Epidemiology

Bimodal distribution with peak incidence in women in the second and third decades and in men in the sixth and

seventh decades.

Pathophysiology

MG is an acquired autoimmune disorder resulting from the production of autoantibodies against the postsynaptic acetylcholine receptor (AChR) or, less commonly, against receptor-associated proteins, including muscle-specific receptor tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4). However, despite the identification of these additional antigens, “seronegative” forms still account for up to 10% of MG patients. One must consider hereditary/congenital forms of MG and avoid mistakenly lumping these patients or the anti-LRP4 or anti-MuSK patients into this group.

Associated Conditions

- MG is often associated with thymus hyperplasia; 10% may have a malignant thymoma. Hyperplasia is more common in those under 40 years of age. Thymoma is more common in MG patients over 30 years of age. Thymectomy is generally recommended in all MG patients with onset of disease under age 55, regardless of the presence of thymic hyperplasia or thymoma.
- Autoimmune thyroiditis (hyper- more common than hypo-) is present in approximately 15% of patients with MG. MG patients also have an increased risk of other autoimmune diseases including lupus, rheumatoid arthritis, polymyositis, and pernicious anemia.

DIAGNOSIS

Clinical Presentation

History

- The cardinal feature of MG is fluctuating weakness that is worse after exercise or prolonged activity and improves with rest.
- More than 50% of patients present with ptosis that may be asymmetric.
- Other common complaints include blurred vision or diplopia, trouble smiling, and difficulties with chewing, swallowing, and speaking (e.g., winded at end of sentences, “staccato” [interrupted] speech, nasal speech, or weak voice).
- Weakness of neck flexors and extensors and proximal arm weakness are common. MG is one of the few neuromuscular disorders to cause prominent neck extensor weakness, creating a “head drop.”
- **Myasthenic crisis** consists of respiratory failure or the need for airway protection and occurs in approximately 15-20% of MG patients (*Neurology 2009;72:1548*). Patients with bulbar and respiratory muscle weakness are particularly prone to respiratory failure, which may develop rapidly and unexpectedly. They require as much vigilance and monitoring as do patients with GBS.
- Respiratory infection, surgery (e.g., thymectomy), medications (e.g., aminoglycosides, quinine, quinolones, β-blockers, lithium, magnesium sulfate), pregnancy, and thyroid dysfunction can precipitate crisis or exacerbate symptoms. However, it is important to note that none of these medications should be withheld if required to treat a concurrent illness. Anticholinergic medications are a notable exception to this rule for obvious reasons, and in the absence of a life-threatening indication, their use should be avoided.

Physical Examination

- Presenting signs include ptosis, diplopia, dysarthria, dysphagia, extremity weakness, and respiratory difficulty.
- Fatigability on examination is a useful diagnostic feature.
- Ptosis may worsen after prolonged upward gaze (usually by 60 seconds). Patients may also begin to develop diplopia after sustained gaze in one direction.
- Carefully evaluate the airway, handling of secretions, ventilation, and the work of breathing.
- NIF and FVC are useful at the bedside to assess for respiratory muscle weakness. The breath count test described earlier in the GBS section is also useful in this population. The same general rules for ventilatory support (inability to protect airway or ventilate adequately) apply.

Differential Diagnosis

- Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease affecting the presynaptic voltage-gated calcium channels of the neuromuscular junction. It is frequently associated with malignancy (small-cell lung cancer). LEMS also presents with fluctuating weakness, but the weakness improves for a brief period of time after exercise. A quick bedside exam finding that may be present is to evaluate for facilitation of reflexes that are absent or diminished at rest but present or increased after 10 seconds of isometric exercise.
- Amyotrophic lateral sclerosis (ALS) may present with bulbar weakness and a “head drop.” However, ALS can be differentiated from MG by presence of upper motor neuron signs in the former. Electrodiagnostic studies are also very useful in distinguishing the two.
- The differential also includes congenital forms of myasthenia, mitochondrial disorders (e.g., chronic progressive external ophthalmoplegia), and acquired and hereditary myopathies or other motor neuronopathies (other than ALS).

Diagnostic Testing

A good rule of thumb is to have two lines of diagnostic evidence (usually serologic and electrodiagnostic) in the appropriate clinical context to make a diagnosis of autoimmune MG.

Laboratories

- Serum **AChR antibodies** are detected in 85-90% of adult generalized MG patients and in 50-70% of ocular MG patients.
- **MuSK antibodies** are detected in about 30-70% of AChR antibody-negative MG patients.
- Thyroid function should be checked to evaluate for autoimmune thyroiditis.

Imaging

Chest CT is indicated to screen for a **thymoma**.

Diagnostic Procedures

Electrodiagnostic studies are an important step in diagnosing MG.

- Repetitive nerve stimulation (RNS) at 2-5 Hz typically shows >10% decrement in the amplitude of the compound muscle action potential (CMAP) in MG. If the patient is taking pyridostigmine, it should be held (if possible) because it could mask a decrement. RNS has a higher yield when it is performed on **weak** proximal muscles. Accordingly, it is only positive in 50% of patients with ocular

MG.

- It should be noted that a decrement on slow RNS is not 100% specific for MG and can also be seen in LEMS, motor neuronopathies/neuropathies, and myopathies.
- In LEMS, the response is incremental with fast RNS (20-50 Hz). Because fast RNS is extremely painful, an adequate supplement is to look for an increment in CMAP amplitude after 10 seconds of tetanic exercise (pre- and postexercise CMAPs).
- Single-fiber EMG has a sensitivity of >95% for both generalized and ocular MG when performed on facial muscles. However, the specificity is much lower (abnormalities also seen in LEMS, motor neuronopathies/neuropathies, and myopathies). It is usually reserved for those with suspected disease (based on clinical symptoms) but negative antibody and RNS testing.
- Edrophonium testing is no longer routinely used.
- Myasthenic weakness is often improved by cold. Although the history obtained from the patient may suggest this phenomenon, the “ice pack test” is an easy and safe, objective “bedside” measure of this phenomenon and is often helpful in the evaluation of ocular MG.

TREATMENT

- Treatment of MG is individualized and depends on the severity of the disease, age, comorbidities, and response to therapy.
- **Myasthenic crisis** requires prompt recognition and aggressive support.
  - Consider intensive care unit (ICU) level care and elective intubation for FVC <20 mL/kg or NIF >-30 cm H_2O (similar parameters to the “20/30” rule used for GBS).
  - Treat superimposed infections and metabolic derangements.
  - **Plasmapheresis** and IVIG are both used to treat MG crises/exacerbations and have equal efficacy with a similar rate of adverse effects. As for GBS, the decision between the two depends on the individual patient's comorbidities and medical history (*Neurology 2011;76:2017*).
  - Because the effects of PLEX or IVIG are relatively rapid in onset but short lived, corticosteroids are typically started soon after initiating PLEX, usually at a dose of 10-20 mg/d and slowly titrated to a dose of 50 mg/d.
  - Anticholinesterases should be temporarily withdrawn from patients who are receiving ventilation support to avoid cholinergic stimulation of pulmonary secretions.
  - Neuromuscular blocking agents should be avoided.

Medications

First Line

Anticholinesterase drugs can produce symptomatic improvement in all forms of MG. **Pyridostigmine** should be started at 30-60 mg PO tid-qid and titrated for symptom relief.

Second Line

- Immunosuppressive drugs are typically used when additional benefit is needed beyond cholinesterase inhibitors.
- High doses of **prednisone** can be used to achieve rapid improvement. **However, up to 50% of**

patients experience a transient worsening of weakness on initiation of prednisone therapy. Hence, it is important to start low and increase slow (see above), especially if the patient has not been or is not being treated with plasma exchange or IVIG.

- Azathioprine, mycophenolate mofetil, cyclosporine A, tacrolimus, and cyclophosphamide are steroid-sparing immunomodulatory agents that have all been used to treat MG with varying degrees of evidence to support their efficacy.
- There is growing evidence that rituximab (anti-CD20 chimeric monoclonal antibody) has great efficacy in treating anti-MuSK MG and can also have some utility in anti-AChR patients medically refractory to the other forms of immunomodulatory therapy listed earlier.

Surgical Management

- Thymectomy may induce remission or reduce medication dependence (*Neurology 2000;55(1):7*).
- Thymectomy in MG patients is indicated in the presence of thymoma and typically in patients younger than 55 years with or without thymoma.

Other Neuromuscular Disorders

GENERAL PRINCIPLES

- **Myopathies:** Rapidly progressive proximal muscle weakness can be caused by many drugs including but not limited to ethanol, steroids, colchicine, cyclosporine, and cholesterol-lowering drugs (particularly in combination). Other common causes include HIV or HIV therapies, particularly zidovudine, and hypothyroidism.
  - **Critical illness myopathy** is increasingly recognized in patients with critical illness and is commonly associated with the use of steroids and neuromuscular blocking agents.
  - **Polymyositis (PM) and dermatomyositis (DM)** fall into a class of diseases now referred to as the idiopathic inflammatory myopathies. Most forms respond well to immunomodulatory therapy with a notable exception being the inclusion body myopathies. DM and PM can also be a component of a syndrome affecting multiple different organ systems. Perhaps the best examples are antisynthetase syndromes, like Jo-1 myositis, which involves skin, joint, lung, and muscle. Patients suspected of having DM or PM should have myositis-specific and myositis-associated autoantibodies checked and should be screened for interstitial lung disease, which has a high degree of morbidity if left untreated (see Chapter 25, Arthritis and Rheumatologic Diseases).
- **Rhabdomyolysis** may produce rapid muscle weakness, leading to hyperkalemia, myoglobinuria (by definition true rhabdomyolysis causes myoglobinuria), and renal failure (for management, see Chapter 12, Fluid and Electrolyte Management, and Chapter 13, Renal Diseases). The potential etiologies include **M**etabolic (deficits of lipid or carbohydrate metabolism), **E**xcessive exercise/exertion (including seizures/dystonia), **D**rugs (abuse and

prescribed), **I**schemic, **C**ompression/crush (trauma), **I**nfection/ **I**nflammatory, **N**oxious (toxins), and **E**lectrolyte abnormalities (diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic syndrome, hypokalemia) (**"MEDICINE"**).
- **Botulism** is a disorder of the **neuromuscular junction** caused by ingestion of an exotoxin produced by *Clostridium botulinum*, acquired through a wound, or via an iatrogenic route.
  - The exotoxin interferes with release of acetylcholine from presynaptic terminals at the neuromuscular

junction.

- In infants, it is commonly attributed to gastrointestinal (GI) colonization in the first 6 months of life when normal gut flora is not yet present. Classically, it is associated with ingestion of raw honey, but inhalation/ingestion of soil-based spores is probably a more common means of absorption.
- Symptoms begin within 12-36 hours of ingestion in food-borne botulism and within 10 days in wound botulism.
- Symptoms include **autonomic dysfunction** (xerostomia, blurred vision, urinary retention, and constipation), followed by **cranial nerve palsies**, **descending weakness**, and **possibly respiratory distress**.
- **Serum assays for botulinum toxin** may aid diagnosis in adults.
- Management includes removing nonabsorbed toxin with **cathartics**, **supportive care**, and neutralizing absorbed toxin with **equine trivalent (A, B, E) antitoxin** (more immunogenic because it contains both the Fab and Fc portions) or **heptavalent (A, B, C, D, E, F, G) antitoxin** [less immunogenic as Fc portion is cleaved off and has $F(ab)_2$ portions]. Penicillin G is often administered, but no formal clinical trials have been performed. There is some evidence that botulism immune globulin can shorten hospital stay by approximately 2 weeks (*N Engl J Med 2006;354:462*).
- Recovery is slow and occurs spontaneously, but with appropriate ventilatory and supportive care, most make a full recovery.

Neuromuscular Disorders with Rigidity

GENERAL PRINCIPLES

- **NMS** is associated with the use of neuroleptic drugs, certain antiemetic drugs (e.g., metoclopramide, promethazine), and sudden withdrawal of dopamine agonists (L-dopa in PD) and can even occur as an "off" phenomenon in PD patients experiencing severe "on-off" fluctuations.
  - Features include hyperthermia, altered mental status, muscular rigidity, and dysautonomia.
  - Laboratory abnormalities include a leukocytosis and a markedly elevated creatine kinase with myoglobinuria.
  - Treatment includes discontinuing precipitating drug(s), restarting medications that were stopped (in the case of a PD patient), cooling and paralytics (if necessary), monitoring and supporting vital functions (arrhythmias, shock, hyperkalemia, acidosis, renal failure, and management of rhabdomyolysis), and administering dantrolene and/or bromocriptine. Treatment is essentially identical to that used for malignant hyperthermia (see the following text).
- **Serotonin syndrome** results from excessive serotonergic activity, especially following recent dosage changes of SSRIs, MAOIs, and TCAs.
  - It presents as a **triad of mental status change**, **autonomic overactivity**, and **neuromuscular abnormalities**. Distinguishing features of serotonin syndrome from NMS include the degree of mental status change, seizures, and the marked hyperreflexia. However, in certain circumstances, the two can be difficult to distinguish from one another.

  - Hyperthermia, tremor, nausea, vomiting, and clonus are common signs.
  - Treatment includes removal of offending drugs, aggressive supportive care, cyproheptadine, and

benzodiazepines (*N Engl J Med 2005;352(11):1112*).

- **Malignant hyperthermia** is the acute development of high fever, obtundation, and muscular rigidity following triggering factors (e.g., halothane anesthesia, succinylcholine).
  - The most common etiology is an autosomal dominant mutation in the ryanodine receptor (RyR1), making a screen of the family history a critical part of the preoperative evaluation. Abnormalities in this calcium channel predispose patients to an elevation in intracytoplasmic calcium triggered by certain anesthetics. Other ion channels have also been identified, and children with dystrophinopathies and other forms of muscular dystrophy are also at an increased risk.
  - **Serum creatine kinase is markedly elevated.** Renal failure from myoglobinuria and cardiac arrhythmias from electrolyte imbalance can be life threatening.
  - Successful management requires prompt recognition of early indicators of the syndrome (increased end-tidal carbon dioxide, tachycardia, acidosis, and/or muscle rigidity; note, hyperthermia comes later if at all); discontinuation of the offending anesthetic agent; aggressive supportive care that focuses on oxygenation/ventilation, circulation, correction of acid-base and electrolyte derangements; and administration of **dantrolene sodium**, 1-10 mg/kg/d, for at least 48-96 hours to reduce muscular rigidity.
- **Tetanus** typically presents with generalized muscle spasm (especially trismus) caused by the exotoxin (tetanospasmin) from *Clostridium tetani*, a gram-positive bacilli commonly found in intestinal flora and soil.
  - The organism usually enters the body through wounds. Onset typically occurs within 7-21 days of an injury (*Expert Rev Anti Infect Ther 2008;6(3):327*).
  - Patients who are **unvaccinated or have reduced immunity** are at risk, underscoring the importance of prevention by tetanus toxoid boosters following wounds. Tetanus may occur in **drug abusers who inject SC**.
  - Management consists of supportive care, particularly airway control (laryngospasm) and treatment of muscle spasms (benzodiazepines, barbiturates, analgesics, and sometimes neuromuscular blockade). Cardiac arrhythmias and fluctuations in BP can occur. Recovery takes months. Shorter incubation periods (≤7 days) portend more severe courses and a worse prognosis.
  - The patient should be kept in quiet isolation, sedated but arousable.
  - Specific measures include wound debridement, **penicillin G or metronidazole**, and **human tetanus immunoglobulin** (3000-6000 units IM).
  - **Active immunization** is needed after recovery (total of three doses of tetanus and diphtheria toxoid spaced at least 2 weeks apart).

28
Toxicology

S. Eliza Halcomb

Evan S. Schwarz

Michael E. Mullins

OVERDOSES

Overdose, General

GENERAL PRINCIPLES

- According to the American Association of Poison Control Centers (AAPCC), there were over 2 million exposures and 2113 fatalities related to toxins in 2013 (*Clin Toxicol 2014;52(10):1032*). Overdoses are common in the emergency department, and although they are rarely fatal, it is important to follow some general guidelines while caring for the poisoned patient.
- Patients who present to the hospital with an overdose can be challenging for the clinician. This section will begin with a review of the general approach to the poisoned patient, followed by a discussion of specific ingestions.
- When managing the poisoned patient, as with all patients, it is vital to make sure the patient has a patent airway, intact breathing, and palpable pulses. Beyond the basics of general emergency management, it is important to remember physiologic principles when approaching the poisoned patient. Quite often, patients can be categorized into one of five common toxidromes based on simple clinical examination findings. However, there are more than five unique toxidromes.

Definition

A **toxidrome**, or toxic syndrome, is a constellation of clinical examination findings that assists in the diagnosis and treatment of the patient who presents following an exposure to an unknown agent. The toxicologic physical examination should include documentation of **vital signs**, **pupillary diameter**, and **skin findings** (dry, flushed, or diaphoretic), as well as the presence or absence of **bowel sounds** and **urinary retention**.

Classification

There are **five general toxidromes** that encompass a variety of xenobiotic exposures. They include the following:

- **Sympathomimetic:** This toxidrome is characterized by widespread activation of the sympathetic nervous system. The vital sign abnormalities include **hypertension** due to α-adrenergic stimulation and **tachycardia** due to increased β-adrenergic tone. Patients may also present with pyrexia. Physical examination will reveal **pupillary dilatation**, **diaphoresis**, and occasionally, altered mental status. Drugs that can cause this type of toxidrome include cocaine, amphetamines, and the newer synthetic analogs (both the cannabinoids and cathinones). Likewise, vasopressors and β-adrenergic agonists can cause a partial syndrome depending on which agent is being used.
- **Cholinergic:** This toxidrome is characterized by the widespread activation of the parasympathetic nervous

system. Classically, the vital signs associated with a cholinergic toxidrome include **bradycardia** due to increased vagal tone, **respiratory depression** due to paralysis, and **decreased oxygen saturations** on pulse oximetry, due to **bronchoconstriction** and **bronchorrhea**. Excess acetylcholine (ACh) affects muscarinic receptors leading to the development of pinpoint pupils and the SLUDGE syndrome of **salivation, lacrimation, urination, defecation, gastrointestinal (GI) distress, and emesis**.

Excess ACh at the neuromuscular junction (NMJ) results in a depolarizing blockade of the muscles, leading to **fasciculations** and **paralysis**. In the central nervous system (CNS), cholinergic overload is associated with the development of **seizures** and **coma**. Agents linked with the development of this toxidrome all block the function of acetylcholinesterase (AChE), resulting in the accumulation of ACh in the synapse. These agents include organophosphate insecticides and nerve gases, as well as carbamate pesticides. Carbamates are also used therapeutically in anesthesia, myasthenia gravis, and the treatment of anticholinergic toxidromes. Certain types of mushrooms can also cause cholinergic symptoms.

- **Anticholinergic:** This toxidrome should perhaps be more appropriately described as an antimuscarinic syndrome. Its features include **tachycardia** due to vagal blockade and **hyperthermia** (which may be mild to severe). CNS effects include **agitation**, **delirium**, and in severe cases, seizures. Other peripheral effects include **mydriasis**; **dry**, flushed skin; **urinary retention**; and **decreased intestinal motility**. These patients classically demonstrate a “picking” motion. Therapeutic agents that cause this toxidrome include atropine, scopolamine, and antihistamines such as diphenhydramine.
- **Opioids:** The opioids produce a classic vital sign combination of **respiratory depression** and oxygen desaturations in conjunction with **miosis**, **decreased GI motility**, and **coma**. Opioids produce this toxidrome by binding to one of the four G protein receptors on the cell membrane, leading to analgesia. However, respiratory depression, miosis, and physical dependence are secondary, undesirable effects. Other agents that produce a similar toxidrome include the imidazolines, including clonidine, dexmedetomidine, tetrahydrozoline, and oxymetazoline.
- **Sedative hypnotic:** The benzodiazepines bind to γ-aminobutyric acid (GABA) receptors in the brain and cause a clinical picture of **sedation or coma** in the setting of **normal** vital signs. A common misconception is that ingested benzodiazepines cause respiratory depression. Although this may be true in the setting of IV administered benzodiazepines or when benzodiazepines are taken in combination with other agents, patients with a **benzodiazepine ingestion generally do not develop respiratory compromise**. Other sedatives can cause similar sedation or coma with respiratory depression.

DIAGNOSIS

Diagnostic Testing

If patients do not fall into any of the aforementioned categories, suspect a mixed or undifferentiated exposure, and several diagnostic tests should be ordered.

Laboratories

- **Finger stick blood glucose (FSBG):** This test should be considered one of the vital signs in the patient with altered mental status.
- **Chemistry:** A basic metabolic profile should be ordered on any patient with a toxic exposure. The two important pieces of information gleaned from the basic metabolic panel (BMP) include the presence or absence of a low bicarbonate and the creatinine. If the patient has a low bicarbonate, a metabolic acidosis is present and the clinician should calculate the **anion gap**. Patients who present with an elevated anion gap acidosis are often subjected to a battery of unnecessary studies because the

differential diagnosis is enormous. To tailor the diagnosis, the clinician should focus on a mechanistic approach and check serum **ketones** and **lactate**. If these are negative and the **creatinine** is normal, then one should suspect the presence of a toxic alcohol and send the appropriate studies.

- **Blood gas:** In most cases of intoxication, pH rather than oxygenation is of great relevance. Therefore, it is reasonable to send **venous blood gases (VBGs)** rather than arterial

blood gases (ABGs) in routine cases of poisoning. However, if adequate oxygenation is a concern (e.g., cyanide, carbon monoxide poisoning, methemoglobinemia), then an ABG should be sent. Co-oximetry can be sent from either arterial or venous samples.

- **Serum drug screen:** In general, the studies included on this panel include acetaminophen, salicylate, and ethanol concentrations. Rarely, laboratories may include a tricyclic antidepressant (TCA) screen.
  - In practice, the piece of information that is critical on this panel is the serum **acetaminophen** (*N*-acetyl-para-aminophenol [APAP]) because patients with this ingestion are often asymptomatic upon presentation and approximately 1 in 500 overdoses have been found to have an unsuspected and treatable APAP concentration (*Ann Emerg Med 1985;14:562*).
  - Acute **salicylate** ingestions, although very serious, produce a clinical syndrome that is readily identifiable at the bedside. Chronic salicylate toxicity should be suspected in elderly patients taking aspirin who present with altered mental status and tachypnea or patients with an unexplained anion gap metabolic acidosis.
  - **Ethanol** concentrations are ***not*** predictive of intoxication, despite the forensic definition of 80 mg/dL as the legal limit for driving. Intoxication is a clinical diagnosis. One of the pitfalls of routinely obtaining ethanol levels is that serious medical conditions may coexist in these often fragile patients. These conditions are frequently missed when the patient is thought to be drunk. The test is useful to exclude ethanol as the cause of altered mental status.
  - **TCA** screens are notoriously unreliable and cross-react with many therapeutic agents. In the absence of the characteristic ECG findings and vital sign abnormalities, a positive result is meaningless and is the source of confusion, leading to unnecessary treatment.
- **Urine drug screen:** Rarely contributes to the management of the patient. Many of the assays produce false-positive or false-negative results and may, in fact, cause harm by leading the clinician to attribute a patient's condition to intoxication rather than a medical emergency. Additionally, these tests are expensive to conduct and therefore are of limited value in the management of the poisoned patient. The urine drug screen tends to vary between hospitals but often tests for the following substances:
  - **Amphetamines:** The assay for amphetamines commonly cross-reacts with over-the-counter cold medications.
  - **Opioids:** This assay frequently misses the presence of the synthetic opioids such as fentanyl, methadone, and meperidine; therefore, it is important to rely on the toxidrome for the diagnosis.
  - **Cocaine:** This assay is not directed at the parent compound; rather, it detects the metabolite benzoylecgonine. Because the parent compound is very short lived, this test is very reliable for the identification of recent use, but in no way confirms intoxication.
  - **Cannabinoids:** Like cocaine, detection of the tetrahydrocannabinolic acid (THCA) metabolite is a reliable indicator of use; however, its presence does not have any bearing on the diagnosis of intoxication. In general, synthetic cannabinoids will ***not*** cause a positive test result.
  - **Benzodiazepines:** The detection of benzodiazepines most commonly relies on the detection of oxazepam; therefore, some commonly used benzodiazepines (such as lorazepam) are often missed by

this screening (*Clin Chem 2003;49:357*). Given that benzodiazepine overdoses tend to be benign, the utility of this component is questionable at best.

- **Phencyclidine (PCP):** Screening assays may cross-react with dextromethorphan, ketamine, and diphenhydramine to produce a false-positive result. Once again, the clinical picture is more important in the diagnosis of PCP intoxication, and the presence of PCP on a drug screen does not alter the management of a patient.

- Specific laboratory testing will be further addressed in the following text.

Electrocardiography

- The ECG is a critical part of the toxicologic evaluation, and certain overdoses produce characteristic ECG changes that guide diagnosis and treatment plans.
- In general, the important cardiac toxins tend to prolong the PR interval (reflecting nodal blockade), the QRS (reflecting sodium channel blockade), or the QT interval (potassium channel blockade).
- ECG changes specific to certain toxins will be further discussed in the following text.

Imaging

- In general, there is a limited role of diagnostic imaging in toxicology. However, there are a few cases when imaging may be helpful in the diagnosis and management of the poisoned patient. The most useful imaging study in overdose is the abdominal radiograph, which may reveal radiodense material in the stomach or gut in the following ingestions (*Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill, 2006:62*):
  - **C**hloral hydrate
  - **H**eavy metals
  - **I**ron
  - **P**henothiazines
  - **E**nteric-coated preparations
  - **S**ustained-release preparations
- Occasionally, subtle abnormalities on the abdominal film will detect the presence of "rosettes" or elongated packets in the GI tract of body packers (patients who swallow hundreds of packets of drugs in an attempt to smuggle them). The abdominal film is of limited utility in body stuffers (*Ann Emerg Med 1997;29:596*).

TREATMENT

As with any patient, it is crucial to maintain the airway, check for adequacy of breathing and circulation, and check an FSBG in the patient with altered mental status or coma.

- **Prevention of absorption:** Traditionally, gastric emptying by either inducing **emesis** or **lavage** has been a mainstay in the treatment of the acutely overdosed patient. However, the literature regarding these methods of decontamination suggests that they are of little benefit (*Med J Aust 1995;163:345*). Furthermore, numerous studies have suggested that patients present approximately 3-4 hours after ingestion on average, which tends to make it less likely that there will be a large recovery of pills (*Ann Emerg Med 1985;14:562*). Therefore, the routine administration of **ipecac** to children and "stomach pumping" have fallen by the wayside except in very specific circumstances.

- **Activated charcoal (AC)** has largely replaced both of these methods of gastric emptying (*Ann Emerg Med 2002;39:273*). However, the clinical utility of this method of decontamination is limited if the ingestion occurred more than 1 hour prior to presentation (*J Toxicol Clin Toxicol 1997;35:721*). As such, fewer toxicologists routinely recommend the administration of AC (*Int J Emerg Med 2014;4:65*). In addition, patients at risk for decreased mental status or seizures should not be given AC due to concerns for aspiration. Certain ingestions benefit from multidose AC because they either bind to concretions in the stomach (aspirin) or they decrease enterohepatic or enteroenteric reabsorption (phenobarbital, phenytoin, theophylline). AC should be dosed at 1 g/kg body weight.
- **Whole-bowel irrigation** is appropriate in patients who have ingested sustained-release medications, body packing, or metals that do not bind to AC. The optimal dose of polyethylene glycol is 1-2 L/h until the rectal effluent is clear. This dose is a large amount of fluid to ingest, so it is often necessary to place a nasogastric tube to achieve this rate of emptying.

- In cases **of life-threatening** ingestions such as colchicine or nondihydropyridine calcium channel blockers (CCBs), it is appropriate to consider **lavage** as well as **AC**.
- **Cathartics** have no role in the management of overdose. They are often present in the premixed AC solutions. If this is the case, only one dose should be administered.
- All of these interventions are **contraindicated** in the presence of airway compromise, persistent vomiting, and the presence of an ileus, bowel obstruction, or GI perforation.

- **Enhanced elimination**
  - **Forced diuresis** with normal saline and Ringer's lactate enhances the elimination of low-molecular-weight agents such as lithium in dehydrated individuals. This should be carefully monitored, and diuretics should be avoided in these patients.
  - **Urinary alkalinization** with IV sodium bicarbonate enhances the elimination of weak acids and is useful in the setting of salicylate overdose. Typical doses are 1-2 mEq/kg, with a goal of maintaining the urinary pH at approximately 7-8. Specific recommendations will be further discussed in the following text.
  - There is no role for **urinary acidification** in the management of overdoses.
  - **Hemodialysis and hemoperfusion** are reserved for life-threatening ingestions of substances that have a low volume of distribution, have a molecular weight of <500 Da, have a low endogenous clearance, are water soluble, and have little protein binding. This treatment modality will be further discussed under specific substances.
- **Antidotes** will be discussed under specific toxicities. The regional poison center or a medical toxicologist should be contacted for specific treatment guidelines.
- **Disposition**
  - Patients who have taken an overdose as a suicidal gesture should all receive a psychiatric evaluation prior to discharge.
  - Most cases of unintentional overdose do not result in significant morbidity, and in cases where the patient is stable and asymptomatic, a brief period of observation may be all that is necessary.
  - In cases where potentially toxic agents have been ingested, most patients should be monitored for 4-6 hours before discharge.

Acetaminophen

GENERAL PRINCIPLES

APAP is available worldwide as an over-the-counter analgesic and antipyretic and has become the most common pharmacologic agent involved in toxicologic fatalities (*Am J Emerg Med 2005;23(5):589*). The recommended maximum dose for adults is 4 g/d.

Classification

- An analgesic. Within the United States, APAP is sold under the trade name Tylenol. The most common trade name for APAP outside the United States is Paracetamol.
- Because of its use as an analgesic and antipyretic, APAP has become a common ingredient in various cold and flu remedies. It is also used in the treatment of fevers, headaches, and acute and chronic pain.
- APAP is often sold in combination preparations together with NSAIDs, opioid analgesics, or sedatives (e.g., Tylenol #3, Percocet, Vicodin, NyQuil, Tylenol PM).

Epidemiology

APAP is the leading cause of toxicologic fatalities per year in the United States, and APAP-induced hepatotoxicity is the most frequent cause of acute liver failure (*Med Clin North Am 2008;92(4):761*).

Etiology

- APAP is available as tablets, capsules, liquids, and suppositories. In addition to the more common immediate-release form, there is also an extended-release preparation (e.g., Tylenol Arthritis Pain).
- Unintentional overdosing is more common than intentional ingestion in suicide attempts, especially in elderly patients on chronic pain regimens including several APAP-containing painkillers (*Hepatol Res 2008;38:3*).
- All patients with presumed APAP overdose should be adequately assessed, evaluated, and treated. However, only the minority of poisoned patients require inpatient care (*Acad Emerg Med 1999;6(11):1115*).

Pathophysiology

- **Absorption:** APAP serum levels peak 30-60 minutes after oral ingestion; the extended-release preparations peak after 1-2 hours. Absorption is often delayed in overdose, and peak levels are usually reached after 2-8 hours. The overdose kinetics of extended-release APAP are not yet well established.
- **Overdose:** The hepatic conjugation pathways become saturated in overdose. A cascade of biochemical changes occurs in the liver, and centrilobular cell necrosis results (*Clin Pharmacol Ther 1974;16(4):676*).
  - Acetaminophen is metabolized predominantly via glucuronidation (47-62%) and sulfation (25-36%) by phase II metabolism in liver as nontoxic conjugate products. However, a small percentage is metabolized via oxidation (5-8%) by the cytochrome P450 (2E1) pathway to a toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI is conjugated by glutathione to nontoxic cysteine and mercapturic acid conjugates.
  - In cases of acetaminophen toxicity, the phase II conjugation enzymes are saturated, and a higher fraction of acetaminophen is conjugated via oxidation to NAPQI. The conjugation of NAPQI by glutathione occurs until glutathione is depleted from hepatic reserves, after which the toxic NAPQI and other free radicals accumulate and cause damage to the hepatocytes.

Risk Factors

- Decreased glutathione stores (fasting, malnutrition, anorexia nervosa, chronic alcoholism, febrile illness, chronic disease)
- P450 enzyme inducers (ethanol, isoniazid [INH], phenytoin and other anticonvulsants, barbiturates, smoking)

DIAGNOSIS

Clinical Presentation

- **First 24 hours—**Asymptomatic stage (stage 1):
  - Early symptoms are very nonspecific and primarily related to the GI tract (nausea, vomiting, anorexia).
  - High-dose APAP can cause pallor or lethargy in some patients. Rarely, very high doses can inhibit aerobic metabolism.
  - This initial phase has few symptoms and patients appear pretty unremarkable. Therefore, always think of other coingestants if a patient exhibits extreme vital sign abnormalities or other significant symptoms during the first 24 hours.
- **24-48 hours—**Hepatotoxic stage (stage 2):
  - Right upper quadrant (RUQ) tenderness is the most common symptom.
  - Transaminitis, bilirubinemia, and elevated prothrombin time (PT)/international normalized ratio (INR) are also common findings during the second phase.
- **2-4 days—**Fulminant hepatic failure stage (stage 3): Significant hepatic dysfunction develops (i.e., a peak in hepatic enzyme elevation along with jaundice, coagulopathy with

  high risk of spontaneous bleeding, hypoglycemia, anuria, and cerebral edema with coma or even death).
- **4-14 days—**Recovery stage (stage 4): If stage 3 is survived, the hepatic dysfunction usually resolves over the following days/weeks.

History

- To predict the risk of hepatotoxicity after acute overdose, a reliable time of ingestion must be obtained from the patient or family/friends.
- Also obtain information about the amount of APAP that has been ingested, in what form (e.g., combination preparations, extended-release form), and over what period of time.
- Inquire about other coingestants (alcohol, other medications, other drugs).

Physical Examination

Assess airway, breathing, and circulation (ABCs) and mental status. The assessment of mental status is crucial, especially in patients who are nauseated or vomiting, to intervene with airway protection in time.

Diagnostic Criteria

- In general, a dose of 150 mg APAP per kilogram is the potentially toxic limit that requires therapeutic intervention. This limit includes an added 25% safety margin that was added by the US Food and Drug Administration (FDA) to adjust for patients with multiple risk factors for increased liver toxicity (*BMJ 1998;316(7146):1724*).
- If the total amount of ingested APAP is >150 mg/kg or cannot be obtained from the patient history, it is crucial to predict the risk of toxicity.

- Obtain an APAP serum level at 4 hours or later after ingestion.
- Plot the APAP concentration on the **Rumack-Matthew nomogram** (APAP serum concentration vs. time after ingestion) to assess the possibility of hepatic toxicity. NOTE: The nomogram should only be used for acute ingestions and cannot be used until 4 hours after the ingestion.
- During treatment of APAP overdose, it is important to assess the risk of progressive liver failure. The King's College Hospital (KCH) criteria provide prognostic markers that help to predict the probability of developing severe liver damage (*Gastroenterology 1989;97(2):439*):
  - pH <7.3, 2 days after ingestion
  - All of the following: PT >100 (INR >6), serum creatinine >3.3 mmol/L, severe hepatic encephalopathy (grade III or IV)
- Elevated serum phosphate levels >1.2 mmol/L (>3.72 mg/dL) on days 2-4 (additional criterion, not originally part of KCH criteria) (*Hepatology 2002;36(3):659*).
- Arterial serum lactate >3.0 mmol/L (>27 mg/dL) after fluid resuscitation (additional criterion, not originally part of KCH criteria) (*Lancet 2002;359(9306):558*).

Diagnostic Testing

- **APAP serum level at 4 hours** after ingestion or later (see earlier discussion).
- **Liver function tests (LFTs)**—Aspartate aminotransferase (AST) is a relatively sensitive nonprognostic marker for hepatic injury.
- **PT/INR**, **serum bicarbonate**, **blood pH**, serum **lactate**, **renal function panel**, and serum **phosphate** level are the prognostic markers for hepatic injury.
- APAP may interfere with some blood sugar test kits causing measurements higher or lower than actual; always recheck FSBG over the course of hospitalization (*Am J Clin Pathol 2000;113(1):75*).

TREATMENT

Gastric lavage is not useful in APAP overdose; however, it may be indicated in presence of certain other coingestants.

Medications

- **AC:** Only indicated in patients with isolated APAP exposure (with no other evidence of mentally altering substances) who present less than 4 hours after ingestion. Give **1 g/kg PO**.
- ***N*-Acetylcysteine (NAC):** NAC is the specific antidote to prevent APAP-related hepatotoxicity (*Toxicol Sci 2004;80(2):343*). NAC replenishes depleted glutathione stores. It should be administered early (i.e., within 8 hours after ingestion) to prevent any liver damage. NAC is a nonspecific antioxidant and will still provide some liver protection if given beyond this time window (*J Clin Invest 1983;71(4):980*).
  - **Oral dosing:** Loading dose of 140 mg/kg PO, then 70 mg/kg PO every 4 hours for a total of 17 doses (i.e., 1330 mg/kg over 72 hours) (*N Engl J Med 1988;319(24):1557*).
  - **IV dosing:** Prepare the infusion by adding 30 g of a 20% NAC solution (150 mL) to 1 L dextrose 5% in water (D5W). This will result in a final concentration of 30 mg/mL. Load with a dose of 150 mg/kg NAC IV over 1 hour. Thereafter, continue to give 14 mg/kg/h IV for 20 hours (i.e., 430 mg/kg over 21 hours) (according to IV NAC treatment protocol used by Toxicology Service at Barnes-Jewish Hospital). (See also *Ann Pharmacother 2011;45(6):713*.) This is a different dosing strategy than what is recommended

in the package insert. Multiple hospitals have modified their dosing strategy to decrease administration errors.
    - **NAC administration** can be safely stopped prior to the completion of the total regimen as soon as the APAP level returns to 0, INR <2.0, and AST normalizes (or reaches less than half of the peak level during acute intoxication).
- **NAC indications:** NAC treatment should be started in the following:
    - Any patient after acute poisoning with a toxic APAP level according to the nomogram.
    - Patients who present beyond 8 hours after acute ingestion. Start NAC therapy while awaiting the initial APAP serum level. Continue treatment if the serum concentration is in the toxic range per nomogram.
    - Patients who present more than 24 hours after acute ingestion and still have a detectable serum APAP level or elevated AST.
    - Patients with chronic APAP exposure (i.e., >4 g/d in adults, >120 mg/kg/d in children) who present with elevated transaminases.
    - Patients with signs of fulminant hepatic failure. NAC treatment should be started immediately, and transfer to a transplant center should be arranged without fail. NAC has been shown to improve survival of patients in fulminant hepatic failure (*Lancet 1990;335(8705):1572*; *N Engl J Med 1991;324(26):1852*; *BMJ 1991;303(6809):1026*).
- **Oral versus IV NAC:**
    - IV administration of NAC is the preferred route because it is used in all of the studies of patients with fulminant hepatic failure.
    - Oral administration may be slightly safer compared to the IV form; however, NAC has a rather bad odor and taste. Rash, flushing, urticaria, nausea/vomiting, angioedema, bronchospasm, tachycardia, and hypotension have been reported as adverse reactions to IV administration (*BMJ 1984;289(6439):217*).
    - If oral NAC is given, dilute the NAC with juice, provide a drinking straw and place a lid on the glass, and give IV antiemetics (e.g., metoclopramide [Reglan], ondansetron [Zofran]).
    - Consider oral over IV NAC in patients who are prone to anaphylactoid reactions (e.g., severe asthmatics).
    - NAC is effective either way when given within 8 hours after ingestion (*N Engl J Med 1988;319(24):1557*).
    - AC adsorbs oral NAC. Both PO and IV NAC regimens provide enough excess of the drug to ensure adequate therapeutic effects. Nevertheless, it is advised to administer AC 2 hours apart from NAC when given PO.

COMPLICATIONS

- Overdose with extended-relief APAP (*Ann Emerg Med 1997;30(1):104*):
    - Get APAP serum level 4 hours after ingestion.
    - If toxic per nomogram, treat with full NAC course.
    - If below toxic level per nomogram, get repeat APAP at 8 hours after ingestion.
    - If now toxic, treat with full course. If remains below toxic level, no therapy necessary.
- Patients with progressing liver failure need to be admitted to an intensive care unit (ICU) bed with close

monitoring for hyperglycemia, electrolyte imbalances, GI bleeding, acid-base disturbances, cerebral edema, infections, and renal failure.

REFERRAL

- Involve a clinical toxicologist in all cases where toxic APAP levels are documented. Discuss the initiation of NAC treatment with the toxicology service where possible.
- Inform your regional poison control center (1-800-222-1222).
- Involve the liver or transplant service early in patients presenting with poor prognostic factors for hepatic failure.
- Patients with toxic liver failure should be transferred to a transplant center as early as possible (*BMJ 1991;303(6796):221*; *J R Soc Med 1997;90(7):368*).

Colchicine

GENERAL PRINCIPLES

Definition

Colchicine is the active alkaloid extracted from two plants of the Liliaceae family: *Colchicum autumnale* (autumn crocus) and *Gloriosa superba* (glory lily). It has been used in the therapy of gout for centuries.

Etiology

Colchicine has a very narrow therapeutic index. Severe poisoning and death can result from the ingestion of as little as 0.8 mg/kg of body weight (*Nouv Presse Med 1977;6:1625*).

Pathophysiology

Colchicine is an effective inhibitor of intracellular microtubule formation, leading to impaired leukocyte chemotaxis, and phagocytosis, resulting in a decrease in the inflammatory cascade (*JAMA 2003;289:2857*). In overdose, colchicine causes mitotic arrest, leading to cellular dysfunction and death (*J Emerg Med 1994;12:171*).

Prevention

Patients who are started on colchicine for gout symptoms should be explicitly directed to stop taking the medication as soon as symptoms of diarrhea occur. They should also be told that increasing the dose in an acute flare can result in significant toxicity; therefore, if they are unable to control the symptoms at home, they should seek expert care early.

DIAGNOSIS

Clinical Presentation

Patients who present with a colchicine overdose tend to develop a syndrome that progresses through three phases. The initial phase usually begins several hours after the overdose and

is characterized by nausea, vomiting, and diarrhea. Over the next 1-7 days, patients may develop multiorgan failure requiring intensive support or sudden cardiac death; death is common at this stage. In the final phase, patients develop alopecia and myoneuropathies.

History

Patients with inadvertent overdoses will present with a recent history of an acute gouty flare, followed by the development of nausea, vomiting, and diarrhea within a few hours after the overdose. Intentional overdoses may present late and should be suspected in patients with a GI syndrome followed by multiorgan failure.

Physical Examination

The exam tends to be somewhat unremarkable in these patients. They may exhibit signs of dehydration with tachycardia and dry mucous membranes. They may also have decreased urine output. As the toxicity progresses, patients may develop signs of worsening distress and confusion requiring aggressive resuscitation measures. As the disease evolves, fatal cardiac arrhythmias and refractory cardiovascular collapse may occur, usually within a week of overdose (*J Forensic Sci 1994;39:280*). Reversible alopecia has been reported in survivors (*J Emerg Med 1994;12:171*).

Differential Diagnosis

As with any ingestion, the differential diagnosis is large. However, GI symptoms are common in patients with overdoses of methylxanthines, podophyllin, digoxin and other cardioactive steroids, chemotherapeutic agents, heavy metals, and salicylates.

Diagnostic Testing

There is a very interesting sequence of laboratory findings that should lead one to consider colchicine poisoning in patients.

Laboratories

- **Complete blood cell count (CBC):** In the initial phase of poisoning that lasts for approximately 12-24 hours, patients develop a leukocytosis. In the next 48-72 hours, signs of bone marrow suppression evolve, starting with a profound decline in the leukocyte count and subsequent pancytopenia.
- **BMP:** Colchicine poisoning has also been associated with renal failure and adrenal hemorrhage (*J Anal Toxicol 1991;15:151*); therefore, electrolytes should be monitored.
- **LFTs:** Colchicine overdoses have been reported to cause hepatotoxicity; therefore, LFTs should be monitored.
- **Coagulation studies:** Disseminated intravascular coagulation (DIC) occasionally occurs; therefore, a full panel, including fibrinogen and fibrin split products, should be obtained.
- **Colchicine concentrations:** Colchicine has a narrow therapeutic index, and plasma concentrations >3 ng/mL may produce significant toxicity. However, this laboratory test is not readily available, and toxicity should be suspected if clinical symptoms and laboratory studies are supportive. This test should be thought of as a confirmatory study.
- **Other studies:** Creatine kinase (CK; or creatine phosphokinase [CPK]), troponin, lipase, and other electrolytes should be obtained depending on the clinical scenario.

Electrocardiography

An ECG should be obtained at presentation, given the patient's predilection for developing cardiac arrhythmias, and the patient should be admitted with continuous cardiac monitoring.

Imaging

Colchicine toxicity has been associated with the development of acute respiratory distress syndrome (ARDS). Therefore, a CXR should be obtained.

TREATMENT

Colchicine overdoses are often fatal and require aggressive supportive measures. As always, airway protection is of paramount importance followed by adequacy of breathing and support of circulation.

Medications

In cases of severe neutropenia, consider **granulocyte colony-stimulating factor (G-CSF)** administration.

Other Nonpharmacologic Therapies

- If the patient is **not** vomiting, consider **gastric lavage** and **AC**. If the patient is altered and vomiting, consider early **endotracheal intubation**. **Fluids** and direct-acting **vasopressors** should be used in cases of hypotension. **Hemodialysis** is not useful for clearing colchicine, given its large volume of distribution; however, it should be used in the setting of colchicine-induced renal failure.
- All symptomatic patients should be admitted to the ICU. Patients without symptoms should be monitored for 8-12 hours prior to discharge.

SPECIAL CONSIDERATIONS

Given its narrow therapeutic window and pharmacokinetics, colchicine should be used cautiously in patients with underlying renal or liver dysfunction. Likewise, colchicine is a P450 drug and is subject to many drug-drug interactions (*Biochem Pharmacol 1997;10:111*). A thorough review of the patient's medication list should be conducted before starting the patient on this agent because toxic concentrations can accumulate rapidly. In this setting, consider using alternative therapies for the management of acute gouty flares.

Nonsteroidal Anti-Inflammatory Drugs

GENERAL PRINCIPLES

- NSAIDs are widely prescribed as analgesics for the management of inflammatory diseases. There are many different classes available; however, the discussion in the following text relates to over-the-counter preparations available in the United States and includes ibuprofen, ketoprofen, and naproxen as well as the selective cyclooxygenase (COX)-2 inhibitors.
- NSAIDs exert their therapeutic effects by inhibiting COX and thereby preventing the formation of prostaglandins. This mechanism accounts for both their therapeutic and toxic side effects, which include ulceration of the GI mucosa and renal dysfunction. In the vast majority of cases, overdose is benign.

DIAGNOSIS

Clinical Presentation

Overdose histories are often unreliable. Consider NSAID overdose in patients who present with **GI distress**. **Massive overdose** with ibuprofen occasionally presents with **coma, a metabolic acidosis, and seizures**.

Diagnostic Testing

Obtain a **BMP** to evaluate renal function and hydration status. An **APAP** concentration should be obtained because many patients confuse over-the-counter analgesics.

TREATMENT

Usually supportive care is all that is necessary for the management of this overdose. IV fluids (IVF) are beneficial for maintaining hydration in vomiting patients.

Medications

- **Antiemetics and antacids** are beneficial in patients with significant distress.
- **Benzodiazepines** should be used for the management of seizures associated with massive ibuprofen overdose.

Opioids

DIAGNOSIS

Clinical Presentation

Symptoms of opioid overdose are respiratory depression, a depressed level of consciousness, and **miosis**. However, the pupils may be dilated with acidosis or hypoxia or after overdoses with meperidine or diphenoxylate plus atropine. Overdose with fentanyl or derivatives such as α-methyl fentanyl ("China white") may result in negative urine toxicology screens.

Diagnostic Testing

Laboratories

Drug concentrations and other standard laboratory tests are of little use. Pulse oximetry and **ABG**s are useful for monitoring respiratory status. Capnography measuring end-tidal CO_2 is more sensitive in detecting impending respiratory arrest as hypercapnia precedes hypoxemia.

Electrocardiography

- **Methadone** has been reported to cause a **prolonged QT_c**. Obtain an ECG in suspected overdose.
- **Propoxyphene** exhibits type IA antidysrhythmic effects due to sodium channel blockade and may present with a **wide complex QRS** on ECG (*Acta Pharmacol Toxicol 1978;42:171*).

Imaging

A CXR should be obtained if pulmonary symptoms are present.

TREATMENT

- Treatment includes airway maintenance, ventilatory support, and judicious use of opioid antagonist.
- Avoid gastric lavage.
- Limit use of whole-bowel irrigation to body packers. Body packers rarely require surgery, except in cases of intestinal obstruction.
- Endoscopic removal should not be attempted due to the danger of rupture.

Medications

- **Naloxone hydrochloride** specifically reverses opioid-induced respiratory and CNS depression and hypotension.
  - The lowest effective dose should be used. The goal of treatment is adequate spontaneous respiration and not alertness. The initial dose is 0.04-2 mg IV, although the lowest effective dose should be used.
  - Larger doses (up to 10 mg IV) may be required to reverse the effects of propoxyphene, diphenoxylate, buprenorphine, or pentazocine. Interestingly, large doses of naloxone following buprenorphine overdose can result in paradoxical respiratory depression.

  - In the absence of an IV line, naloxone can be administered sublingually (*Ann Emerg Med 1987;16:572*), via endotracheal tube, IM, or intranasally (*Emerg Med J 2006;23:221*). Isolated opioid overdose is unlikely if there is no response to a total of 10 mg naloxone. Repetitive doses may be required (duration of action is 45 minutes), and this should prompt hospitalization despite the patient's return to an alert status.
  - Methadone overdose may require therapy for 24-48 hours, whereas levo-α-acetylmethadol may require therapy for 72 hours. A continuous IV drip that provides two-thirds of the initial dose of naloxone hourly, diluted in D5W, may be necessary to maintain an alert state (*Ann Emerg Med 1986;15:566*).
  - Ventilatory support should be provided for the patient who is unresponsive to naloxone and for pulmonary edema.
- **Disposition**
  - If the patient is alert and asymptomatic for 4-6 hours after a single dose of naloxone or for 4 hours after a single treatment for an IV overdose, he or she can be discharged safely (*N Engl J Med 2012;367(2):146*).
  - Body packers should be admitted to an ICU for close monitoring of the respiratory rate and level of consciousness and remain so until all packets have passed, as documented by CT.

SPECIAL CONSIDERATIONS

- Heroin may be adulterated with scopolamine, cocaine, clenbuterol, or caffeine, complicating the clinical picture. Less common complications include hypotension, bradycardia, and pulmonary edema.
- Be aware of body packers who smuggle heroin in their intestinal tracts. Deterioration of latex or plastic containers may result in drug release and death (*Am J Forensic Med Pathol 1997;18:312*).

Salicylates

GENERAL PRINCIPLES

- Salicylate toxicity may result from **acute or chronic** ingestion of acetylsalicylic acid (aspirin is a generic name in the United States, but a brand name in the rest of the world). Toxicity is usually mild after acute ingestions of <150 mg/kg, moderate after ingestions of 150-300 mg/kg, and generally severe with overdoses of 300-500 mg/kg.
- Toxicity from chronic ingestion is typically due to intake of >100 mg/kg/d over a period of several days and

usually occurs in elderly patients with chronic underlying illness. Diagnosis is often delayed in this group of patients, and mortality is approximately 25%. Significant toxicity due to chronic ingestion may occur with blood concentrations lower than those associated with acute ingestions.

- Topical preparations containing methyl salicylate or oil of wintergreen can cause toxicity with excessive topical use or if ingested.

DIAGNOSIS

Clinical Presentation

- Nausea, vomiting, tinnitus, tachypnea, hyperpnea, and malaise are common. Hyperthermia results from uncoupled mitochondrial oxidative phosphorylation and suggests a poor prognosis.
- Severe intoxications may include lethargy, acidosis, convulsions, and coma, which may result from cerebral edema and energy depletion in the CNS.

- Noncardiogenic pulmonary edema may occur and is more common with chronic ingestion, cigarette smoking, neurologic symptoms, and older age.
- Severe overdoses of >300 mg/kg may present with tachypnea, dehydration, pulmonary edema, altered mental status, seizures, or coma.

Diagnostic Testing

Laboratories

- Obtain electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and salicylate concentration.
- Obtain either ABGs or VBGs.
- ABGs may reveal an early respiratory alkalosis, followed by metabolic acidosis.
  - Approximately 20% of patients exhibit either respiratory alkalosis or metabolic acidosis alone (*J Crit Illness 1986;1:77*).
  - Most adults with pure salicylate overdose have a primary metabolic acidosis and a primary respiratory alkalosis.
  - After mixed overdoses, respiratory acidosis may become prominent (*Arch Intern Med 1978;138:1481*).
- Serum salicylate concentrations drawn after acute ingestion of salicylates assist in prediction of severity of intoxication and patient disposition. However, **do not rely upon the Done nomogram**.
  - Salicylate concentrations >70 mg/dL at any time represent moderate to severe intoxication.
  - Salicylate concentrations >100 mg/dL are very serious and often fatal. This information is useful only for acute overdoses of non-enteric-coated aspirin.
  - Enteric-coated aspirin may have delayed absorption and delayed peak concentration.
  - Chronic ingestion can cause toxicity with lower salicylate concentrations.
  - Bicarbonate concentrations and pH are more useful than salicylate concentrations as prognostic indicators in chronic intoxication.
  - Be aware of units. The majority of hospitals report salicylate concentrations in mg/dL. However some hospitals still report concentrations in mg/L, which has caused multiple interpretation errors.

Imaging

- Repeated blood salicylate concentrations that fail to adequately decline could indicate the formation of a bezoar or concretion and may require imaging. Salicylate concretions may require endoscopy, multiple-

dose AC, or bicarbonate lavage.

- Consider whole-bowel irrigation with polyethylene glycol.

TREATMENT

Medications

- Administer 50-100 g of **AC** if presentation is within 1 hour of ingestion.
- **Multidose charcoal** may be useful in severe overdose (*Pediatrics 1990;85:594*) or in cases in which salicylate concentrations fail to decline (due to possible gastric bezoar formation).
- In an acute overdose, most patients will be volume depleted and benefit from receiving 1-2 L of saline. Caution should be used in patients with renal failure or congestive heart failure.
- **Alkaline diuresis** is indicated for symptomatic patients with salicylate blood concentrations >30-40 mg/dL.
  - Administer 150 mEq (three ampules) sodium bicarbonate in 1000 mL D5W at a rate of 10-15 mL/kg/h if the patient is clinically volume depleted until urine flow is achieved.

  - Maintain alkalinization using the same solution at 2-3 mL/kg/h, and monitor urine output, urine pH (target pH, 7-8), and serum potassium. Successful alkaline diuresis requires the simultaneous administration of potassium chloride. Hypokalemia will prevent adequate alkalinization.
  - Give **40 mEq potassium chloride** IV piggyback (IVPB) over 4-5 hours. Give additional potassium chloride either orally or IV as needed to maintain serum potassium concentration above 4 mEq/L.
  - **Use caution with alkaline diuresis in older patients**, who may have cardiac, renal, or pulmonary comorbidity, because pulmonary edema is more likely to occur in this population.
- **Do not use acetazolamide** (carbonic anhydrase inhibitor). Although acetazolamide alkalinizes the urine, it increases salicylate toxicity because it also alkalinizes the CNS (trapping more salicylate in the brain) and worsens acidemia.
- **Hyperventilate any patient requiring endotracheal intubation.** In salicylate-poisoned patients with tachypnea and hyperpnea, the respiratory alkalosis partially compensates for the metabolic acidosis. Mechanical ventilation with neuromuscular paralysis, sedation, and "normal" ventilator rates will remove the respiratory alkalosis, worsen acidosis, and cause rapid deterioration or death. Administering one to two ampules of sodium bicarbonate (50-100 mEq) immediately prior to the intubation should be considered. Patients requiring intubation will most likely also require hemodialysis.
- **Treat altered mental status with IV dextrose**, despite normal blood glucose.
- Treat cerebral edema with hyperventilation and osmotic diuresis.
- Treat **seizures** with a **benzodiazepine** (diazepam, 5-10 mg IV q15min up to 50 mg) followed by **phenobarbital**, 15 mg/kg IV. Give **dextrose** 25 g IV immediately following seizure control.

Other Nonpharmacologic Therapies

- **Hemodialysis** is indicated for blood concentrations >100 mg/dL after acute intoxication. However, patients with rising levels despite therapy, acidosis, pulmonary edema, or cerebral edema, and patients who cannot receive a large amount of fluid may also require hemodialysis even with concentrations <100 mg/dL. Hemodialysis rapidly removes salicylate and corrects acidosis. Hemodialysis may be useful with chronic toxicity when salicylate concentrations are as low as 40 mg/dL in patients with any of the following: persistent acidosis, severe CNS symptoms, progressive clinical deterioration, pulmonary

edema, or renal failure.

- Treatment of pulmonary edema may also require mechanical ventilation with a high fraction of inspired oxygen concentration and positive end-expiratory pressure (in addition to high respiratory rate).

SPECIAL CONSIDERATIONS

- Admit moderately symptomatic patients for at least 24 hours. Repeat serum salicylate concentration, electrolytes, BUN, creatinine, and glucose at least every 6 hours to confirm declining salicylate concentration, improving bicarbonate concentration, and stable potassium concentration. Measure urine pH at least every 6 hours (if patient has urinary bladder catheter) or with each spontaneous void to confirm urinary alkalinization.
- Admit patients with severe overdoses to an ICU. Even in patients with hemodynamic stability, the nursing requirements may be too intensive to be managed on the floor. Monitor laboratory studies as with moderately ill patients. Closely monitor ABGs. Arrange for immediate hemodialysis. Use great caution with mechanical ventilation, and hyperventilate any patient who requires mechanical ventilation.

ANTICONVULSANTS

Phenytoin and Fosphenytoin

GENERAL PRINCIPLES

Classification

There are four major mechanisms by which anticonvulsants exert therapeutic activity— sodium channel blockade, GABA agonism, calcium channel antagonism, and inhibition of excitatory amino acids. In overdose, these features are enhanced.

Pathophysiology

- Phenytoin has been a first-line treatment for seizures since its introduction. Fosphenytoin was developed as a response to some of the toxicity associated with IV phenytoin administration. Fosphenytoin is a prodrug that is converted to phenytoin after IV or IM injection and therefore will be referred to as phenytoin in the following text.
- **Neither of these drugs is indicated for the treatment of toxin-induced seizures** (*N Engl J Med 1985;313:145*), **including ethanol withdrawal seizures** (*Ann Emerg Med 1991;20:520*).
- Phenytoin exerts therapeutic activity by binding to sodium channels and inhibiting reactivation (*J Neural Transm 1988;72:173*). Phenytoin exhibits saturable kinetics, and at plasma levels >20 µg/mL, toxic effects become rapidly apparent.
- Acute toxicity is associated with the development of a **neurologic syndrome** that appears to be cerebellar in origin. **Cardiotoxicity** is **not** associated with phenytoin **ingestion** (*Heart Lung 1997;26:325*); however, it has been **reported with IV administration** of phenytoin. Rapid IV administration slows cardiac conduction and decreases systemic vascular resistance and myocardial contractility. The cardiac toxicity associated with IV phenytoin administration is due in part to the presence of propylene glycol and ethanol in the diluent, which are known myocardial depressants and vasodilators (*Am J Cardiol 1966;17:332*). The introduction of fosphenytoin has decreased the incidence

of cardiac complications.

Risk Factors

Other than overdose, risk factors for developing phenytoin toxicity are associated with the coadministration of drugs that affect the **cytochrome P450** system.

DIAGNOSIS

There are several classic clinical findings that point to the diagnosis of phenytoin toxicity.

Clinical Presentation

History

Patients exhibiting toxicity from phenytoin will often be brought in by family members who will describe the patient as **ataxic** and increasingly **confused**. There is usually a history of seizure disorder, and the medication list will include phenytoin. In intentional overdoses, the patient may be lethargic with slurred speech and an extrapyramidal movement disorder (*Ann Emerg Med 1989;7:61*).

Physical Examination

- At plasma concentrations of >15 µg/mL, patients will exhibit **nystagmus**. **Ataxia** develops at levels of 30 µg/mL. **Confusion** and **frank movement disorders** occur at levels of 50 µg/mL or greater. Chronic phenytoin ingestion is also associated with **gingival hyperplasia**, which is a very useful clinical finding when uncertain of the diagnosis. **Ingestions** are **not** associated with **cardiotoxicity** or vital sign abnormalities (*Ann Emerg*

Med 1991;20:508). Rapid **IV** administration of phenytoin results in **hypotension** and **bradycardia**. **Death** has been reported (*JAMA 1968;20:2118*).
- **Extravasation** injury is a serious complication of IV phenytoin administration and can result in severe tissue injury described as **the purple glove syndrome**. This injury will occasionally require surgical debridement (*Neurology 1998;51(4):1034*).
- **Given the potential for these complications**, unless a patient is unable to tolerate PO administration, it is preferable to administer phenytoin by the PO route.

Differential Diagnosis

Phenytoin toxicity is similar in presentation to carbamazepine poisoning; however, carbamazepine tends to exhibit cardiotoxicity. Other considerations include a convulsive status epilepticus, meningitis, encephalitis, or other intracerebral lesion.

Diagnostic Testing

Laboratories

- **Serial phenytoin concentrations** (corrected for albumin, because phenytoin is highly protein bound) should be obtained on any patient with a potential history of exposure.
- CBC: Phenytoin has been reported to occasionally cause agranulocytosis.
- LFTs: Phenytoin is associated with the occasional development of hepatotoxicity.

Electrocardiography

ECGs and telemetry are generally not needed in oral overdoses (*Ann Emerg Med 1991;20:508*). However,

in IV infusions, it is necessary to have the patient in a monitored setting.

TREATMENT

- Admission is warranted for patients with ataxia, and serial levels should be obtained while in the hospital.
- Supportive care is the mainstay of treatment for acute or chronic phenytoin toxicity.

  Multidose AC (MDAC) is useful in decreasing the serum half-life; however, given the pharmacokinetic profile of this drug, it is possible to rapidly lower the serum concentration below therapeutic levels and precipitate a seizure.
- **Benzodiazepines** are the mainstay of treatment for seizures.
- Hypotension and bradycardia in the setting of IV administration are usually self-limiting and will resolve with supportive care. In refractory bradycardia or hypotension, advanced cardiac life support (ACLS) principles apply.
- Cases of agranulocytosis are responsive to **G-CSF** administration.
- Hepatotoxicity usually resolves with the discontinuation of the drug.

Surgical Management

In cases of extravasation, it is important to have a surgical evaluation to determine the need for operative debridement.

SPECIAL CONSIDERATIONS

Phenytoin is generally of limited use in the treatment of active seizures. Because the mainstay of treatment is benzodiazepine administration and IV phenytoin is associated with significant toxicity, it is better to orally load patients whenever possible.

OUTCOME/PROGNOSIS

Phenytoin overdoses tend to be benign and self-limiting with supportive care. Deaths are exceedingly unusual even in the setting of massive overdose.

Carbamazepine/Oxcarbazepine

GENERAL PRINCIPLES

Definition

Carbamazepine and oxcarbazepine are structurally related to TCAs. Like fosphenytoin, oxcarbazepine is a prodrug that is metabolized to an active metabolite. Carbamazepine and oxcarbazepine are anticonvulsants.

Pathophysiology

- The therapeutic efficacy of carbamazepine and oxcarbazepine is due to **sodium channel blockade**, which prevents the propagation of an abnormal focus. The therapeutic serum concentration of carbamazepine is 4-12 mg/L. There is no routine laboratory testing for oxcarbazepine; however, the

carbamazepine assay will detect the presence of oxcarbazepine.

- The toxicity associated with carbamazepine is likely due to its chemical structure. TCA-like effects include sodium channel blockade, QT prolongation, and anticholinergic features.
- In overdose, carbamazepine is erratically absorbed and may form concretions in the GI tract causing prolonged toxicity.
- Persistently high levels of carbamazepine have been reported to increase antidiuretic hormone secretion leading to syndrome of inappropriate antidiuretic hormone release (SIADH) (*Prog Neuropsychopharmacol Biol Psychiatry 1994;18:211*).

Risk Factors

Carbamazepine toxicity may be enhanced by concomitant use of drugs that are metabolized by the cytochrome P450 system.

DIAGNOSIS

There are several key features of carbamazepine toxicity.

Clinical Presentation

History

Toxicity should be suspected in individuals who present with a history of a seizure disorder and altered mental status. **Delayed toxicity** has been reported after an acute overdose given the variability in GI absorption (*J Toxicol Clin Toxicol 1979;14:263*). Patients may exhibit a relapsing syndrome of coma and altered consciousness due to bezoar formation and enterohepatic recirculation.

Physical Examination

- The predominant clinical findings in carbamazepine toxicity are neurologic and cardiovascular effects. In mild to moderate toxicity, patients may present with ataxia, nystagmus, and mydriasis. In serious overdose, patients may develop **coma** and **seizures**, including status epilepticus. Vital sign abnormalities include **tachycardia**, due to the anticholinergic effects of the drug, as well as **hypotension** and **bradycardia**, due to direct myocardial depressant effects.
- The combination of cerebellar findings on exam, in conjunction with an anticholinergic toxidrome, should prompt the clinician to consider carbamazepine as a potential toxicant.

Differential Diagnosis

Mild to moderate carbamazepine toxicity resembles phenytoin toxicity. Other considerations include a convulsive status epilepticus, meningitis, encephalitis, or other intracerebral lesion.

Diagnostic Testing

- Serum carbamazepine concentrations should be obtained on any patient who presents with a history of ingestion. The therapeutic range is from 4-12 mg/L. Serial levels should be obtained every 4-6 hours to evaluate for delayed toxicity or prolonged absorption. Concentrations of >40 mg/L are associated with the development of cardiotoxicity (*J Toxicol Clin Toxicol 1993;31:449*).
- Patients with carbamazepine overdoses will often develop signs of cardiac toxicity. ECG findings include QRS and QT_c prolongation and atrioventricular (AV) conduction delays. Cardiotoxicity will occasionally

be delayed, so all patients should be admitted with telemetry.

TREATMENT

Medications

Maintain airway protection at all times, and treat seizures with **benzodiazepines**. Although there is a paucity of data regarding the efficacy of **sodium bicarbonate** in this setting, its use should be considered if the QRS duration is >100 milliseconds, given the structural similarity to TCAs.

Other Nonpharmacologic Therapies

Like phenytoin, carbamazepine's half-life is reduced by the administration of **MDAC** by decreasing enterohepatic recirculation of the drug (*Eur J Clin Pharmacol 1980;17:51*).

Use caution with administration of MDAC in the setting of this overdose because patients may develop seizures and coma, which pose a significant aspiration risk.

Lamotrigine

GENERAL PRINCIPLES

Definition

Lamotrigine, an anticonvulsant, is widely prescribed as a mood stabilizer as well as for the treatment of partial complex seizures.

Pathophysiology

Lamotrigine exerts its therapeutic effects by blocking presynaptic and postsynaptic sodium channels. In overdose, excess sodium channel blockade may result in widening of the QRS on the ECG and conduction blocks. Idiopathic cases of dermatologic pathology including Steven-Johnson syndrome and toxic epidermal necrolysis have been reported with the therapeutic administration of lamotrigine.

DIAGNOSIS

Clinical Presentation

History

Suspect lamotrigine toxicity in patients with a seizure disorder and altered mental status.

Physical Examination

Patients with lamotrigine toxicity present with lethargy, ataxia, and nystagmus. Overdose may present with seizures as well.

Differential Diagnosis

Lamotrigine toxicity is similar to other sodium channel-blocking anticonvulsant agents.

Diagnostic Testing

Laboratories

Therapeutic concentrations range from 3-14 mg/L; concentrations >15 mg/L are associated with the development of toxicity.

Electrocardiography

Lamotrigine overdose has been associated with the development of conduction delays and QRS widening. Patients should be admitted on telemetry.

TREATMENT

AC should be administered to alert patients with an intact airway. Seizures should be treated with **benzodiazepines**. There are theoretical benefits of administering **sodium bicarbonate**, 150 mEq in 1 L of 5% dextrose, in patients with a QRS >100 milliseconds; however, there is a paucity of experimental data to support this practice. In the setting of bicarbonate administration, close monitoring of **serum potassium** levels is required to avoid life-threatening hypokalemia.

Levetiracetam

GENERAL PRINCIPLES

- Levetiracetam, an anticonvulsant, is becoming increasingly used in the management of several of the different subtypes of epilepsy.
- The mechanism by which levetiracetam exerts its therapeutic effect is not well described; however, it does block N-type calcium channels on the presynaptic terminals of neurons.

DIAGNOSIS

Clinical Presentation

Very little data exist on levetiracetam overdoses. Lethargy and respiratory depression have been reported in the setting of overdose.

Differential Diagnosis

In patients with a seizure disorder and lethargy, intoxication, infectious, and metabolic disorders should be considered.

Diagnostic Testing

Although a test is available for measuring serum levels, this assay is not routinely available.

TREATMENT

Generally, **supportive care** is required. In cases where respiratory depression is evident, the patient should be intubated and ventilated. Avoid AC in patients with an altered mental status and an unprotected airway.

Valproic Acid

GENERAL PRINCIPLES

Valproic acid (VPA), an anticonvulsant, is widely used for the management of seizures and mood disorders and exerts its effects by inhibiting the function of voltage-gated sodium and calcium channels as well as enhancing the function of GABA.

Pathophysiology

VPA is metabolized by the hepatocytes through a complicated biochemical process that involves β-oxidation in the mitochondria. This drug may result in fatty infiltrates in the liver and accumulation of ammonia.

Risk Factors

Hepatic dysfunction can occur even at therapeutic levels and therefore should be monitored. The therapeutic range is 50-100 mg/L. In overdose, the risk of hepatic dysfunction and hyperammonemia increases.

DIAGNOSIS

Clinical Presentation

Patients with valproate overdoses may present with tremor, ataxia, sedation, altered sensorium, or coma. Occasionally, patients will present with abdominal pain.

Diagnostic Testing

- Therapeutic concentrations range from 50-100 mg/L. Patients who present with overdoses should have a **BMP** drawn to evaluate for hyponatremia and metabolic acidosis.
- In cases of massive overdose, a **CBC** should be sent because cases of pancytopenia have been reported in the literature (*Scott Med J 1987;32:85*). Hematopoietic disturbances may occur up to 5 days after overdose.
- Chronic VPA therapy has been associated with the development of hepatotoxicity and may result in a fatal hepatitis. In cases of chronic toxicity, **LFTs** should be sent to evaluate for transaminitis. Likewise, any patient with VPA toxicity should have an **ammonia** level sent.
- There have been occasional reports of pancreatitis (*J Toxicol Clin Toxicol 1995;33:279*); therefore, in massive overdose, consider sending **lipase** as well.

TREATMENT

- Most cases of toxicity resolve with supportive care. In patients who are awake with adequate airway protection, **AC** is warranted.
- In patients with hyperammonemia >35 mmol/L (>80 µg/dL) **L-carnitine** therapy should be instituted. In awake patients, oral carnitine is the preferred route at 50-100 mg/kg/d divided every 6 hours up to 3 g/d. In cases where patients are not able to tolerate PO, IV L-carnitine may be administered at 100 mg/kg, up to 6 g, as a loading dose, and then 15 mg/kg every 4 hours. Therapy may be discontinued when the patient's ammonia level declines to <35 mmol/L.

ANTIDEPRESSANTS

Monoamine Oxidase Inhibitors

GENERAL PRINCIPLES

Although several different classes of monoamine oxidase inhibitors (MAOIs) exist, the drugs most frequently implicated in toxicity are the first-generation antidepressant drugs: **phenelzine**, **isocarboxazid**, and **tranylcypromine**. **Clorgiline**, a later generation drug, is also associated with a similar toxic profile. The third-generation drugs, including **moclobemide**, have a better safety profile.

Pathophysiology

Monoamine oxidase is an enzyme responsible for the inactivation of biogenic amines such as **epinephrine**, **norepinephrine**, **tyramine**, **dopamine**, and **serotonin**. Inhibition of this

enzyme results in an increase of synaptic concentrations of biogenic amines. An increase in norepinephrine and serotonin, in particular, is thought to be responsible for mood elevation. MAOIs are structurally similar to amphetamine. In overdose, a significant amount of neurotransmitter is released, resulting in a **sympathomimetic** toxidrome. Phenelzine and isocarboxazid are also hydrazine derivatives and, in overdose, have been associated with the development of **seizure** activity. As neurotransmitters become depleted, patients develop cardiovascular collapse, which is often refractory to therapy. Given the fact that MAOIs affect an enzymatic pathway, there is often a **significant delay** in the development of toxicity after overdose, with most cases occurring in a **24-hour** period after ingestion, although there are cases of toxicity occurring **up to 32 hours** after overdose (*Ann Emerg Med 1984;13:1137*). This effect may occur with seemingly small overdoses of five or six pills (*J Clin Psychiatry 1983;44:280*).

Risk Factors

The classic risk factors for developing toxicity include increasing a prescribed dose or eating foods rich in **tyramine**, such as aged cheddar cheese or red wine. Drug-drug interactions occur when a new antidepressant (often a selective serotonin reuptake inhibitor [SSRI]) is introduced without an adequate **washout period** of several weeks after discontinuing the MAOI.

Prevention

Patients should be well educated on the risk associated with these drugs. The **duration of action of these drugs significantly outlasts their half-lives**; therefore, physicians should always use a reference guide or consult a pharmacist prior to prescribing a new drug in addition to or as a replacement for the MAOI.

Associated Conditions

- MAOIs have been associated with severe **hypertensive crises** in the setting of coingestions of **tyramine-**containing foods such as **aged cheddar and red wine**. Likewise, coingestion of **indirect-acting sympathomimetics**, which cause presynaptic release of norepinephrine, may precipitate a hypertensive crisis. Agents included in this category are **amphetamine-based drugs, dopamine, and pseudoephedrine**.
- **Serotonin syndrome** is also associated with the coingestion of **SSRIs**, **St. John's wort**, **meperidine**, and **dextromethorphan**.

DIAGNOSIS

Clinical Presentation

MAOI overdose is associated with a considerable risk of mortality and morbidity.

History

- In overdose, there may be a **significant delay** in the development of symptoms. Anyone who presents with normal vital signs and history of MAOI overdose must be **admitted and monitored** for at least 24 hours.
- Overdose should be suspected in patients who are taking MAOIs and present in extremis with a florid **sympathomimetic** toxidrome.

Physical Examination

Patients may initially present with minimal signs of toxicity. Subsequently, they will develop **agitation**, **diaphoresis**, **tachycardia**, **severe hypertension**, **dilated pupils**, and **headache**. As their illness progresses, they may develop **hyperthermia, rigidity, and seizures**. Ultimately, there is depletion of neurotransmitter stores, and the patient develops refractory cardiovascular collapse.

Differential Diagnosis

MAOI overdose produces a clinical picture that is similar to severe serotonin syndrome and severe sympathomimetic toxicity. Serotonin syndrome has a relatively faster onset of action and occurs within minutes to hours of ingestion.

Diagnostic Testing

Laboratories

These include routine labs such as a **BMP**, looking for metabolic acidosis, hyperkalemia, and renal failure; **CK** to look for rhabdomyolysis; and **troponins** to evaluate for myocardial infarction in severe cases. **Coagulation studies** are important because these patients may develop DIC.

Electrocardiography

ECG analysis may reveal a range of disorders from a simple sinus tachycardia to a wide complex dysrhythmia.

Imaging

A **head CT** should be obtained on altered patients and patients complaining of a headache to evaluate for intracranial hemorrhage.

TREATMENT

- The management of first-generation MAOI overdose can be very difficult because the patient may have dramatically variable vital signs. Patients with MAOI overdose should be aggressively managed with **orogastric lavage**, even if they are asymptomatic on arrival to the hospital.
- In hyperthermic patients, **rapid cooling measures** should be instituted.

Medications

First Line

- **AC** (1 g/kg) should be administered to the patient after the airway is secured. Many patients will be awake and alert and may not need immediate intubation; however, these patients should receive AC as well.
- Given the propensity for wildly fluctuating blood pressure (BP), titratable and short-acting agents are the mainstay of treatment in these patients. Hypertension should be managed with **nitroglycerin**, **nitroprusside**, **or phentolamine**. If the patient develops hypotension, a direct-acting α-agonist such as **norepinephrine** should be used. **Avoid dopamine** in the setting of MAOI overdose because it often fails to improve BP due to catecholamine depletion.
- **Benzodiazepines** should be used for seizures and agitation. Rigidity that does not respond to benzodiazepine administration may be managed with **nondepolarizing** paralytics. There are case reports describing the resolution of rigidity after the administration of **cyproheptadine** (*J Clin Psychopharmacol 1993;13:312*).

Second Line

In patients with refractory seizures, early administration of **pyridoxine** is warranted because MAOIs may deplete pyridoxine concentrations. Doses of 70 mg/kg, not to exceed 5 g, should be administered early as an IV infusion of 0.5 g/min.

SPECIAL CONSIDERATIONS

- Patients with MAOI overdoses require admission with monitoring for at least 24 hours, given the propensity for delayed toxicity. Aggressive decontamination measures should

  be taken, even if the patient seems to be asymptomatic because decompensation is rapid and frequently fatal.
- The **exception** to this is an overdose of **moclobemide**, which has a much better safety profile and tends to have a benign course because of its short duration of MAO inhibition.

PATIENT EDUCATION

- Patients who are placed on MAOIs should be educated about food and drug interactions and warned about the risk of interactions with herbal supplements, including St. John's wort.
- A washout period of at least 2 weeks after discontinuation of an MAOI should be observed before starting another antidepressant.

Tricyclic Antidepressants

GENERAL PRINCIPLES

- Multiple TCAs are on the market, including amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, and amoxapine.
- TCAs interact with a wide variety of receptors with many consequent effects in the setting of an overdose. The primary antidepressant effect is due to the inhibition of serotonin and norepinephrine reuptake. Additionally, TCAs modulate the function of central sympathetic and serotonergic receptors, which is thought to contribute to their antidepressant effects.
- TCAs have antimuscarinic effects, resulting in tachycardia, dry mucous membranes and skin, urinary

retention, and decreased GI motility. Patients will also have dilated pupils (*Psychopharmacology 1994;114:559*). Sedation is likely due to antihistamine effects. Furthermore, these agents are potent α_1-antagonists, leading to the development of hypotension and a reflex tachycardia. Cardiac toxicity is due to sodium channel blockade, resulting in a wide complex rhythm on the ECG (*Annu Rev Med 1984;35:503*). TCAs also exhibit a complex interaction with the GABA receptor, which in overdose likely contributes to seizure activity (*Life Sci 1988;43:303*).

DIAGNOSIS

TCA overdose exhibits its own toxidrome. Patients with an acute overdose may present to the emergency department with a normal mental status and vital signs but then rapidly decompensate.

Clinical Presentation

History

As with any overdose, a history is often unreliable. The clinical picture in serious toxicity is fairly stereotypical, and a careful physical examination can help establish the diagnosis.

Physical Examination

- Often present with a rapid onset of **CNS depression**
- **Tachycardia** and **hypotension** due to vasodilatation
- **Dilated pupils**, **dry mucous membranes**, and **urinary retention** due to the antimuscarinic effects
- May present with **seizure** activity, if significant overdose present

Diagnostic Criteria

The TCA toxidrome is a fairly consistent constellation of signs including hypotension, tachycardia, coma, and seizures.

Diagnostic Testing

Laboratories

- **Serum TCA concentrations** have a **limited role** in the management of acute TCA toxicity because they are **not predictive of severity of illness** (*N Engl J Med 1985;313:474*). Qualitative measurements of TCA concentrations in the urine are unreliable because there are many common drugs that cross-react on the assay, including diphenhydramine and cyclobenzaprine.
- Serial **VBG**s should be measured in patients undergoing alkalinization. Because bicarbonate treatment can cause profound hypokalemia, serial $\mathbf{K^+}$ should be followed and repleted.
- **Dextrose** should be checked in any patient with an altered mental status.

Electrocardiography

The ECG has proved to be a valuable tool in predicting the degree of morbidity in TCA overdose. In one classic study, one-third of patients with a **QRS of ≥100 milliseconds** developed **seizures**. Fifty percent of patients with a QRS of ≥160 milliseconds developed

ventricular dysrhythmias (*N Engl J Med 1985;313:474*). A terminal 40-millisecond axis of >120 degrees is found in patients who are taking TCAs and may help narrow the diagnosis in patients with an altered mental status of unknown etiology. Simply put, the ECG will show an **R′ in aVR** and an S wave in leads I and aVL. An R′ in aVR of >3 mm has been demonstrated to be predictive of neurologic and cardiac complications in TCA-poisoned patients (*Ann Emerg Med 1995;26(2):195*).

TREATMENT

- Patients with TCA overdose require early aggressive intervention.
- In patients with altered mental status, early **intubation**, **resuscitation**, and **GI decontamination** are warranted.
- Orogastric lavage may be beneficial in patients who are intubated with large ingestions because of decreased GI motility. Avoid this in small children because they only typically take one to two pills.
- **Hyperventilation** to achieve rapid serum alkalinization may be used as a bridge until bicarbonate therapy is started.

Medications

First Line

- **After the patient's airway is protected**, an **AC** dose of 1 g/kg is warranted even in delayed presentations.
- **Sodium bicarbonate** has been demonstrated to narrow the QRS, decrease the incidence of ventricular arrhythmias, and improve hypotension (*Emerg Med 2001;13:204*). A bolus of 1-2 mEq/kg every 3-5 minutes should be given with continuous ECG monitoring until the QRS narrows or the BP improves. Serial VBGs should be obtained with a goal of maintaining the blood pH at 7.50-7.55.
  - A bicarbonate drip should be titrated to the QRS narrowing and resolution of hypotension. The patient should be monitored in an ICU with serial pH and serum potassium measurements as well as monitoring for fluid overload.
  - Alkalinization should continue for 12-24 hours until the clinical picture and the ECG improve.
- **Norepinephrine** is the pressor of choice in hypotensive patients who do not respond to alkalinization because of its direct effects on the vasculature.
- **Lidocaine** may be considered in the presence of ventricular dysrhythmias precipitated by TCA toxicity. However, class **Ia and Ic antidysrhythmics are contraindicated in the management of TCA-poisoned patients**.

- **Benzodiazepines** are the mainstay of treatment for seizures. **Phenytoin should be avoided.**

Second Line

Propofol and **barbiturates** may be beneficial in refractory seizures.

Other Nonpharmacologic Therapies

Cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO) have been used in critically ill patients with refractory hypotension (*Ann Emerg Med 1994;23:480*; *Am J Emerg Med 1994;12:456*).

Selective Serotonin Reuptake Inhibitors

GENERAL PRINCIPLES

Classification

This class of drugs includes **fluoxetine**, **fluvoxamine**, **paroxetine**, **sertraline**, **citalopram**, and **escitalopram**. These drugs have a much better safety profile than the earlier drugs marketed for the management of depressive disorders and, as such, have largely supplanted MAOIs and TCAs in the treatment of depression.

Pathophysiology

These drugs enhance serotonergic activity by preventing its reuptake into the presynaptic terminal of the neuron, which may partially explain their antidepressant effects. Unlike other antidepressants, SSRIs have limited effects on other receptors and therefore tend to be less toxic in overdose.

DIAGNOSIS

Clinical Presentation

The vast majority of these overdoses have a benign clinical course. However, patients may present with signs of serotonin excess. Patients who have ingested **citalopram** or **escitalopram** may develop delayed toxicity.

History

Overdose histories are unreliable. Many patients who claim to have taken an overdose yet who look well actually took SSRIs.

Physical Examination

Signs of toxicity are usually absent unless the patient has taken a massive overdose. In these cases, patients may present with nausea, vomiting, and tachycardia. Patients with **citalopram** or **escitalopram** ingestions may present with **seizures**.

Diagnostic Testing

Laboratories

- Obtain **BMP** because SSRIs have been implicated in the development of **SIADH**.
- **FSBG** should be checked in patients with an altered mental status or seizures.
- Check **CK**, **lactate**, and **coagulation profile** in patients with **serotonin syndrome**.

Electrocardiography

Patients will occasionally present with a sinus tachycardia. Patients with citalopram or escitalopram ingestions may develop QT_c prolongation as late as 24 hours after an overdose (*J Toxicol Clin Toxicol 1997;35:237*).

TREATMENT

- The vast majority of overdoses require only 6 hours of observation and supportive care. Patients with intentional **citalopram** and **escitalopram** overdoses should be admitted to the floor with 24 hours of telemetry to monitor for QT_c prolongation.
- In patients who are awake and alert, 1 g/kg of **AC** may be administered.
- Treat seizures with **benzodiazepines**.
- Treat torsades de pointes (TdP) with **magnesium**, correction of electrolytes, **lidocaine**, and **overdrive pacing**.

Serotonin Syndrome

GENERAL PRINCIPLES

Definition

Serotonin syndrome is a disorder that can be precipitated by the introduction of a serotonergic agent and has been reported to occur even after ingestion of a single pill (*Ann Emerg Med 1999;33:457*).

Pathophysiology

Serotonin syndrome is thought to occur secondary to excess stimulation of 5HT2A receptors (*J Psychopharmacol 1999;13:100*). This syndrome can result from the coadministration of two or more serotonergic agents including SSRIs, MAOIs, meperidine, amphetamines, cocaine, TCAs, and various other drugs.

DIAGNOSIS

Clinical Presentation

History

Suspect serotonin syndrome in any patient who presents with a rapid onset of tremor and clonus after administration of a serotonergic agent. It is important to avoid the addition of other serotonergic agents in the management of these patients.

Physical Examination

- Patients will present with signs of excess serotonergic activity including restlessness, shivering, diaphoresis, and diarrhea.
- Patients may develop myoclonus, ocular clonus, and muscle rigidity later.
- Vital sign abnormalities include tachycardia and hyperpyrexia.

Diagnostic Criteria

- Serotonin syndrome is diagnosed by the presence of four of the following major criteria: alteration of consciousness, coma, or mood elevation; shivering, myoclonus, rigidity, or hyperreflexia; pyrexia; or diaphoresis.
- Additional minor criteria include restlessness or insomnia; mydriasis or akathisia; tachycardia; diarrhea; and respiratory or BP abnormalities (*Med Hypotheses 2000;55:218*).

Differential Diagnosis

Patients who present with altered mental status, rigidity, and hyperpyrexia may be misdiagnosed with neuroleptic malignant syndrome (NMS). NMS tends to develop over days to weeks, whereas serotonin syndrome has a faster onset, usually manifesting over a 24-hour period.

Diagnostic Testing

Serotonin syndrome is diagnosed by a constellation of symptoms and signs rather than any specific laboratory findings; however, as the disease evolves, laboratory abnormalities develop.

Laboratories

- As with any critical illness, patients may succumb to multiorgan failure, and therefore, laboratory studies

should be obtained on the basis of the presentation.

- Patients may have no lab abnormalities if they present early with mild form.
- On the other hand, more severe presentations may develop complications from psychomotor agitation and muscle rigidity including elevated **CK**, **metabolic acidosis**, and an **elevated lactate**.
- Check **BMP** because **renal failure** may occur in the presence of rhabdomyolysis.
- Check **coagulation studies** because patients with hyperthermia may develop **coagulopathy**.

Electrocardiography

The typical ECG will show a sinus tachycardia; however, there are no specific diagnostic ECG criteria associated with serotonin syndrome.

TREATMENT

- The treatment of serotonin syndrome is largely supportive and requires the removal of the offending agent. Aggressive cooling and hydration measures should be taken in the hyperthermic patient.
- **Benzodiazepines** should be used liberally to treat psychomotor agitation and myoclonus. In severe cases, **nondepolarizing paralytics** should be used to limit the degree of rhabdomyolysis.
- In patients with mild to moderate symptoms, **cyproheptadine**, an antihistamine with $5HT_{1A}$ and $5HT_{2A}$ antagonism, should be considered. A **4- to 8-mg** initial dose should be given orally, which often results in a rapid reversal of symptoms. If there is no response, the dose may be repeated in 2 hours. Subsequent dosing is 2-4 mg orally every 6 hours until the patient improves or a maximum dose of 32 mg/d is reached.

Lithium

GENERAL PRINCIPLES

Classification

Toxicity may be classified as **acute, chronic, or acute on chronic**. Lithium, an antidepressant, has a narrow therapeutic index, and therefore, risk of toxicity is high in patients on chronic therapy. The therapeutic range is approximately 0.6-1.2 mmol/L (or mEq/L).

Pathophysiology

- The mechanism by which lithium exerts its antimanic properties is not well understood. There is some evidence that lithium enhances serotonin function, which may contribute to its mood-stabilizing properties (*Science 1981;213:1529*).
- Acute toxicity is associated with the development of a GI illness because lithium is a metal.
- Chronic toxicity is primarily associated with neurologic dysfunction.
- Although serum levels are helpful in the management of these patients, the clinical picture should be the basis for therapy.
  - Generally, in **chronically** exposed patients, levels of less than 2.5 mEq/L are associated with tremulousness, ataxia, and nystagmus.
  - Levels greater than 2.5 mEq/L are associated with a deteriorating neurologic syndrome and are an indication for aggressive intervention including dialysis.

- A serum concentration of 4.0 mEq/L in an **acute** overdose is also an indication for dialysis (*Q J Med 1978;47:123*).

Risk Factors

Lithium has peripheral effects, which may enhance its toxicity, including the development of nephrogenic diabetes insipidus. This phenomenon is thought to occur through the reduction in the binding of aquaporins in the collecting duct of the kidney (*Annu Rev Physiol 1996;58:619*). This development enhances toxicity by causing dehydration, which leads to an increase in proximal tubular reabsorption of lithium (*J Physiol 1991;437:377*). Other dehydration states may enhance toxicity as well.

Prevention

Patients on chronic lithium therapy should have serum levels monitored and regular follow-up with their psychiatrist, which should include evaluation for the clinical signs of toxicity.

Associated Conditions

Lithium therapy has been associated with the development of chronic tubulointerstitial nephropathy (*J Am Soc Nephrol 2000;11:1439*), thyroid dysfunction (*J Toxicol Clin Toxicol 2000;38:333*), serotonin syndrome (*Medicine 2000;79:201*), and other endocrine effects.

DIAGNOSIS

Clinical Presentation

History

Although the history is often unreliable in overdose patients, acutely intoxicated patients may present complaining of nausea and abdominal discomfort. In chronic toxicity, patients may present with worsening confusion.

Physical Examination

- **Acute overdose** presents with a predominately GI syndrome of nausea, vomiting, diarrhea, and abdominal pain. As the illness progresses, patients may develop signs of volume depletion with tachycardia and hypotension. Severe toxicity is associated with neurologic dysfunction including altered mental status, nystagmus, ataxia, or coma.
- **Chronic toxicity** is associated with tremor, nystagmus, and ataxia. Confusion, dysarthria, fasciculations, and myoclonus are frequent physical findings. Seizures are reported in the literature (*Biol Psychiatry 1987;22:1184*).

Diagnostic Testing

Laboratories

- Obtain serial lithium levels in patients who present with evidence of toxicity.
  - A high initial level may be due to the timing of the last dose; therefore, the clinical picture should guide therapy.
  - **Obtain the serum sample in a lithium-free tube.**
- Other laboratories should include a **BMP** to evaluate electrolyte levels, renal function, and hydration

status.

- Lithium induces an elevation in the **white blood cell (WBC) count**.

Electrocardiography

The ECG may show nonspecific T-wave flattening or QT_c prolongation; however, cardiac dysfunction is unusual in this overdose.

TREATMENT

- AC does not bind to lithium and therefore has no role in the management of these overdoses.
- Whole-bowel irrigation with **polyethylene glycol** at a rate of 2 L/h is indicated for overdoses of sustained-release preparations (*Ann Emerg Med 1991;20:536*).

- The mainstay of therapy is the infusion of **0.9% saline solution** at twice the maintenance rate. Closely monitor fluid status in these patients to avoid overload.

Other Nonpharmacologic Therapies

Consider **dialysis** for patients who present with signs of severe toxicity, with altered mental status, or with other neurologic dysfunction but are unable to tolerate the required fluid load for enhanced elimination. In patients with acute overdose and a serum lithium concentration >4.0 mEq/L or chronic overdose and a serum level >2.5 mEq/L, dialysis should be considered.

Bupropion

GENERAL PRINCIPLES

Bupropion is an atypical antidepressant of the monocyclic aminoketone class and is structurally related to amphetamines. It acts by selectively inhibiting dopamine and norepinephrine reuptake.

DIAGNOSIS

Bupropion has been associated with more severe symptoms than the other atypical agents. Common features of toxicity include tachycardia, drowsiness, hallucinations, and convulsions. **Seizures** have been reported at therapeutic doses (*J Clin Psychiatry 1991;52:450*). **QRS prolongation** has also been described in overdose. Symptoms may be **delayed for up to 10 hours** after ingestion of sustained-release pills.

TREATMENT

Treatment of bupropion overdose includes airway protection. **Whole-bowel irrigation** and **MDAC** should be considered in patients who present early with a normal mental status and ingestion of a sustained-release preparation. This modality is **contraindicated** in seizing patients. Seizures should be treated with **benzodiazepines**. Barbiturates and propofol should be considered in patients with status epilepticus.

Antipsychotics, General

GENERAL PRINCIPLES

Epidemiology

According to the AAPCC's 2007 report, antipsychotic/sedative hypnotic agents were the fourth leading cause of fatal overdoses in the United States (*Clin Toxicol 2008;46:927*).

Pathophysiology

Antipsychotic agents exert their therapeutic effect largely by binding to dopamine receptors in the CNS, which tends to mitigate the positive symptoms of schizophrenia. Dopamine receptor blockade is also associated with the development of movement disorders, and the newer neuroleptic agents attempt to address this by modulating serotonergic tone. Most antipsychotics affect multiple receptors in the nervous, endocrine, and cardiovascular systems, which accounts for a wide range of toxic symptoms. In general, the older "typical" agents in the phenothiazine class tend to have more cardiac toxicity, with varying degrees of sodium channel blockade (wide QRS) and potassium channel blockade (QT_c prolongation).

Furthermore, these agents tend to have more significant extrapyramidal effects. The newer or "atypical" antipsychotics tend to exhibit less cardiac toxicity, but they often have pronounced α_1-antagonism, causing hypotension. The atypicals are also associated with the idiosyncratic development of other medical problems. For example, olanzapine has been associated with the development of fatal diabetic ketoacidosis (DKA) (*Am J Psychiatry 2003;160(12):2241*), and clozapine was briefly withdrawn from the market because a small percentage of patients developed agranulocytosis (*J Clin Psychiatry 2000;61:14*).

Phenothiazines

GENERAL PRINCIPLES

These are the prototypic antipsychotic drugs and include chlorpromazine, thioridazine, prochlorperazine, perphenazine, trifluoperazine, fluphenazine, mesoridazine, haloperidol (a butyrophenone), and thiothixene.

DIAGNOSIS

Clinical Presentation

History

The history is often difficult to obtain in these patients.

Physical Examination

- Overdoses are characterized by agitation or delirium, which may progress rapidly to coma. Pupils may be mydriatic, and deep tendon reflexes are depressed. Seizures may occur.
- Vital sign abnormalities may include hyperthermia, hypotension (due to strong α-adrenergic antagonism), tachycardia, arrhythmias (including TdP), and depressed cardiac conduction.

Diagnostic Testing

Laboratories

- Serum concentrations are generally not available or useful.
- FSBG and a BMP should be checked on all patients with altered mentation.

Imaging

Abdominal radiographs may reveal pill concretions.

TREATMENT

- Assess airway and breathing, place an IV, and institute cardiac monitoring.
- Hypotensive patients should receive a 20 mL/kg bolus of normal saline (NS).
- Consider whole-bowel irrigation for ingestion of sustained-release formulations.
- Treat ventricular arrhythmias with lidocaine. Class Ia agents (e.g., procainamide, quinidine, disopyramide) are contraindicated; avoid sotalol.
- Treat hypotension with IVF administration and α-adrenergic vasopressors (norepinephrine or phenylephrine). **Avoid epinephrine** because vasodilation may occur because of unopposed α-adrenergic response in the setting of strong β-adrenergic antagonism.
- TdP may require magnesium, isoproterenol, or overdrive pacing (see Chapter 7, Cardiac Arrhythmias).
- Treat seizures with benzodiazepines.
- Treat dystonic reactions with benztropine, 1-4 mg, or diphenhydramine, 25-50 mg, IM or IV.
- Treat hyperthermia with cooling.

SPECIAL CONSIDERATIONS

- NMS, which may complicate use of these agents, is characterized by rigidity, hyperthermia, altered mental status, and elevated CK. NMS should be treated with aggressive cooling measures, benzodiazepines, and bromocriptine (2.5-10 mg IV tid until the patient improves, then taper the dose over several days to avoid recrudescence of symptoms).
- Admit patients who have ingested a significant overdose for cardiac monitoring for at least 48 hours.

Clozapine

GENERAL PRINCIPLES

An atypical neuroleptic.

DIAGNOSIS

Clinical Presentation

- Overdose is characterized by altered mental status, ranging from somnolence to coma.
- Anticholinergic effects occur, including blurred vision, dry mouth (although hypersalivation may occur in overdose), lethargy, delirium, and constipation. Seizures occur in a minority of overdoses. Coma may occur.
- Vital sign abnormalities include hypotension, tachycardia, fasciculations, tremor, and myoclonus.

Diagnostic Testing

- Obtain CBC and LFTs; follow the WBC counts weekly for 4 weeks.
- Clozapine levels are not useful.

TREATMENT

- As always, support ABCs. Place an IV and institute cardiac monitoring.
- Consider AC 1 g/kg if the patient presents within an hour of ingestion.
- Treat hypotension with 20 mL/kg of IVF; if resistant, treat with norepinephrine or dopamine.
- Treat seizures with benzodiazepines.
- Consider filgrastim for agranulocytosis.
- Forced diuresis, hemodialysis, and hemoperfusion are not beneficial.
- Admit and monitor patients with severely symptomatic overdoses for 24 hours or more.

Olanzapine

GENERAL PRINCIPLES

Definition

An atypical neuroleptic.

DIAGNOSIS

Clinical Presentation

- Overdose is characterized by somnolence, slurred speech, ataxia, vertigo, nausea, and vomiting (*Ann Emerg Med 1999;34:279*).

- Anticholinergic effects occur, including blurred vision, dry mouth, and tachycardia.
- Seizures are uncommon. Coma may occur.
- Vital sign abnormalities include hypotension and tachycardia. Serious dysrhythmias rarely occur.
- **Pinpoint pupils are unresponsive to naloxone.**

TREATMENT

- Pay attention to ABCs, place an IV, and institute cardiac monitoring.
- Give AC if presentation is within 1 hour of ingestion.
- Treat hypotension with fluids and, if ineffective, norepinephrine.
- Give benzodiazepines for seizures.
- Treat DKA aggressively, if present.

Risperidone, Ziprasidone, and Quetiapine

GENERAL PRINCIPLES

These are newer neuroleptic agents and reports of overdoses have increased significantly. Quetiapine overdose is associated with more adverse outcomes than other neuroleptic agents (*Ann Emerg Med 2008;52:541*) and

requires aggressive therapy.

DIAGNOSIS

Clinical Presentation

- Clinical effects include CNS depression, tachycardia, hypotension, and electrolyte abnormalities.
- Clinically significant ventricular dysrhythmias are uncommon.
- Quetiapine overdose is associated with respiratory depression (*Ann Emerg Med 2008;52:541*).
- Miosis is a common finding.

Diagnostic Testing

QRS and QT_c prolongation have been reported (*Ann Emerg Med 2003;42:751*).

TREATMENT

- Scrupulous attention should be paid to ventilatory and circulatory support.
- Treat hypotension with 20 mL/kg fluid boluses and, if severe and persistent, consider a direct-acting pressor such as norepinephrine.
- Replete electrolytes as needed.
- Diuresis, hemodialysis, and hemoperfusion do not appear to be useful.

β-Adrenergic Antagonists

GENERAL PRINCIPLES

Definition

Of all of the agents available, propranolol tends to exhibit the most toxicity because it is lipophilic, is widely distributed throughout the body, and possesses significant membranestabilizing activity. Sotalol, which is classically thought of as a class III antiarrhythmic, also has some β-adrenergic antagonist activity and, in toxic doses, can result in a prolonged QT_c and TdP.

Classification

Cardiovascular agents are a frequent cause of serious poisonings and, according to the 2007 annual report of the National Poison Data System, were the fifth leading cause of fatal drug exposures (*Clin Toxicol 2008;46:927*). Patients with these overdoses require aggressive intervention and close monitoring.

Pathophysiology

The toxicity associated with an overdose of β-blockers is largely due to the effects of antagonism at catecholamine receptors. In general, selectivity is lost in overdose, so bronchospasm may occur in the setting of β_1-selective antagonists.

DIAGNOSIS

Clinical Presentation

- Patients with a significant ingestion of an immediate-release product will exhibit signs of toxicity within 6 hours. The exception to this rule is sotalol, which in overdose can have delayed toxicity and prolonged effects, with one report of QT_c prolongation persisting up to 100 hours after ingestion (*Eur Clin J Pharmacol 1981;20:85*).
- With the exception of propranolol and sotalol, β-blocker overdose in healthy people tends to be benign, with a significant number of patients remaining asymptomatic after ingestion (*J Toxicol Clin Toxicol 1993;31:531*).

History

Suspect β-antagonist overdose in patients with altered mental status, bradycardia, and hypotension.

Physical Examination

Patients with significant ingestions present with bradycardia and congestive heart failure (CHF). Patients with propranolol ingestions may develop coma, seizures, and hypotension. Propranolol overdoses have a high mortality (*J Toxicol Clin Toxicol 1997;35:353*).

Differential Diagnosis

In patients with symptomatic bradycardia, also consider overdose of CCB, clonidine, or digoxin.

Diagnostic Testing

Laboratories

Patients with β-antagonist overdoses occasionally become hypoglycemic; therefore, a **FSBG** should be obtained. Likewise, any patient with an altered mental status should have a **BMP** sent. Consider obtaining a **lactate** because patients with profound hypotension may develop mesenteric ischemia.

Electrocardiography

The ECG may reveal sinus bradycardia or AV block. In propranolol ingestions, a wide QRS manifesting sodium channel blockade may be present. With sotalol, QT_c prolongation may appear as a delayed presentation and TdP may develop.

TREATMENT

The treatment of β-blocker overdose is largely supportive in mild to moderate cases. The patient should have an IV placed, and continuous cardiac monitoring should be instituted.

Hypoglycemia should be treated with 50 mL of 50% **dextrose (D_{50})**. Consider **AC** if patients present within 1 hour of ingestion. Intubation and ventilation should be instituted in patients with altered mental status. Likewise, consider **orogastric lavage** in patients with potential for severe toxicity such as propranolol overdoses.

Medications

- Patients with significant toxicity from propranolol or sotalol ingestions should be treated more aggressively.

- **Atropine** 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually ineffective because the bradycardia is not vagally mediated.
- **A fluid bolus** of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
- **Glucagon** 2-4 mg IV may be given over 1-2 minutes. Then start infusion of 2-5 mg/h, not to exceed 10 mg/h. One of the significant side effects of glucagon administration is nausea and vomiting; monitor for vagally mediated bradycardia.
- **Calcium gluconate** 3-9 g IV may be given through a peripheral line in patients with hypotension. Alternatively, consider **calcium chloride** 1-3 g through a central line slow IV push over 10 minutes. Calcium chloride is sclerosing and can cause severe extravasation injury.
- Any patient with hypotension is a candidate for **high-dose insulin euglycemia therapy**. Although the mechanism for improvement is unclear, this is routinely used in the management of severe CCB overdose (*J Toxicol Clin Toxicol 1999;37:463*). Animal studies of severe propranolol overdose have shown a survival benefit (*Ann Emerg Med 1997;29:748*). This involves a bolus of **1 unit/kg of regular insulin, followed by an infusion of 0.5-1.0 unit/kg/h of regular insulin**. This should be accompanied by a dose of **50 mL of D_{50} and a dextrose drip at 1 g/kg/h of dextrose**. That calculates to 10 mL/kg/h of D_{10} or 2 mL/kg/h of D_{50} (*Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill, 2006:933*). FSBG should be obtained every 30 minutes, and potassium levels should be followed every 2 hours with repletion because **profound hypokalemia** may complicate this treatment modality. The BP response tends to be delayed by 15-30 minutes.
- **Lipid therapy** is emerging as a promising treatment modality in these often fatal poisonings. Theoretically, lipid administration causes lipophilic drugs to partition into the plasma and away from the heart. The current protocol, which can be found at *http://www.lipidrescue.org*, starts with **1.5 mL/kg of 20% intralipid administration over 1 minute, followed by an infusion rate of 0.25 mL/kg/min**. If there is no response, the patient may have repeat boluses every 3-5 minutes until a **3 mL/kg** total dose, and the infusion rate may be increased to **0.5 mL/kg/min**. **The maximum total dose recommended is 8 mL/kg** (*J Med Toxicol 2011;7(2):151*).
- **Catecholamines** should be approached with caution in these patients because α-stimulation in conjunction with β-blockade may precipitate acute heart failure. Therefore, **hemodynamic monitoring** should be instituted with careful titration of **epinephrine at 0.02 µg/kg/min or norepinephrine at 0.10 µg/kg/min**. **Isoproterenol at 0.10 µg/kg/min** may be useful as well; however, monitor closely for the development of hypotension. It is important to note that high doses of these agents may be required.

Other Nonpharmacologic Therapies

- In cases of refractory hypotension and bradycardia, it is reasonable to consider an intra-aortic balloon pump (IABP) (*Ann Emerg Med 1987;16:1381*) and ECMO (*Arch Mal Coeur Vaiss 2001;94:1386*).

- Transvenous pacing may be attempted, but it is generally difficult to achieve capture, given the degree of myocardial depression.

Calcium Channel Blockers

GENERAL PRINCIPLES

Definition

CCBs are widely used for the management of tachyarrhythmias and hypertension. Generally speaking, the overdoses of dihydropyridines, such as amlodipine, nimodipine, nicardipine, and nifedipine, tend to be more benign; although in massive overdose, selectivity may be lost and may result in significant symptoms. Nondihydropyridines, verapamil and diltiazem, can produce severe toxicity, even in the setting of a small overdose.

Pathophysiology

CCBs exert their effects by blocking L-type calcium channels on the smooth muscle of the vasculature and the myocardium. This decreases inotropy and chronotropy and results in a decrement of BP and heart rate. In overdose, these effects are accentuated. L-type calcium channels are also involved in the release of insulin from the β-islet cells of the pancreas. In CCB overdose, patients will often present with elevated blood sugars.

DIAGNOSIS

Clinical Presentation

Patients with diltiazem or verapamil overdoses should be considered critically ill and require aggressive intervention.

History

Patients will often present with an unintentional ingestion where they missed a dose and attempted to "catch up" by doubling their next dose. Intentional ingestions will often not be accurately reported.

Physical Examination

Patients with verapamil or diltiazem overdoses will present with profound **hypotension and bradycardia and generally have a normal mental status until they arrest**. It is thought that CCBs have somewhat of a neuroprotective effect that may explain the preservation of mentation. In the setting of dihydropyridine CCB overdoses, patients usually present with hypotension and a reflex tachycardia.

Differential Diagnosis

CCB toxicity may resemble β-antagonist or clonidine overdoses.

Diagnostic Testing

This is a clinical diagnosis; serum concentrations are not useful in the management of CCB overdose.

Laboratories

- **FSBG** should be checked and is elevated in the setting of CCB toxicity. This is part of the toxidrome associated with this particular overdose.

- A **BMP** should be obtained as well to follow serum calcium levels. In patients on a calcium drip, ionized calcium should be followed.

Electrocardiography

The ECG may show sinus bradycardia, conduction delays, or even complete heart block. With dihydropyridine overdose, a sinus tachycardia may be present.

TREATMENT

The treatment of dihydropyridine CCB overdose is largely supportive in mild to moderate cases. The patient should have an IV placed, and continuous cardiac monitoring should be instituted. Consider **AC** if patients present within 1 hour of ingestion. Intubation and ventilation should be instituted in unstable patients. Likewise, consider **orogastric lavage** in patients with potential for severe toxicity. **Whole-bowel irrigation** with polyethylene glycol should be instituted for sustained-release preparations.

Medications

Patients with significant toxicity, such as verapamil or diltiazem ingestions, should be treated more aggressively.

- **Atropine** 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually ineffective because the bradycardia is not vagally mediated.
- **A fluid bolus** of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
- **Calcium gluconate** or **calcium chloride** may be given as described in the treatment section of β-blocker overdose. In addition, a calcium gluconate drip may be started and run up to 2 g/h. Close monitoring of calcium is required.
- Any patient with hypotension is a candidate for **high-dose insulin euglycemia therapy**. See discussion of this topic under treatment of β-blocker overdose.
- **Lipid therapy**, as described in the treatment section of β-blocker overdose, should be initiated early.
- **Catecholamines** should be approached with caution in these patients because α stimulation may precipitate acute heart failure. Therefore, **hemodynamic monitoring** should be instituted with careful titration of **epinephrine starting at 0.02 µg/kg/min or norepinephrine at 0.10 µg/kg/min**.
- **It is important to note that calcium and catecholamines are generally ineffective at treating this overdose because the L-type calcium channel is blocked, preventing calcium entry into the cell. Therefore, lipid or insulin should be considered first-line therapy in the management of these patients.**

Other Nonpharmacologic Therapies

- In cases of refractory hypotension and bradycardia, it is reasonable to consider IABP (*Clin Cardiol 1991;14:933*) and cardiopulmonary bypass (*Ann Emerg Med 1989;18:984*).
- Transvenous pacing may be attempted, but it is generally difficult to achieve capture, given the degree of myocardial depression.

SPECIAL CONSIDERATIONS

Patients with ingestions of a sustained-release preparation should be monitored in an intensive care setting. Immediate-release preparations should be monitored for 6-8 hours prior to discharge or psychiatric evaluation.

Clonidine

GENERAL PRINCIPLES

- Clonidine is an orally administered agent used in the management of hypertension.
- Clonidine is an imidazoline drug with centrally acting antihypertensive effects related to α_2-agonism, which decreases sympathetic outflow from the CNS (*N Engl J Med 1975;293:1179*). Other drugs in this family include oxymetazoline and tetrahydrozoline, nasal decongestants that exhibit similar toxicity when orally administered. In overdose, peripheral effects include an initial release of norepinephrine with a **transient increase** in BP, followed by hypotension (*Clin Pharmacol Ther 1976;21:593*).

DIAGNOSIS

Clinical Presentation

Although the clinical presentation of these overdoses can be quite concerning, most patients recover with supportive care. Patients tend to develop symptoms within 30 minutes to an hour after their overdose.

History

The history is unreliable in these patients because they are often somnolent or comatose on arrival to the hospital.

Physical Examination

Suspect clonidine overdose in patients with hypotension, bradycardia, and CNS depression. Occasionally, patients may develop hypoventilation, which is usually responsive to vocal or tactile stimulation (*Ann Emerg Med 1981;10:107*). Pupillary examination reveals miosis, and this finding in the setting of hypotension and bradycardia is highly suggestive of clonidine overdose.

Differential Diagnosis

β-Antagonists, digoxin, and CCB overdose should be included in the differential.

Diagnostic Testing

Laboratories

Serum clonidine concentrations are not routinely used in the management of these patients. An **FSBG** and **BMP** should be obtained on any patient with altered mental status.

Electrocardiography

The ECG generally shows a sinus bradycardia.

TREATMENT

- Patients generally respond with supportive care. In severely poisoned patients, consider intubation and ventilation; however, this is rarely needed.
- **Avoid GI decontamination and AC in these patients because they tend to develop altered mental status quickly.**
- **Atropine** 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually not necessary because the bradycardia tends to resolve on its own.
- **A fluid bolus** of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
- An initial dose of 0.4 mg of **naloxone** may be useful in reversing the hypotension and bradycardia associated with clonidine overdose (*Hypertension 1984;69:461*). Occasionally, high doses may be

required, with redosing every 2-3 hours because naloxone has a shorter duration of action than clonidine.

SPECIAL CONSIDERATIONS

Withdrawal syndromes have been reported in patients who have stopped taking clonidine. It is usually manifested as rebound severe hypertension, agitation, and palpitations. Treatment is to administer clonidine and taper the dose gradually. Benzodiazepines are also useful in this situation.

Other Antihypertensives

- These agents include **diuretics**, **α_1-antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs)**.
- **Diuretics** tend to be benign in overdose. Occasionally, they cause dehydration and electrolyte imbalances. Laboratory studies should include a BMP. Management usually only requires gentle fluid hydration.
- **α_1-Antagonists** cause peripheral vasodilation, which usually responds to hydration. Occasionally, they cause enough hypotension to require vasopressors. In these cases, norepinephrine should be administered.
- **ACE inhibitors** rarely cause significant toxicity, although there are case reports of fatal overdoses. Treatment is supportive. In patients with hypotension, naloxone may be useful (*Clin Pharmacol Ther 1985;38:560*).
- **ARBs** may cause hypotension in overdose. Treatment is supportive.

Parasympathetic Agents

ACh is a neurotransmitter of the peripheral nervous system and CNS, acting on nicotinic and muscarinic receptors.

Anticholinergics

GENERAL PRINCIPLES

Anticholinergic effects are primarily due to blockade of muscarinic receptors (i.e., antimuscarinic effects) and, therefore, mainly affect parasympathetic functions.

Epidemiology

Anticholinergic poisoning occurs either from intentional ingestion of certain plants or over-the-counter medications (e.g., Jimson weed, diphenhydramine) (*Can J Emerg Med 2007;9(6):467*) or from accidental overdosing (e.g., medical noncompliance, polypharmaceutical regimens) (*Rev Neurol 2006;43(10):603*).

Etiology

Drugs and medications with anticholinergic effects include the following:

- **Anticholinergics:** Atropine, scopolamine, benztropine, glycopyrrolate, ipratropium
- **Antihistamines:** Diphenhydramine, promethazine, doxylamine
- **Antipsychotics:** Chlorpromazine, clozapine, olanzapine, quetiapine
- **Antidepressants:** Amitriptyline, nortriptyline, imipramine, desipramine
- **Antiparkinson drugs:** Benztropine, trihexyphenidyl

- **Mydriatics:** Cyclopentolate, homatropine, tropicamide
- **Muscle relaxants:** Cyclobenzaprine
- **Plants:** Belladonna, Jimson weed, *Amanita* mushrooms

Pathophysiology

- Blockade of muscarinic receptors (i.e., parasympathetic autonomic nervous system [ANS], except for the sympathetically innervated sweat glands) leads to the so-called

  anticholinergic toxidrome.
- **Tachycardia** is one of the main symptoms in anticholinergic poisoning. Vagal blockade of cardiac muscarinic receptors leads to unopposed sympathetic stimulation of the myocardium.
- Some anticholinergic drugs can also cross the blood-brain barrier and interact with muscarinic receptors in the cortex and subcortical regions of the brain causing anticholinergic **CNS manifestations**.

Associated Conditions

- Antihistamines and cyclic antidepressants also block sodium channels and cause additional cardiac symptoms such as dysrhythmias and QRS prolongations.
- Potassium channel blockade may result in QT_c prolongation and TdP.

DIAGNOSIS

Clinical Presentation

Anticholinergic Toxidrome

- **Central effects:** Confusion, agitation, euphoria/dysphoria, hallucinations, incoherent thoughts and speech, lethargy, ataxia, choreoathetoid movements, and rarely, seizures or coma.
- **Peripheral effects:** Tachycardia, mouth dryness, decreased perspiration with flushed skin and hyperthermia, dilated pupils with photophobia and blurred vision, decreased bowel sounds, and urinary retention.
- A helpful mnemonic for antimuscarinic effects is “RED as a beet, DRY as a bone, BLIND as a bat, MAD as a hatter, and HOT as a hare.”

TREATMENT

- All patients presenting with an anticholinergic toxidrome need **cardiovascular monitoring**. Serial evaluation of vital signs and serial physical exams are essential to address sudden worsening of the patient’s condition (dysrhythmia, seizure).
- GI decontamination is only indicated if the patient is fully awake and cooperative due to the high risk of aspiration or loss of airway control in unconscious or combative patients.

  Gastric lavage for GI decontamination may be appropriate, given decreased stomach emptying and slowed GI motility from the anticholinergic effect.
- Patients with hyperthermia may benefit from cooling measures.

Medications

- **Physostigmine** is a reversible **anticholinesterase** that leads to increased ACh in synapses to overcome receptor blockade. It is useful in the management of severe anticholinergic poisoning with delirium, hallucinations, and seizures (*Int J Clin Pharmacol Ther Toxicol 1980;18(12):523*).
  - In the emergency department setting, the use of physostigmine as a diagnostic tool in patients with high suspicion of anticholinergic agitation or delirium has been found to be relatively safe (*Ann Emerg Med 2003;42(1):14*).
  - **Contraindications:** Underlying cardiovascular disease, wide QRS complex or AV block on ECG, asthma, bowel or bladder obstruction, peripheral vascular disease

    (PVD), or gangrene. Its use is also contraindicated in the setting of cyclic antidepressant overdose.
  - **Adult dosing:** 0.5 mg IV over 5 minutes every 5 minutes up to 2 mg total or until improved level of consciousness.
  - Physostigmine has a short duration of action (20-60 minutes), and redosing might be necessary if agitation recurs.
  - NOTE: Always have **atropine** at bedside for reversal if needed, that is, in case of severe bradycardia or asystole from unopposed cholinergic stimulation or other dysrhythmias from sodium channel blockade (e.g., in TCA overdose) (*J Emerg Med 2003;25(2):185*).
- **Benzodiazepines** should be used as adjuncts to treat anticholinergic agitation or delirium. There is no benefit of benzodiazepine monotherapy in anticholinergic central symptoms (*Ann Emerg Med 2000;35(4):374*).

Cholinesterase Inhibitors

- Cholinesterase inhibitors are chemical compounds that inhibit the enzyme cholinesterase. Blockade of **AChE** function leads to excess ACh in synapses of the ANS and sympathetic nervous system (SNS).
- Cholinesterase inhibitors are divided into two classes:
  - Organophosphates (OPs)
  - Carbamates

Organophosphates

GENERAL PRINCIPLES

Epidemiology

- OPs are commonly used as pesticides and insecticides. Some also have medical indications (e.g., malathion in lice shampoo).
- In the developing world, OP and other pesticide poisonings represent the most common cause of overdose deaths (*BMC Public Health 2007;7:357*).
- OPs are also potent chemical terrorism and warfare agents (“nerve gas” agents) (e.g., sarin in the Tokyo subway attack or in Syria, tabun in the Iraq-Iran War) (*Anesthesiology 2002;97(4):989*).
- Although self-inflicted OP poisoning with suicidal intent occurs, exposure is primarily occupational or accidental (*Intern Med 2007;46(13):965*). Because absorption occurs through skin and airways, the handling

of OPs requires appropriate protective gear.

Pathophysiology

- Inhibition of AChE leads to accumulation of ACh at nicotinic and muscarinic receptors, resulting in **excessive cholinergic stimulation**.
- The severity of symptoms varies depending on the route of exposure (dermal, inhalation, oral, parenteral), dose, lipid solubility of OP, type of OP, and enzyme affinity (*Lancet 2008;371(9612):597*).
- Initially, most OPs bind AChE reversibly. Some OPs, however, become permanently bound over time, a phenomenon known as "**aging**." If aging occurs, the only way to overcome the inhibitory effect is for the body to synthesize new enzyme.
- OPs are hepatically metabolized. Some OPs become active toxins after liver metabolism and thus can have delayed effects (e.g., parathion) (*Bull World Health Organ 1971;44(1):289*).

DIAGNOSIS

Clinical Presentation

The cholinergic toxidrome is a result of overstimulation of nicotinic and muscarinic receptors (*Bull World Health Organ 1971;44(1):289*; *Lancet 2008;371(9612):597*). Although patients classically present with muscarinic features, because both receptors are being stimulated, patients can present with a mixture of muscarinic and nicotinic effects.

- **Muscarinic effects**
  - **SLUDGE syndrome: S**alivation, **L**acrimation, **U**rination, **D**iarrhea, **G**I cramping, **E**mesis.
  - **Bradycardia, bronchorrhea, bronchoconstriction** (NOTE: Asphyxia and cardiovascular collapse are lethal features of OP poisoning.)
  - **Other effects:** Miosis, diaphoresis.
- **Nicotinic effects**
  - **Ganglionic:** Tachycardia, hypertension, diaphoresis, mydriasis
  - **Neuromuscular:** Neuromuscular depolarization, fasciculations, motor weakness, paralysis with respiratory failure (analogous to succinylcholine, which is related to ACh)
  - **Central:** Confusion, agitation, lethargy, seizures, coma

Diagnostic Testing

- **Cholinesterase concentrations:** There are two different cholinesterases that are routinely measured in red blood cells and plasma (*Bull World Health Organ 1971;44(1):289*).
- Both assays are relatively useless in assessing the severity of exposure in acute intoxications because of their wide ranges of normal values.
- They are mostly used as sensitivity markers to compare changes from baseline enzyme activity (e.g., in chronic occupational exposure or after OP elimination) (*Lancet 2008;371(9612):597*).

TREATMENT

- **Protection:** OP-intoxicated patients pose a significant risk for further contamination of others through direct contact. Health care personnel should use special **personal protective equipment** (PPE) (gowns, gloves, masks) until the patient is properly decontaminated (*Lancet 2008;371(9612):597*). If the OP was ingested, PPE may be required until any emesis is discarded because off-gassing from the emesis can result in bystander illness. PPE should not consist of latex or vinyl, because OPs are lipophilic and may penetrate such materials.
- **Decontamination**
  - Remove patient from potential source of poisoning (*Crit Care Med 2002;30(10):2346*). All clothing, especially leather, should be removed from the patient and discarded in a ventilated area (*Crit Care Med 2002;30(10):2346*). Skin and hair decontamination requires thorough irrigation with water and might be enhanced through use of alcohol-based soaps (*Crit Care Med 2002;30(10):2346*). Eyes should be irrigated with only water (*Crit Care Med 2002;30(10):2346*).
  - Gastric lavage might be indicated in stable patients who ingested contaminated fluids (*Clin Toxicol 2009;47(3):179*).
  - NOTE: All lavaged/aspirated fluids need to be safely discarded.
- **Stabilization**
  - ABCs: Have a low threshold for early intubation to obtain airway protection. NOTE: Intubation alone may not improve hypoxia due to the large amount of pulmonary edema and bronchospasm.
  - **Avoid** mouth-to-mouth resuscitation because of contamination risk.
  - Start IVF as an initial bolus of 20 mL/kg (*Crit Care 2004;8(6):R391*).

- **Atropine** is an antimuscarinic agent that competes with ACh for receptor binding.
  - **Goal: Atropinization** (i.e., drying of bronchial secretions with normalized oxygen saturation [which may require 10-100 times the usual atropine dose]), heart rate >80 bpm, and systolic BP >80 mm Hg (*Lancet 2008;371(9612):597*).
  - The initial **adult dose** is 1-3 mg IV bolus. Then titrate according to persistence of bronchorrhea by doubling the previously used dose every 5 minutes until atropinization is achieved (*Lancet 2008;371(9612):597*).
  - The initial **pediatric dose** is 0.02 mg/kg IV. Titrate as in adults (*BMJ 2007; 334(7594):629*).
  - Once the patient is stabilized, an infusion of atropine should be started with 10-20% of the initial atropinization dose per hour and should be held once anticholinergic effects occur (e.g., absent bowel sounds, urinary retention, agitation) (*Lancet 2008;371(9612):597*). Infusions can last as long as 32 days after exposure to fat-soluble OPs (*Vet Hum Toxicol 1987;29:483*).
  - If atropine supplies are exhausted, other antimuscarinic agents can be considered (e.g., diphenhydramine, glycopyrrolate) (*Crit Care Med 1990;18:956*).
- **Pralidoxime** (2-PAM): Pralidoxime forms a complex with OPs that are bound to AChE. The pralidoxime-OP complex is then released from the enzyme and thus regenerates AChE function. Its use is controversial, but the best available evidence suggests that oximes should be administered.
  - Once the AChE-bound OPs start aging, pralidoxime is rendered ineffective. Therefore, if it is used, it is crucial to start pralidoxime therapy early.
  - Pralidoxime also binds to some degree to free OPs and thus prevents further AChE binding.
  - **Adult dosing:** New evidence favors an infusion regimen: 1-2 g of pralidoxime in 100 mL NS IV over 20

minutes, then infusion of 500 mg/h (*Lancet 2008;371(9612):597*). One trial indicated that a high-dose regimen (2-g loading dose followed by 1 g/h infusion for 48 hours) improved mortality (*Lancet 2006;368:2136*).
    - NOTE: Pralidoxime use longer than 24 hours might be indicated if unaged OPs are redistributed from fat tissue. In such cases, infusions should be continued until the patient remains symptom free for at least 12 hours without additional atropine doses or until the patient is extubated (*Lancet 2008;371:597*).
    - Cardiac and respiratory failure have been reported after administration of pralidoxime (*Crit Care Med 2006;34(2):502*).
- **Benzodiazepines** are the first-line agents for OP-induced seizures (*BMJ 2007;334:629*).

COMPLICATIONS

- **Intermediate syndrome (IMS)**
    - This syndrome is a postacute exposure paralysis from persistent ACh excess after the acute cholinergic phase has been controlled and is not related to the severity of the acute phase. Some believe incomplete or insufficient oxime therapy explains this syndrome (*J Toxicol Clin Toxicol 1992;30:347*).
    - It is characterized by weakness of proximal extremity muscles and the muscles supplied by cranial nerves that occurs hours to days after acute OP poisoning and can lead to respiratory failure if unnoticed (*PLoS Med 2008;5(7):e147*).
- **OP-induced delayed neurotoxicity (OPIDN)**
    - Besides AChE, some OPs also inhibit other neurotoxic esterases, resulting in polyneuropathy or spinal cord damage due to demyelination of the long nerve fibers.
    - OPIDN usually occurs several days to weeks after acute OP poisoning, leading to temporary, chronic, or recurrent motor or sensory dysfunction (*Annu Rev Pharmacol Toxicol 1990;30:405*).

MONITORING/FOLLOW-UP

- All patients with severe or moderate poisoning should be admitted to an ICU after initial stabilization for further monitoring and treatment (*Crit Care 2004;8(6):R391*).
- Asymptomatic patients presenting with a history of unintentional poisoning or patients with only mild symptoms do not always require hospital admission but should be observed for 6-12 hours (*BMJ 2007;334:629*).

Carbamates

GENERAL PRINCIPLES

Epidemiology

Carbamates are reversible AChE inhibitors that also lead to ACh excess in the synaptic junction. They are occasionally found in pesticides. However, their most common use in this country is medicinal.

- **Physostigmine** is a naturally occurring methyl carbamate found in the Calabar bean. Other common carbamates are pyridostigmine and neostigmine.

- **Pyridostigmine** has been used in the treatment of myasthenia gravis.

Pathophysiology

- Inhibition of ACh breakdown through blockage of AChE leads to accumulation of ACh at nicotinic and muscarinic receptors with **excess cholinergic stimulation**.
- Carbamates are reversible enzyme inhibitors; they release AChE spontaneously. There is no "aging" phenomenon with carbamates.

DIAGNOSIS

Clinical Presentation

The clinical picture of the carbamate-induced cholinergic toxidrome is analogous to the one seen in OP poisoning because nicotinic and muscarinic receptors of the ANS and SNS are stimulated.

- Look for **SLUDGE** syndrome, **bradycardia**, **bronchorrhea**, and **bronchoconstriction** as well as neuromuscular depolarization, and be aware of the risk of cardiovascular or respiratory failure.
- Symptoms from carbamate poisoning are generally milder compared to OP poisoning and of shorter duration.

Diagnostic Testing

Cholinesterase concentrations are used to compare changes from baseline enzyme activity in exposures but are not useful in acute toxicity (*Clin Chem 1995;41:1814*).

TREATMENT

- The same measures of **protection** and **decontamination** as with OP poisoning apply to carbamates.
- **Stabilization**
  - ABCs: Have a low threshold for early intubation to obtain airway protection.
  - Avoid mouth-to-mouth resuscitation because of contamination risk.

Medications

First Line

Atropine is an antimuscarinic agent that competes with ACh for receptor binding. **Goal: Atropinization**. See Treatment under Organophosphates section for dosing guidelines.

Second Line

- Pralidoxime can be considered if there is no clear evidence for isolated carbamate poisoning because additional OP exposure should always be suspected.
- **Benzodiazepines** are the first-line agents for carbamate-induced seizures.

Barbiturates

GENERAL PRINCIPLES

The use of barbiturates has largely fallen by the wayside because safer drugs are now available. Barbiturates

are still used as induction agents for anesthesia as well as second-line agents for seizure control.

DIAGNOSIS

Suspect barbiturate overdose in patients who present with CNS and respiratory depression.

Clinical Presentation

History

It is often difficult to elicit a history because these patients are generally sedated or comatose on arrival.

Physical Examination

Typical examination findings include **respiratory depression** and **coma**. Other vital sign abnormalities may include hypothermia. Patients may develop cutaneous bullae known as **"barb blisters"** (*Cutis 1990;45:43*). The blisters are most likely from being on the ground for a prolonged time and not a direct effect of the barbiturates. **Miosis** may be present.

Differential Diagnosis

The differential diagnosis includes benzodiazepine overdose, opioid overdose, hypoglycemia, ethanol intoxication, other sedatives (e.g., zolpidem, γ-hydroxybutyric acid [GHB]), CNS depressants, and other metabolic causes of coma.

Diagnostic Testing

Laboratories

This should include routine testing for any presentation of coma: **blood glucose, BMP, LFTs, and thyroid function tests**.

Electroencephalography

In barbiturate overdose, electroencephalography recordings may show no electrical activity.

Imaging

- A **CXR** should be obtained on all of these patients to evaluate for aspiration.
- **Head CT** may help evaluate for the presence of CNS lesions contributing to coma.

Diagnostic Procedures

Consider **lumbar puncture (LP)** in patients with undifferentiated coma to evaluate for meningitis or subarachnoid hemorrhage.

TREATMENT

The most important management strategy in barbiturate overdose is airway and breathing protection. Patients with respiratory depression should be intubated.

Medications

First Line

- Consider **MDAC** in patients with a protected airway and bowel sounds.
- Hypotension should be treated with IVF. If this fails, consider a direct-acting vasopressor such as

norepinephrine.

Second Line

Urine alkalinization with sodium bicarbonate is reserved for phenobarbital overdoses refractory to MDAC that do not improve with supportive care. It is inferior to MDAC (*J Toxicol Clin Toxicol 2004;42:1*).

Other Nonpharmacologic Therapies

Consider **hemoperfusion** in the setting of life-threatening phenobarbital overdose that is refractory to conventional management (*Chest 2003;123:897*). **Hemodialysis** has been reported to be useful as well (*Am J Kidney 2000;36:640*). However, renal replacement therapies are generally not necessary because most patients do well with general supportive care.

Benzodiazepines

GENERAL PRINCIPLES

In general, benzodiazepines have a wide safety margin. Deaths are usually related to the presence of a coingestant or ethanol.

DIAGNOSIS

Clinical Presentation

History

This is often difficult to elicit because patients are frequently sedated or comatose.

Physical Examination

The typical presentation of a pure oral benzodiazepine overdose is **coma with normal vital signs**. Respiratory depression is exceedingly unusual in an oral overdose of benzodiazepines.

Differential Diagnosis

The differential diagnosis includes barbiturate overdose, hypoglycemia, ethanol intoxication, CNS depressants, other sedatives (e.g., zolpidem, GHB), and other metabolic causes of coma.

Diagnostic Testing

Laboratories

- This should include routine testing for any presentation of coma: **blood glucose, BMP, LFTs, and thyroid function tests**. Consider **LP** in patients with undifferentiated coma to evaluate for meningitis or subarachnoid hemorrhage.
- **Urine drug screens** are unreliable in the setting of benzodiazepine overdose because the target metabolite, oxazepam or desmethyldiazepam, is not produced by the metabolism of many of the benzodiazepines. Classically, clonazepam, flunitrazepam, alprazolam, and lorazepam are not detected. Therefore, routine screening is not recommended (*Clin Chem 2003;49:357*).

Imaging

- A **CXR** should be obtained on all of these patients to evaluate for aspiration.
- A **head CT** may help evaluate for the presence of CNS lesions contributing to coma.

TREATMENT

Supportive care with observation is the mainstay of therapy. In patients with coingestions and respiratory depression, intubation and ventilation may be required. Because this is a benign overdose, **gastric lavage and AC are not necessary**. These interventions may cause aspiration in an otherwise stable patient.

Medications

- Traditional recommendations include the use of **flumazenil**; however, given the propensity to precipitate seizures and acute benzodiazepine withdrawal in patients on long-term benzodiazepine therapy, this therapy is generally **avoided**. **Contraindications** include a seizure history, coingestion of a cardiotoxic or epileptogenic drug, or ECG evidence of cyclic antidepressant ingestion.
- In **special cases** such as reversal of iatrogenically induced respiratory depression, reversal of sedation, or pediatric benzodiazepine ingestion, flumazenil may be given as a 0.1 mg/min dose IV. Repeat injections may be given, because resedation occasionally occurs. If the patient develops respiratory failure, flumazenil can also be considered.

Sympathomimetics, General

GENERAL PRINCIPLES

Definition

Patients who overdose on sympathomimetic agents exhibit a syndrome of excess adrenergic tone due to direct stimulation of adrenergic receptors or the effects of norepinephrine and epinephrine. Many of the agents in this category are drugs of abuse, although several therapeutic agents can produce a similar toxidrome.

Classification

Agents that fall into this category include amphetamines, cocaine, vasopressors, methylxanthines, synthetic cannabinoids and cathinones, and β-agonists.

Epidemiology

Stimulants and street drugs were the fourteenth most common human exposure but were the fourth leading cause of fatal exposures according to the AAPCC in 2013 (*Clin Toxicol 2014;52:1032*).

Pathophysiology

- Agents that stimulate the sympathetic nervous system generally do so by either causing the release or preventing the reuptake of **endogenous catecholamines** or **directly stimulating** α- and/or **β-receptors**.
- **Methylxanthines** (theophylline, caffeine) and **β-agonists** (albuterol, dobutamine, isoproterenol) enhance chronotropy and inotropy by **facilitating calcium entry into the myocardium**. They also enhance the function of β_2-receptors leading to **bronchodilatation**. Stimulation of the β_2-rich vascular beds to skeletal muscle results in **vasodilatation** as well. Therefore, in a pure β-agonist overdose, **hypotension and tachycardia** predominate.
- **Epinephrine, norepinephrine, cocaine, and amphetamines** have both α and β effects, resulting in **hypertension and tachycardia**.

- Other α-receptors are found on the **iris**, which, when stimulated, results in **pupillary dilatation**.
- Sympathetic stimulation of **sweat glands** is a **cholinergic** effect.

Amphetamines

GENERAL PRINCIPLES

Drugs of abuse in this class include **amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and the synthetic cathinones (bath salts)**. MDMA is a potent inducer and/or reuptake inhibitor of presynaptic serotonin, dopamine, and norepinephrine.

DIAGNOSIS

Clinical Presentation

- Suspect amphetamines in any patient presenting with a sympathomimetic toxidrome of **hypertension**, **tachycardia**, **dilated pupils**, and **diaphoresis**.
- Severely intoxicated patients may develop **hyperthermia**, **seizures**, **stroke**, **coma**, and **cardiovascular collapse**.

History

Drug abusers will often deny illicit use; therefore, the history is often unreliable.

Physical Examination

Patients may have **agitation** and **altered mental status** depending on the degree of intoxication.

Differential Diagnosis

The differential includes anything that may result in a sympathomimetic toxidrome including cocaine, ephedrine, pseudoephedrine, and various amphetamine-derived designer drugs.

Diagnostic Testing

Laboratories

Patients with a sympathomimetic toxidrome should be evaluated for end-organ dysfunction.

- A **BMP** is useful to assess the degree of hydration and renal function. MDMA is also associated with the development of hyponatremia due to either SIADH or ingestion of large quantities of water.
- A **CK** should be checked to evaluate for rhabdomyolysis in agitated patients.
- Patients complaining of chest pain should have a **troponin** drawn.
- **Urine drug screens** are often associated with false-negative and false-positive results, are expensive, and **do not contribute to the management of this syndrome**.

Electrocardiography

An ECG should be obtained to evaluate for ischemia and electrolyte disturbances.

Imaging

In select cases, imaging may be useful.

- Obtain a **head CT** in patients complaining of a headache or altered mental status to evaluate for an intracranial hemorrhage.

- Obtain a **CXR** in patients complaining of chest pain.

- In patients with severe chest pain that radiates to the back or is associated with marked agitation, consider obtaining a **chest CT** to evaluate for aortic dissection.

TREATMENT

Mild to moderate cases usually respond to supportive care, including IV hydration and benzodiazepines. In hyperthermic cases, aggressive cooling measures should be taken, which may include intubation and paralysis. As always, priority should be given to airway protection, breathing, and circulation.

Medications

First Line

- Treat agitation and seizures with **benzodiazepines**. In refractory seizures, consider **barbiturates and propofol**.
- Hypertension and tachycardia may be managed with **CCBs**. ***Avoid* β-antagonists because they may be associated with the development of a hypertensive crisis.**
- **Nitroglycerin**, **nitroprusside**, **nicardipine**, and **phentolamine** may be used in the setting of severe hypertension.
- Ventricular arrhythmias should be treated with **lidocaine** or **amiodarone**.

Second Line

- Although benzodiazepines remain the treatment of choice, some data suggest that antipsychotics are useful in the management of agitated delirium in these patients (*N Engl J Med 1968;278:1361*). Consider administration of **haloperidol 5.0 mg IV or droperidol 2.5 mg IV** in patients with hallucinations (*Eur J Emerg Med 1997;4:130*). In particular, antipsychotics may be useful in patients with delirium from bath salts.
- In hyperthermic-agitated patients, consider **paralysis** with a nondepolarizing agent to prevent rhabdomyolysis.

Other Nonpharmacologic Therapies

Patients with renal failure and rhabdomyolysis may require **hemodialysis**.

SPECIAL CONSIDERATIONS

MDMA may cause hyponatremia and serotonin syndrome (see earlier discussion).

REFERRAL

Obtain a chemical dependency consult in patients hospitalized as a result of drug abuse.

Cocaine

GENERAL PRINCIPLES

- Cocaine exerts its effects by inhibiting the reuptake of norepinephrine, serotonin, epinephrine, and dopamine. Excess adrenergic tone in the setting of toxicity is reflected by the development of hypertension and

tachycardia. Drug-seeking behavior is likely modulated by dopaminergic effects in the ventral tegmental area of the brain.

- Cocaine has also been implicated in the development of early cardiovascular disease (*Circulation 2001;103:502*), likely due to a combination of vasospastic (*N Engl J Med 1989;321:1557*), prothrombotic (*Heart 2000;83:688*), and atherogenic effects (*J Am Coll Cardiol 2006;47:2120*).

DIAGNOSIS

Clinical Presentation

- Patients with cocaine intoxication often present with complaints of ischemic chest pain.
- Suspect cocaine in any patient presenting with a sympathomimetic toxidrome of **hypertension**, **tachycardia**, **dilated pupils**, and **diaphoresis**.
- Severely intoxicated patients may develop **hyperthermia**, **seizures**, **coma**, and **cardiovascular collapse**.

History

Drug abusers will often deny illicit use; therefore, the history is often unreliable.

Physical Examination

Patients may have **agitation** and **altered mental status** depending on the degree of intoxication.

Differential Diagnosis

The differential includes anything that may result in a sympathomimetic toxidrome, including amphetamines, ephedrine, pseudoephedrine, and various amphetamine-derived designer drugs.

Diagnostic Testing

Laboratories

Patients with a sympathomimetic toxidrome should be evaluated for end-organ dysfunction.

- A **BMP** is useful to assess the degree of hydration and renal function.
- A **CK** should be checked to evaluate for rhabdomyolysis in agitated patients.
- Patients complaining of chest pain should have a **troponin** drawn.
- **Urine drug screens**, although reliable in determining recent use, should not modify the acute management of these patients.

Electrocardiography

- An ECG should be obtained to evaluate for ischemia and electrolyte disturbances.
- Cocaine is a known sodium channel blocker, which may be reflected as a wide complex rhythm (*J Pharmacol Exp Ther 1992;261:910*) or Brugada pattern (*Heart 2010;96:643*) on the ECG.
- Cocaine has been reported to increase the QT_c (*Emerg Med J 2004;21:252*).

Imaging

In select cases, imaging may be useful.

- Obtain a **head CT** in patients complaining of a headache or altered mental status.
- Obtain a **CXR** in patients complaining of chest pain.

- In patients with severe chest pain that radiates to the back or is associated with marked agitation, consider obtaining a **chest CT** to evaluate for aortic dissection.

TREATMENT

Mild to moderate cases usually respond to supportive care, including IV hydration. In hyperthermic cases, aggressive cooling measures should be taken. As always, priority should be given to airway protection, breathing, and circulation.

Medications

First Line

- Treat agitation and seizures with **benzodiazepines**. In refractory seizures, consider **barbiturates and propofol**.

P.919

- Hypertension and tachycardia may be managed with **CCBs**, benzodiazepines, and vasodilators (e.g., nitroglycerin, nitroprusside, phentolamine).
- ***Avoid* β-antagonists because they may be associated with the development of a hypertensive crisis and vasospasm.**
- Sodium channel blockade should be treated with **sodium bicarbonate** (*Circulation 1991;83:1799*). Give **1-2 mEq/kg** as an IV bolus; this may be repeated. Monitor for QRS narrowing.
- Ventricular arrhythmias should be treated with **lidocaine**.

Second Line

In hyperthermic-agitated patients, consider **paralysis** with a nondepolarizing agent to prevent rhabdomyolysis.

Other Nonpharmacologic Therapies

Patients with renal failure and rhabdomyolysis may require **hemodialysis**.

SPECIAL CONSIDERATIONS

- Body packers (patients smuggling large amounts of drugs by swallowing multiple packets of drugs) with suspected cocaine toxicity or obstructive symptoms should have emergent surgical intervention. A patient who is running from the police and swallows drugs (body stuffer) is unlikely to need surgical intervention. Consider whole-bowel irrigation in patients who present without signs of toxicity.
- Increasingly, cocaine has been found to be adulterated with **levamisole**. This veterinary dewormer has been demonstrated to cause agranulocytosis and vasculitis, which reverse with cessation of cocaine use. Any patient who presents with an unexpected decrease in their WBC or necrotic skin rash should be counseled to stop using cocaine. G-CSF may be used to treat serious neutropenia (*Semin Arthritis Rheum 2011;41(3):445*).

Theophylline

GENERAL PRINCIPLES

Definition

Theophylline is a methylxanthine used in the treatment of obstructive pulmonary diseases such as asthma and emphysema. Its use has largely fallen by the wayside as alternative, less toxic medications have been developed. However, patients with refractory pulmonary disease may still be prescribed this drug.

Classification

Toxicity is classified as **acute** or **chronic**. The management strategy is different depending on whether the drug is an **immediate-** or **sustained-release** preparation.

Pathophysiology

Theophylline exerts its therapeutic effects by promoting catecholamine release, which results in enhanced β-agonism (*Circulation 1983;67:162*). Additionally, at high doses, theophylline is a phosphodiesterase inhibitor, which prolongs the effects of β-agonism by preventing the breakdown of cyclic adenosine monophosphate (cAMP). Theophylline is also an adenosine antagonist, which in therapeutic doses enhances bronchodilatation. However, in toxic doses, adenosine antagonism is associated with the development of tachydysrhythmias and seizures.

DIAGNOSIS

Clinical Presentation

- **Acute toxicity:** Patients with serum concentrations >**20 µg/mL** will present complaining of **nausea** and multiple episodes of **vomiting, which may be very difficult to control**. On examination, the patient will be **tremulous** and **tachycardic**. **Hyperventilation** is often present. In more severe cases, **hypotension** and **seizures** occur. **Refractory status epilepticus** is due to adenosine antagonism in the CNS (*Neuroscience 1994;58:245*). These effects are most often present at serum concentrations **>90 µg/mL** in the acutely intoxicated patient.
- **Chronic toxicity** usually occurs in patients with a large body burden of theophylline who develop a concurrent illness or are administered a drug that delays the P450 metabolism and theophylline clearance. Subtle symptoms such as nausea and anorexia may occur; tachycardia is usually present. Severe toxicity may occur at serum levels of **40-60 µg/mL**. Patients with these serum concentrations may present with seizures.

Diagnostic Testing

Laboratories

- Therapeutic concentrations are 5-15 µg/mL.
- **Acute toxicity** is associated with the development of **hypokalemia** and **hyperglycemia**. In severe cases, expect a **metabolic acidosis**. Obtain a **BMP and blood glucose**.
- **Serial theophylline** concentrations should be obtained every 1-2 hours until a downward trend is present; remember, with sustained-release preparations, a peak may not be evident for 16 hours or later after ingestion.
- **Calcium, magnesium, and CK** should be checked as well.
- **Chronic toxicity** can occur with lower concentrations than in acute toxicity. Many laboratories (e.g., potassium, glucose) may be unremarkable, unless seizures are present, but should still be obtained. **Serial theophylline** concentrations are also warranted in these patients.

Electrocardiography

Adenosine antagonism and increased catecholamines may result in a sinus tachycardia or supraventricular tachycardia (SVT) on the ECG. In overdose, premature ventricular contractions (PVCs) may be apparent.

TREATMENT

Patients with theophylline toxicity do not require gastric lavage because they tend to vomit. Sustained-release preparations occasionally form bezoars. Severely intoxicated patients require intubation and ventilation. Sustained-release formulations should be treated with **whole-bowel irrigation**. Replete potassium and electrolytes as needed.

Medications

- Administer **AC 1 g/kg**. Consider **MDAC** because theophylline clearance is increased by this modality (*Clin Pharmacol Ther 1983;33:351*). Ensure patients have adequate airway protection because vomiting and aspiration may occur.
- **Vomiting** should be managed with **ondansetron** or **metoclopramide**. **Phenothiazines are contraindicated** because they lower the seizure threshold.
- **Seizures** are often refractory and should initially be treated with **benzodiazepines**. If this modality fails, consider moving to **phenobarbital** as a 10 mg/kg loading dose at a rate of 50 mg/min, followed by up to a total of 30 mg/kg at a rate of 50 mg/min, followed by 1-5 mg/kg/d to maintain therapeutic plasma levels. **Propofol** is a reasonable alternative if these fail. Monitor for hypotension.

- **Hypotension** should be treated with 20 mL/kg bolus of IVF, which may be repeated. Direct pressors such as **phenylephrine** and **norepinephrine** may be added if fluid boluses are not sufficient. Because much of the hypotension is mediated by β_2-agonism, **avoid epinephrine**. Consider using short-acting β-antagonists such as **esmolol**, which, although counterintuitive, may reverse β_2-mediated vasodilatation. Monitor for bronchospasm.
- **Arrhythmias** should be treated with β-antagonists. Use short-acting agents such as **esmolol** and monitor for bronchospasm. Because theophylline is an adenosine antagonist, adenosine may fail to treat SVT.

Other Nonpharmacologic Therapies

Hemoperfusion (charcoal or resin) or **hemodialysis** is indicated for the following:

- Intractable seizures or life-threatening cardiovascular complications, regardless of drug level
- A theophylline level of >100 mg/mL after an **acute** overdose
- A theophylline level >60 mg/mL in acute intoxication, with worsening symptoms, or inability to tolerate oral charcoal administration
- A theophylline level >60 mg/mL in **chronic** intoxication without life-threatening symptoms
- A theophylline level >40 mg/mL in a patient with chronic intoxication and CHF, respiratory insufficiency, hepatic failure, or age >60 years (*J Emerg Med 1993;11:415*)

Toxic Alcohol, General

GENERAL PRINCIPLES

- High alcohol concentrations increase the measured plasma osmolality and subsequently widen the osmolar gap. A normal gap is <10 mmol/dL and varies from −14 to +10 mmol/dL (*J Toxicol Clin Toxicol 1993;31:81*).
- In presence of a widened gap, the actual serum alcohol level can be estimated if done early after ingestion (*BMC Emerg Med 2008;8:5*) with the following calculation:

$$\text{Osmol gap} \times \frac{\text{Molecular weight of alcohol}}{10} = \text{[Serum alcohol] (mg/dL)}$$

- As the alcohol is metabolized, the osmolar gap falls, and the anion gap rises (*Clin J Am Soc Nephrol 2008;3(1):208*). Therefore, the osmolar gap should only be used to support the diagnosis of toxic alcohol poisoning and not to draw conclusions about the actual amount of ingested toxin.

$$\text{Calculated osmolarity} = 2\text{Na}^+ + \frac{\text{BUN}}{2.8} + \frac{\text{Glucose}}{18} + \frac{\text{Alcohol/Molecular weight of alcohol}}{10}$$

- The specific molecular weights for each alcohol can be found in the following sections.
- Unlike methanol and ethylene glycol, isopropanol (rubbing alcohol) does not form a toxic metabolite.

TREATMENT

The general approach to toxic alcohol ingestions is to (*Clin Toxicol 2002;40(4):415*):

- Prevent the formation of toxic metabolites by inhibiting alcohol dehydrogenase (ADH) (in methanol and ethylene glycol poisoning only).
- Eliminate the toxic alcohol and toxic metabolites from the blood.

- Correct acid-base imbalance.
- Replenish cofactors.

Methanol

GENERAL PRINCIPLES

Definition

Methanol is used in gasoline, antifreeze, deicers, windshield washer fluid, paint and varnish removers, fuel, photocopy fluid, and embalming fluids. It can be found in “moonshine” liquor and is used as a denaturant for ethanol.

Etiology

Ingestions are mostly intentional, occurring as suicide attempts.

Pathophysiology

Methanol is oxidized to formic acid, which is responsible for the anion gap metabolic acidosis in methanol poisoning (*Intern Med 2004;43(8):750*).

DIAGNOSIS

Clinical Presentation

- **Early stage**
  - Early after ingestion, mild CNS depression or headache evolves, but profound obtundation or inebriation can occur as well.
  - These early symptoms are directly caused by methanol prior to being metabolized.
- **Late stage**
  - After a latent period, a severe anion gap metabolic acidosis without significant lactate or ketone formation develops.
  - Formate accumulation within the retina and optic nerve fibers causes "snow field vision," blurred vision, visual field defects, and blindness (*Arch Ophthalmol 1991;109(7):1012*).
  - Other CNS symptoms during the late phase are lethargy, convulsion, delirium, and coma. Basal ganglia hemorrhage with dyskinesia or hypokinesia has been observed (*Int J Clin Pract 2004;58(11):1042*).
  - Abdominal complaints include nausea, vomiting, pain, and acute pancreatitis (*Clin Toxicol 2000;38(3):297*).

History

Obtain history of what, when, how, and how much of the toxic substance was ingested.

Physical Examination

- Assess mental status and respiratory and cardiovascular stability.
- Kussmaul respirations may indicate underlying metabolic acidosis.
- Visual field testing may reveal central scotoma or other visual field defects. A thorough funduscopic exam may show hyperemia, disk edema, or atrophy (*Med J Aust 1978;2(10):483*).

Diagnostic Testing

- Address possible causes of an anion gap acidosis
  - BMP: Acidosis, anion gap, renal function
  - Urinalysis (UA): Ketones
  - Serum lactate

- Accu-Cheks.
- Obtain serum osmolality if toxic alcohol ingestion is suspected. Molecular weight of methanol is 32.04 g/mol.
- ABG or VBG: To assess acid-base status and treatment success.
- Ethanol concentration: If >100 mg/dL, toxic methanol manifestations may be delayed; if elevated in presence of acidosis, the acidosis is unlikely to be related to a toxic alcohol ingestion because ethanol blocks the metabolism of the parent compound (unless the toxic alcohol ingestion occurred hours before the ethanol ingestion).
- Serum methanol concentration: Usually not readily available; therefore, clinically may not be useful.

TREATMENT

- ABCs and general supportive care.
- GI decontamination: Nasogastric lavage is only indicated in patients who present <30 minutes after ingestion or who ingested large amounts of methanol while maintaining a normal mental status.
- **Do not use AC** because the GI tract rapidly absorbs methanol. AC bears a high risk of aspiration in acutely intoxicated patients.
- Sodium bicarbonate: Give 50 mg IV every 4 hours for arterial pH <7.30 (*N Engl J Med 2009;360(21):2216*).
  - Serum alkalinization limits the amount of undissociated formic acid, which prevents CNS toxicity.
  - Urine alkalinization enhances clearance of formate. CAVEAT: Watch for fluid overload and hypokalemia if giving large amounts of bicarbonate.
- Ethanol (EtOH) therapy: EtOH serum levels of 100 mg/dL block ADH sufficiently to inhibit formation of toxic metabolites.
  - Loading dose of **7.6 mL/kg of 10% ethanol** solution IV (correlates with an EtOH serum level of 100-200 mg/dL)
  - Maintenance dose of **0.8 mL/kg/h (nondrinker), 2.0 mL/kg/h (drinker), or 2.0-3.3 mL/kg/h (on hemodialysis)** of 10% ethanol solution IV (*Clin J Am Soc Nephrol 2008;3(1):208*)
- **Fomepizole** therapy: 4-Methylpyrazole (Antizol) is an FDA-approved competitive inhibitor of ADH for the treatment of methanol poisoning (*Intensive Care Med 2005;31(2):189*).
  - Loading dose of **15 mg/kg IV**, maintenance dose of **10 mg/kg IV** every 12 hours for 48 hours, then 15 mg/kg IV every 12 hours until methanol level <20 mg/dL.
  - Dose adjustment may be needed for patients on hemodialysis (*N Engl J Med 2009;360(21):2216*). If on intermittent hemodialysis, re-dose can be done after hemodialysis is completed and other dose adjustments are not needed.
  - Continue treatment until methanol levels <20 mg/dL and acidosis resolves (*Curr Opin Nephrol Hypertens 2000;9(6):695*).
- Indication: Ethanol or fomepizole therapy should be started if:
  - Strong evidence of methanol ingestion
  - Methanol serum concentration >20 mg/dL
  - Osmolar gap >10 mmol/dL
  - Arterial pH <7.3
  - Serum CO_2 <20 mmol/L
  - Unexplained anion gap metabolic acidosis is present (*N Engl J Med 2009;360(21):2216*)

Other Nonpharmacologic Therapies

- **Hemodialysis** should be used in addition to the aforementioned therapies to prevent end-organ toxicity.

- **Hemodialysis** corrects metabolic abnormalities and eliminates nonmetabolized methanol. Indications for hemodialysis are a methanol level >50 mg/dL, severe acidemia (bicarbonate <15 mmol/L, pH <7.30), and/or optic injury from toxicity (*Hum Exp Toxicol 2005;24(2):55*). If the methanol concentration is very elevated, hemodialysis should also be considered even if the patient is not acidotic given the long half-life of methanol and expense of fomepizole.

- Folic acid 1 mg/kg (up to 50 mg) IV every 4-6 hours and folinic acid (leucovorin) 1 mg/kg (up to 50 mg) IV every 4-6 hours enhance formate metabolism and should be given until metabolic acidosis resolves (*Alcoholism 1980;4(4):378*).

SPECIAL CONSIDERATIONS

- Ethanol therapy has significant disadvantages (e.g., complex dosing regimen, hard to titrate therapeutic levels, intensive care requirements, and severe side effect profile). Although very expensive ($500/dose), fomepizole has become the preferred agent in the treatment of methanol intoxication (*Ann Emerg Med 2009;53(4):451*).
- Admit all patients on ethanol infusions to the ICU (risk of hypotension, tachycardia, hypoglycemia, and CNS and respiratory depression).
- Stable patients on fomepizole infusion can be safely admitted to the floor. Adverse effects of fomepizole are usually mild and include headache, nausea, and dizziness but not sedation (*Alcoholism 1988;12(4):516*; *Lancet 1999;354(9181):831*).
- Report all cases of methanol intoxication to the local poison control center (1-800-222-1222).
- Get a clinical toxicologist involved early.
- Consult ophthalmology or neurology service if signs of optic injury or other neurologic deficits are present.

Ethylene Glycol

GENERAL PRINCIPLES

Etiology

Ingestions are mostly due to intentional suicide attempts.

Pathophysiology

- Ethylene glycol is oxidized to glycolic acid and oxalic acid.
- Glycolate accumulation is responsible for the anion gap metabolic acidosis in ethylene glycol poisoning.
- Oxalate accumulation is responsible for the development of acute renal failure in ethylene glycol poisoning (*Clin Toxicol 1986;24(5):389*).

DIAGNOSIS

Clinical Presentation

- Neurologic stage
  - CNS depression with altered mental status, hallucinations, ataxia, slurred speech, and cranial nerve palsies are directly caused by ethylene glycol prior to metabolization.
  - Seizures, coma, and respiratory depression can occur in severe intoxications.
- Cardiovascular stage: Glycolate affects the cardiopulmonary system and causes tachycardia, hypotension, heart failure, pulmonary edema, and ARDS.

- Renal stage
  - Glycolic acid is further metabolized to oxalic acid. Oxalate is a calcium chelator, and accumulation of oxalate leads to **hypocalcemia**.

    P.925
  - Calcium oxalate can precipitate in the renal tubules, which subsequently causes acute tubular necrosis with flank pain and acute renal failure (*Acta Clin Belg 1999;54(6):351*).
- Within 4-6 hours after ingestion, development of an anion gap metabolic acidosis from glycolic acid formation in the absence of significant lactate or ketone concentrations occurs.
- Abdominal complaints (nausea, vomiting, pain) are also common.

History

Obtain history of what, when, how, and how much of the toxic substance was ingested.

Physical Examination

- Assess mental status and respiratory and cardiovascular stability.
- Kussmaul respiration may indicate severe metabolic acidosis.

Diagnostic Testing

- Address causes of a high anion gap metabolic acidosis:
  - BMP: Acidosis, anion gap, renal function.
  - UA: Ketones, oxalate crystals (usually a late sign during intoxication).
  - Serum lactate.
  - **Glycolic acid may also be misinterpreted as a high lactic acid on a point-of-care blood gas analyzer.** Serum levels should be obtained in these cases.
- Obtain serum osmolality if toxic alcohol ingestion is suspected. The molecular weight of ethylene glycol is 62.07 g/mol.
- ABG or VBG to assess acid-base status and treatment success.
- Ethanol level: If elevated, toxic ethylene glycol manifestations may be delayed; if elevated in presence of acidosis, unlikely to be toxic alcohol ingestion (unless toxic alcohol ingestion occurred hours before ethanol ingestion).
- Obtain serum ethylene glycol concentration: Usually not readily available; therefore, clinically often not useful.
- Serum calcium concentration: Low if increased formation of calcium oxalate.
- Repeated renal function testing: Increased risk of acute kidney injury (AKI).
- Urine microscopy: Calcium oxalate might be visible as envelope-shaped crystals (*Emerg Med J 2007;24(4):310*).
- Wood lamp examination of urine to detect fluorescence after assumed antifreeze ingestion is not a reliable screening tool (*Am J Emerg Med 2005;23(6):787*).

TREATMENT

- ABCs and supportive care; monitor urine output.
- GI decontamination: Nasogastric lavage is only indicated in patients who present <30 minutes after

ingestion or who ingested large amounts of ethylene glycol while maintaining a normal mental status.

- **Do not use AC** because the GI tract rapidly absorbs ethylene glycol. AC bears a high risk of aspiration in acutely intoxicated patients.
- **Thiamine** (vitamin B_1) 100 mg IV every 4-6 hours and **pyridoxine** (vitamin B_6) 50 mg IV every 6-12 hours enhance glycolate metabolism and should be given until metabolic acidosis resolves (*Eur J Emerg Med 2005;12(2):78*).
- Sodium bicarbonate: Give 50 mg IV every 4 hours for arterial pH <7.30 (*N Engl J Med 2009;360(21):2216*).
  - Serum alkalinization limits the amount of undissociated glycolic acid, which prevents CNS toxicity.
  - Urine alkalinization enhances clearance of glycolate. CAVEAT: Watch for fluid overload and hypokalemia if giving large amounts of bicarbonate.

- Ethanol therapy: EtOH serum concentrations of 100 mg/dL block ADH sufficiently to inhibit formation of toxic metabolites. See discussion of methanol overdose treatment for dosing.
- **Fomepizole** therapy: See discussion of methanol overdose treatment for dosing.
- **Indications:** Ethanol or fomepizole therapy should be started if:
  - Strong evidence of ethylene glycol ingestion
  - Ethylene glycol serum concentration >20 mg/dL
  - Osmolar gap >10 mmol/dL
  - Arterial pH <7.3
  - Serum CO_2 <20 mmol/L
  - Unexplained anion gap metabolic acidosis is present (*N Engl J Med 2009;360(21):2216*)

Other Nonpharmacologic Therapies

- **Hemodialysis** should be used in addition to the aforementioned therapies to prevent end-organ toxicity.
- **Hemodialysis** corrects metabolic abnormalities and eliminates nonmetabolized ethylene glycol. Indications for hemodialysis are an ethylene glycol concentration >50 mg/dL, severe acidemia (bicarbonate <15 mmol/L, pH <7.30), hyperviscosity from very elevated concentrations, and/or optic injury from toxicity (*Hum Exp Toxicol 2005;24(2):55*). Recent literature demonstrates that in otherwise well patients, hemodialysis may not be required even with markedly elevated ethylene glycol concentrations (*J Med Toxicol 2007;3(3):125*).

Ethanol

GENERAL PRINCIPLES

- Elimination rate: 20-25 mg/dL/h (zero-order kinetics, faster in chronic alcoholics).
- Ethanol is present in all alcoholic beverages, some food extracts, mouthwash, and cold syrups, but is also industrially used as a solvent in its denatured form.

Pathophysiology

Ethanol is oxidized to acetic acid (acetate), which is further metabolized to nontoxic intermediates.

DIAGNOSIS

Clinical Presentation

- CNS depression with ataxia, drowsiness, and confusion are common symptoms at blood concentrations >100 mg/dL. Respiratory depression can occur at higher concentrations (*Emerg Med 1984;2(1):47*).
- Chronic alcohol abuse induces tolerance, and patients appear asymptomatic even with high blood concentrations (*J Emerg Med 1997;15(5):687*).
- Hypoglycemia is due to an altered NADH/NAD^+ ratio with the development of a reduced state. Pyruvate is then shunted from the gluconeogenesis pathway, and lactate production is favored due to increased NADH. Severe hypoglycemia is common in chronic alcoholics and in children.
- Chronic intoxication causes further gluconeogenesis disturbances, an increase in ketogenesis (β-hydroxybutyrate), and eventually the development of alcoholic ketoacidosis (AKA) (*Hum Exp Toxicol 1996;15(6):482*).

Diagnostic Testing

- Obtain glucose concentrations, hepatic function tests, and BMP (especially in chronic alcoholics).

- Serum ethanol concentrations are only relevant to rule out poisoning from other alcohols or in the evaluation of patients presenting with a coma or altered mental status.
- Serum osmolality (if coingestion with other alcohols is suspected). The molecular weight of ethanol is 46.07 g/mol.
- May also have mild lactic acidosis if dehydrated or has hepatic dysfunction.

TREATMENT

Treatment is mainly supportive; however, hemodialysis may be indicated in severe poisoning (e.g., cardiovascular collapse from ethanol). Administer 100 mg **thiamine** IV followed by 50 mL of D_{50} in water IV to any **comatose alcoholic patient** with hypoglycemia. Thiamine should be administered in all alcoholic patients. Patients may require intubation for respiratory depression or for airway protection.

SPECIAL CONSIDERATIONS

- Increased morbidity and mortality result from chronic toxicity (liver and GI injuries) and AKA.
- Traumatic injuries and severe hypothermia are frequent findings due to risky behavior or decreased judgment capability during acute intoxication.
- Ethanol withdrawal can lead to life-threatening conditions and requires special attention.
- Patients should be observed until signs of clinical intoxication resolve.

Cyanide

GENERAL PRINCIPLES

Cyanide is one of the most rapidly acting and lethal poisons in existence. Cyanide has an odor of bitter almonds; however, only 50% of the population can detect it (*Clin Toxicol 1981;18(3):367*).

Etiology

- Inhalation of smoke from structural fires is the most common source of cyanide exposure in the United States and Western countries.
- Other etiologies include artificial nail remover, older rodenticides, electroplating solutions, photographic developer solutions, laboratory reagents, laetrile, plants (e.g., pits from the *Prunus* species), food such as cassava, and metabolism of sodium nitroprusside.

Pathophysiology

- Cyanide is a chemical asphyxiant. It induces cellular hypoxia by inhibiting complex IV (also known as cytochrome c oxidase or cytochrome oxidase aa_3) in the electron transport chain and thus preventing the formation of adenosine triphosphate (ATP).
- Hyperlactemia occurs from inhibition of aerobic metabolism.

DIAGNOSIS

Clinical Presentation

- The dose, duration of exposure, route of exposure, and etiology of the exposure all contribute to the severity of the illness. Signs and symptoms can be nonspecific, so physicians must have a high degree of clinical suspicion to avoid missing the diagnosis (*Hum Exp Toxicol 2007;26:191*).
- Transient increases in heart rate, BP, and respiratory rate can be followed by cardiovascular collapse and respiratory failure. Initially, patients can present with bradycardia and

hypertension; this is followed by tachycardia and hypotension, before they experience cardiovascular collapse.
- The heart and CNS have high demands for oxygen and are commonly affected. Signs and symptoms include headache, anxiety, lethargy, seizures, coma, respiratory failure, and cardiovascular collapse. Cyanide does not cause cyanosis.
- The cherry-red skin that is classically associated with cyanide toxicity is an uncommon finding. If it occurs, it occurs very late in the clinical course. Retinal veins may be bright red.

Laboratories

- Blood and serum concentrations are not available in a timely fashion so are not clinically useful. Smokers may have a slightly elevated baseline concentration compared to nonsmokers.
- Due to inhibition of aerobic metabolism, patients can have elevated lactate concentrations. In smoke inhalation victims, a lactate greater than 10 mmol/L was suggestive of cyanide toxicity (*N Engl J Med 2007;26(3):191*).
- Patients may have an “arterialization” of their venous blood because the venous oxygen saturation may be very elevated due to inhibition of aerobic metabolism. The partial pressure of oxygen in venous and arterial samples can be nearly identical. In addition, venous samples may appear bright red, similar to arterial samples. This can be seen when comparing ABGs and VBGs that are drawn simultaneously.

TREATMENT

Two antidotes are available for patients with cyanide toxicity.

- The cyanide antidote kit contains **amyl nitrite pearls** and **sodium nitrite**. The pearls can be broken and placed under the patient's nose while IV access is obtained. Sodium nitrite (300 mg) is administered as a 3% solution given over 2-4 minutes IV in adults. Nitrites are given to induce a methemoglobinemia, which cyanide will preferentially bind to instead of the electron transport chain. However, in patients with smoke inhalation, this can be dangerous because they may already have elevated levels of carboxyhemoglobin, and the combination can cause a very severe functional anemia. Nitrites can also cause or exacerbate hypotension. The second part of the antidote is **sodium thiosulfate**, administered as 12.5 g IV in adults. Its time of onset is slower than the nitrites; at times, it is given prophylactically to patients on nitroprusside infusions (*Ann Pharmacother 1992;26(4):515*).
- **Hydroxocobalamin** (5 g IV) is another antidote. It combines with cyanide to form cyanocobalamin (vitamin B_{12}). It has few side effects. It turns the urine red and causes skin discoloration, which negatively interferes with co-oximetry. It will also interfere with certain laboratory tests such as bilirubin, creatinine, and serum glucose (*Crit Rev Toxicol 2009;39(7):541*). Although more expensive, it is generally the preferred antidote.
- The rest of care is supportive, including adequate volume resuscitation, airway support, and vasopressor and inotropic support as needed (*Hum Exp Toxicol 2007;26:191*).

Carbon Monoxide

GENERAL PRINCIPLES

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas that is produced during incomplete combustion of carbon-containing fuels. It is the leading cause of poisoning morbidity and mortality in the United States (*JAMA 1991;266:659*).

Etiology

Common sources of exposure include smoke inhalation in house fires, malfunctioning heaters and electric generators, automobile exhaust, smoking, forklifts, and chemicals such as methylene chloride (*Emerg Med Clin North Am 2004;22:985*).

Pathophysiology

- CO binds with hemoglobin to form carboxyhemoglobin, which causes a functional anemia and shifts the oxyhemoglobin dissociation curve to the left.
- CO inhibits cellular respiration by binding to mitochondrial cytochrome oxidase and disrupting the electron transport chain (*J Toxicol Clin Toxicol 1989;27(3):141*).
- Nitric oxide levels, which cause vasodilation, are also increased (likely secondary to activation of nitric oxide synthase) (*Emerg Med Clin North Am 2004;22:985*).

DIAGNOSIS

The diagnosis of CO poisoning is challenging due to its many vague signs and symptoms that can wax and wane depending on the patient’s source of exposure.

Clinical Presentation

- Patients may present with flu- or viral-like symptoms, which include headache, myalgias, fatigue, lethargy, nausea, vomiting, and dizziness. If these patients remove themselves from the exposure, such as when they leave their house to seek medical attention, the symptoms may improve before they are evaluated by a physician.
- The heart and CNS have higher oxygen demands, and thus, patients can present with chest pain, myocardial infarctions, cardiac dysrhythmias, syncope, stroke-like symptoms, seizures, coma, and other psychoneurologic symptoms.
- Patients may present with persistent neurologic sequelae (PNS), which occur at the time of exposure, or delayed neurologic sequelae (DNS), which can occur anywhere between 2-40 days after the exposure (*Ann Emerg Med 1995;25:474*).

Diagnostic Testing

- Carboxyhemoglobin (CO-Hgb) levels are readily available. They can be obtained on either arterial or venous specimens (*Ann Emerg Med 1995;25:4813*). Levels greater than 5% in nonsmokers and greater than 10% in smokers generally confirm an exogenous exposure. However, levels do not correlate well with a patient's symptoms or prognosis.
- New handheld pulse co-oximeters can be used to noninvasively measure CO-Hgb. Standard pulse oximeters may be falsely reassuring because they cannot detect a difference between oxyhemoglobin and CO-Hgb. This results in a "gap" between the measured pulse oximetry using a finger probe and the true value found by using co-oximetry.
- Levels need to be interpreted in the context of how long it has been since the exposure and when oxygen therapy was initiated. Both will cause the level to be "falsely low."
- Head CTs may show bilateral lesions in the globus pallidus.
- A lactic acidosis may be present due to the disruption of aerobic respiration.

TREATMENT

- Treatment involves administering oxygen. One hundred percent oxygen administered through a non-rebreather will decrease the half-life of CO to 60-90 minutes. Hyperbaric oxygen (HBO) will decrease it to 20-30 minutes. Most patients will need to be transported to tertiary centers to receive HBO; hence, improving PNS or preventing DNS and not just decreasing the half-life of CO is the rationale for the use of HBO.
  - Randomized studies have both supported HBO for CO poisoning (*Ann Emerg Med 1995;25:474*; *N Engl J Med 2002;347(14):1057*) and concluded that it was ineffective (*Lancet 1989;334:414*; *Med J Aust 1999;170(5):203*). The studies differed in their inclusion criteria, exclusion criteria, treatment protocols, and outcome assessment.
  - Indications for and the benefits of HBO are controversial, and more research is needed (*Cochrane Database Syst Rev 2011;4:CD002041*). Suggested indications include syncope, coma, neurologic deficits, PNS, cardiac ischemia, severe metabolic acidosis,

    pregnancy, and CO >25%. Given the controversy, a treatment approach using shared decision making is recommended.
- Additional care includes airway and ventilator support, vasopressors for hypotension, and treating any additional concurrent injury, such as if the patient has a burn, trauma, or cyanide toxicity from a house

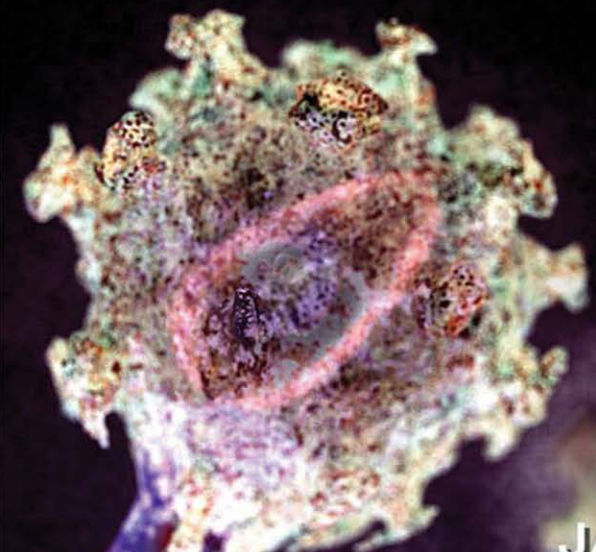
fire.

COMPLICATIONS

- If the patient survives the exposure, DNS and PNS are the most feared long-term complications after CO poisoning.
- The signs and symptoms of DNS are variable, and a standard definition does not exist. They can include malaise, fatigue, headache, memory problems, paralysis, dementia, neuropathy, psychosis, and cortical blindness (*Ann Emerg Med 1995;25:474*). The methods used to test for DNS and the definition of DNS varied between the different randomized trials cited earlier.

19th Edition

HARRISON'S™ MANUAL OF MEDICINE



KASPER
FAUCI
HAUSER
LONGO
JAMESON
LOSCALZO

Mc Graw Hill Education

GLOSSARY

A_2	aortic second sound
ABGs	arterial blood gases
ACE	angiotensin converting enzyme
AF	atrial fibrillation
AIDS	acquired immunodeficiency syndrome
ALS	amyotrophic lateral sclerosis
ANA	antinuclear antibody
ARDS	acute respiratory distress syndrome
bid	two times daily
biw	twice a week
bp	blood pressure
BUN	blood urea nitrogen
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CF	complement fixation
CHF	congestive heart failure
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CT	computed tomography
CVP	central venous pressure
CXR	chest x-ray
DIC	disseminated intravascular coagulation
DVT	deep venous thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EMG	electromyogram
ENT	ear, nose, and throat
EOM	extraocular movement
ESR	erythrocyte sedimentation rate
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in first second
GFR	glomerular filtration rate
GI	gastrointestinal
G6PD	glucose-6-phosphate dehydrogenase
Hb	hemoglobin
Hct	hematocrit
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
hs	at bedtime
HSV	herpes simplex virus
ICU	intensive care unit
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IP	intraperitoneal
IV	intravenous
IVC	inferior vena cava
IVP	intravenous pyelogram

19th Edition

HARRISON'S™ MANUAL OF MEDICINE

EDITORS

Dennis L. Kasper, MD, MA(HON)
William Ellery Channing Professor of Medicine,
Professor of Microbiology and Immunobiology,
Department of Microbiology and Immunobiology,
Harvard Medical School; Division of Infectious Diseases,
Brigham and Women's Hospital,
Boston, Massachusetts

Anthony S. Fauci, MD, ScD(HON)
Chief, Laboratory of Immunoregulation;
Director, National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, Maryland

Stephen L. Hauser, MD
Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology,
University of California, San Francisco,
San Francisco, California

Dan L. Longo, MD
Professor of Medicine, Harvard Medical School;
Senior Physician, Brigham and Women's Hospital;
Deputy Editor, *New England Journal of Medicine*,
Boston, Massachusetts

J. Larry Jameson, MD, PhD
Robert G. Dunlop Professor of Medicine;
Dean, Perelman School of Medicine at the University of Pennsylvania;
Executive Vice President, University of Pennsylvania for the Health System, Philadelphia, Pennsylvania

Joseph Loscalzo, MD, PhD
Hersey Professor of the Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine, and
Physician-in-Chief, Brigham and Women's Hospital,
Boston, Massachusetts



19th Edition

HARRISON'S™ MANUAL OF MEDICINE

EDITORS

Dennis L. Kasper, MD

Anthony S. Fauci, MD

Stephen L. Hauser, MD

Dan L. Longo, MD

J. Larry Jameson, MD, PhD

Joseph Loscalzo, MD, PhD



New York Chicago San Francisco Athens London Madrid
Mexico City Milan New Delhi Singapore Sydney Toronto

Copyright © 2016 by McGraw-Hill Education. Previous editions copyright © 2013, 2009, 2005, 2002, 1998, 1995, 1991, 1988 by The McGraw-Hill Companies, Inc. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-0-07-182854-3

MHID: 0-07-182854-0

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-182852-9, MHID: 0-07-182852-4.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education books are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us pages at www.mhprofessional.com.

NOTE: Dr. Fauci's work as editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

This book was set in Minion Pro by Cenveo® Publisher Services. The editors were James F. Shanahan and Kim J. Davis. The production supervisor was Catherine H. Saggese; project management was provided by Anupriya Tyagi, Cenveo Publisher Services. The designer was Alan Barnett; the cover designer was Dreamit, Inc. RR Donnelly was printer and binder.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

CONTENTS

Contributors xv
Preface xvii
Acknowledgments xix

SECTION 1 CARE OF THE HOSPITALIZED PATIENT

1 Electrolytes/Acid-Base Balance 1
2 Diagnostic Imaging in Internal Medicine 23
3 Procedures Commonly Performed by Internists 26
4 Principles of Critical Care Medicine 31
5 Pain and Its Management 35
6 Assessment of Nutritional Status 40
7 Enteral and Parenteral Nutrition 43
8 Transfusion and Pheresis Therapy 46
9 Palliative and End-of-Life Care 48

SECTION 2 MEDICAL EMERGENCIES

10 Cardiovascular Collapse and Sudden Death 57
11 Shock 61
12 Sepsis and Septic Shock 65
13 Acute Pulmonary Edema 69
14 Acute Respiratory Distress Syndrome 71
15 Respiratory Failure 73
16 Confusion, Stupor, and Coma 76
17 Stroke 82
18 Subarachnoid Hemorrhage 91
19 Increased Intracranial Pressure and Head Trauma 93
20 Spinal Cord Compression 98
21 Hypoxic-Ischemic Encephalopathy 100
22 Status Epilepticus 101
23 Diabetic Ketoacidosis and Hyperosmolar Coma 104
24 Hypoglycemia 107
25 Oncologic Emergencies 109
26 Anaphylaxis 114
27 Bites, Venoms, Stings, and Marine Poisonings 115

SECTION 3 COMMON PATIENT PRESENTATIONS

28 Fever, Hyperthermia, and Rash....127
29 Generalized Fatigue....131
30 Weight Loss....135
31 Chest Pain....137
32 Palpitations....141
33 Dyspnea....142
34 Cyanosis....145
35 Cough and Hemoptysis....146
36 Edema....150
37 Abdominal Pain....154
38 Nausea, Vomiting, and Indigestion....158
39 Dysphagia....162
40 Diarrhea, Malabsorption, and Constipation....167
41 Gastrointestinal Bleeding....174
42 Jaundice and Evaluation of Liver Function....178
43 Ascites....187
44 Lymphadenopathy and Splenomegaly....189
45 Anemia and Polycythemia....194
46 Azotemia and Urinary Abnormalities....197
47 Pain and Swelling of Joints....203
48 Back and Neck Pain....207
49 Headache....215
50 Syncope....222
51 Dizziness and Vertigo....226
52 Acute Visual Loss and Double Vision....229
53 Weakness and Paralysis....233
54 Tremor and Movement Disorders....236
55 Aphasia....239
56 Sleep Disorders....241
57 Dysuria and Bladder Pain....245

SECTION 4 OTOLARYNGOLOGY

58 Sore Throat, Earache, and Upper Respiratory Symptoms....247

SECTION 5 DERMATOLOGY

59 General Examination of the Skin 255
60 Common Skin Conditions 258

SECTION 6 HEMATOLOGY AND ONCOLOGY

61 Examination of Blood Smears and Bone Marrow 265
62 Red Blood Cell Disorders 267
63 Leukocytosis and Leukopenia 274
64 Bleeding and Thrombotic Disorders 277
65 Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes 283
66 Lymphoid Malignancies 293
67 Skin Cancer 305
68 Head and Neck Cancer 308
69 Lung Cancer 310
70 Breast Cancer 316
71 Tumors of the Gastrointestinal Tract 321
72 Genitourinary Tract Cancer 333
73 Gynecologic Cancer 338
74 Prostate Hyperplasia and Carcinoma 342
75 Cancer of Unknown Primary Site 345
76 Paraneoplastic Endocrine Syndromes 348
77 Neurologic Paraneoplastic Syndromes 352

SECTION 7 INFECTIOUS DISEASES

78 Infections Acquired in Health Care Facilities 357
79 Infections in the Immunocompromised Host 362
80 Infective Endocarditis 372
81 Intraabdominal Infections 382
82 Infectious Diarrheas 386
83 Sexually Transmitted and Reproductive Tract Infections 399
84 Infections of the Skin, Soft Tissues, Joints, and Bones 415
85 Pneumococcal Infections 422
86 Staphylococcal Infections 425

87 Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species 434
88 Meningococcal and Listerial Infections 443
89 Infections Caused by *Haemophilus*, *Bordetella*, *Moraxella*, and HACEK Group Organisms 448
90 Diseases Caused by Gram-Negative Enteric Bacteria and *Pseudomonas* 453
91 Infections Caused by Miscellaneous Gram-Negative Bacilli 462
92 Anaerobic Infections 469
93 Nocardiosis, Actinomycosis, and Whipple's Disease 477
94 Tuberculosis and Other Mycobacterial Infections 482
95 Lyme Disease and Other Nonsyphilitic Spirochetal Infections 494
96 Rickettsial Diseases 500
97 *Mycoplasma pneumoniae*, *Legionella* Species, and *Chlamydia pneumoniae* 510
98 *Chlamydia trachomatis* and *C. psittaci* 514
99 Herpesvirus Infections 516
100 Cytomegalovirus and Epstein-Barr Virus Infections 525
101 Influenza and Other Viral Respiratory Diseases 530
102 Rubeola, Rubella, Mumps, and Parvovirus Infections 538
103 Enteroviral Infections 543
104 Insect- and Animal-Borne Viral Infections 546
105 HIV Infection and AIDS 554
106 Fungal Infections 568
107 *Pneumocystis* Infections 583
108 Protozoal Infections 586
109 Helminthic Infections and Ectoparasite Infestations 599

SECTION 8 CARDIOLOGY

110 Physical Examination of the Heart 613
111 Electrocardiography 618
112 Noninvasive Examination of the Heart 622
113 Congenital Heart Disease in the Adult 627

114 Valvular Heart Disease 632
115 Cardiomyopathies and Myocarditis 639
116 Pericardial Disease 644
117 Hypertension 649
118 Metabolic Syndrome 656
119 ST-Segment Elevation Myocardial Infarction 658
120 Unstable Angina and Non-ST-Elevation Myocardial Infarction 668
121 Chronic Stable Angina 672
122 Bradyarrhythmias 677
123 Tachyarrhythmias 679
124 Heart Failure and Cor Pulmonale 687
125 Diseases of the Aorta 693
126 Peripheral Vascular Disease 696
127 Pulmonary Hypertension 699

SECTION 9 PULMONOLOGY

128 Respiratory Function and Pulmonary Diagnostic Procedures 705
129 Asthma 711
130 Environmental Lung Diseases 715
131 Chronic Obstructive Pulmonary Disease 718
132 Pneumonia, Bronchiectasis, and Lung Abscess 722
133 Pulmonary Thromboembolism and Deep-Vein Thrombosis 730
134 Interstitial Lung Disease 734
135 Diseases of the Pleura and Mediastinum 740
136 Disorders of Ventilation 744
137 Sleep Apnea 745

SECTION 10 NEPHROLOGY

138 Acute Renal Failure 747
139 Chronic Kidney Disease and Uremia 752
140 Dialysis 754
141 Renal Transplantation 756

142 Glomerular Diseases 759
143 Renal Tubular Disease....769
144 Urinary Tract Infections and Interstitial Cystitis....775
145 Nephrolithiasis 779
146 Urinary Tract Obstruction....782

SECTION 11 GASTROENTEROLOGY

147 Peptic Ulcer and Related Disorders 785
148 Inflammatory Bowel Diseases 790
149 Colonic and Anorectal Diseases 794
150 Cholelithiasis, Cholecystitis, and Cholangitis 799
151 Pancreatitis 804
152 Acute Hepatitis 809
153 Chronic Hepatitis....816
154 Cirrhosis and Alcoholic Liver Disease....826
155 Portal Hypertension....831

SECTION 12 ALLERGY, CLINICAL IMMUNOLOGY, AND RHEUMATOLOGY

156 Diseases of Immediate-Type Hypersensitivity 835
157 Primary Immune Deficiency Diseases 840
158 Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Connective Tissue Diseases....843
159 Vasculitis 850
160 Ankylosing Spondylitis 854
161 Psoriatic Arthritis....857
162 Reactive Arthritis....859
163 Osteoarthritis....861
164 Gout, Pseudogout, and Related Diseases 863
165 Other Musculoskeletal Disorders....867
166 Sarcoidosis 870
167 Amyloidosis 873

SECTION 13 ENDOCRINOLOGY AND METABOLISM

168 Disorders of the Anterior Pituitary and Hypothalamus....877
169 Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone 883

170 Thyroid Gland Disorders....886
171 Adrenal Gland Disorders....895
172 Obesity....901
173 Diabetes Mellitus....904
174 Disorders of the Male Reproductive System....912
175 Disorders of the Female Reproductive System....917
176 Hypercalcemia and Hypocalcemia....924
177 Osteoporosis and Osteomalacia....931
178 Hypercholesterolemia and Hypertriglyceridemia....936
179 Hemochromatosis, Porphyrias, and Wilson's Disease....942

SECTION 14 NEUROLOGY

180 The Neurologic Examination....947
181 Seizures and Epilepsy....956
182 Dementia....968
183 Parkinson's Disease....976
184 Ataxic Disorders....981
185 ALS and Other Motor Neuron Diseases....984
186 Autonomic Nervous System Disorders....988
187 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders....995
188 Spinal Cord Diseases....1002
189 Tumors of the Nervous System....1008
190 Multiple Sclerosis....1012
191 Acute Meningitis and Encephalitis....1020
192 Chronic and Recurrent Meningitis....1031
193 Peripheral Neuropathies, Including Guillain-Barré Syndrome....1040
194 Myasthenia Gravis....1050
195 Muscle Diseases....1053

SECTION 15 PSYCHIATRY AND SUBSTANCE ABUSE

196 Psychiatric Disorders....1063
197 Psychiatric Medications....1071
198 Eating Disorders....1079

199 Alcohol Use Disorder 1080
200 Narcotic Abuse 1084

SECTION 16 DISEASE PREVENTION AND HEALTH MAINTENANCE

201 Routine Disease Screening 1087
202 Cardiovascular Disease Prevention 1092
203 Prevention and Early Detection of Cancer 1094
204 Smoking Cessation 1102
205 Women's Health 1104

SECTION 17 ADVERSE DRUG REACTIONS

206 Adverse Drug Reactions 1107

Index 1109

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

CONTRIBUTORS

ASSOCIATE EDITORS

S. ANDREW JOSEPHSON, MD
Professor; Senior Executive Vice Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California

CAROL A. LANGFORD, MD, MHS
Harold C. Schott Endowed Chair; Director, Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, Ohio

LEONARD S. LILLY, MD
Professor of Medicine, Harvard Medical School; Chief, Brigham and Women's/Faulkner Cardiology, Brigham and Women's Hospital, Boston, Massachusetts

DAVID B. MOUNT, MD
Associate Physician, Brigham and Women's Hospital; Assistant Professor of Medicine, Harvard Medical School; Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

EDWIN K. SILVERMAN, MD, PhD
Professor of Medicine; Chief, Channing Division of Network Medicine, Harvard Medical School, Boston, Massachusetts

NEERAJ K. SURANA, MD, PhD
Instructor in Pediatrics, Harvard Medical School; Assistant in Medicine, Boston Children's Hospital, Boston, Massachusetts

Numbers indicate the chapters written or co-written by the contributor.

ANTHONY S. FAUCI, MD
26, 42, 43, 47, 59, 60, 105, 150-167

GREGORY K. FOLKERS, MPH
105, 153, 159

STEPHEN L. HAUSER, MD
3, 5, 16-22, 48-56, 77, 180-200, 204

J. LARRY JAMESON, MD, PhD
2, 6, 7, 23, 24, 29, 30, 118, 168-179, 198, 201, 205

S. ANDREW JOSEPHSON, MD
5, 16-22, 48-56, 77, 180-197, 199, 200, 204

DENNIS L. KASPER, MD
12, 27, 28, 57, 58, 78-104, 106-109, 132, 144

SHYAMASUNDARAN KOTTILIL, MD
153

CAROL A. LANGFORD, MD
26, 42, 43, 47, 59, 60, 105, 150-167

LEONARD S. LILLY, MD
10, 11, 13, 31, 32, 34, 110-117, 119-127

DAN L. LONGO, MD
8, 9, 25, 37-41, 44, 45, 61-76, 147-149, 203

JOSEPH LOSCALZO, MD, PhD
4, 10, 11, 13-15, 31-36, 46, 110-117, 119-143, 145, 146, 202

DAVID B. MOUNT, MD
36, 46, 138-143, 145, 146

EDWIN K. SILVERMAN, MD, PhD
4, 14, 15, 33, 35, 128-137

NEERAJ K. SURANA, MD, PhD
12, 27, 28, 57, 58, 78-104, 106-109, 132, 144

PREFACE

Harrison's Principles of Internal Medicine (HPIM), the premier medical textbook for students and clinicians, provides a detailed body of information important to an understanding of the biological and clinical aspects of quality patient care. *Harrison's Manual of Medicine* aims to fulfill a different need: As a concise, fact-rich resource for bedside care, the *Manual* presents clinical information drawn from the 19th edition of *HPIM*, covering the key features of the diagnosis, clinical manifestations, and treatment of the major diseases that are likely to be encountered on a medical service.

First published in 1988, the *Manual* has become ever more useful with the rapid expansion of medical knowledge and the increasing time constraints associated with heavy patient-care responsibilities in modern health care settings. The *Manual*'s popularity and value reflect its abbreviated format, which has proven extremely useful for initial diagnosis and management in time-restricted clinical settings. In particular, the book's full-color format allows readers to locate and use information quickly. In addition, numerous tables and graphics facilitate decisions at the point of care.

The *Manual* has been written for easy and seamless reference to the full text of the 19th edition of *HPIM*, and the Editors recommend that the full textbook be consulted as soon as time allows. Although not a substitute for in-depth analysis of clinical problems, the *Manual* serves as a ready source of informative summaries that will be useful "on the spot" and that will prepare the reader for more in-depth analysis through more extensive reading at a later time. Like previous editions, this latest edition of the *Manual* is intended to keep up with the continual evolution of internal medicine practices. To this end, every chapter from the prior edition has been closely reviewed and updated, with substantial revisions and new chapters provided where appropriate. The 19th edition of the *Manual* is available in print and in portable format for the smartphone and tablet.

ACKNOWLEDGMENTS

The Editors and McGraw-Hill wish to thank their editorial staff, whose assistance and patience made this edition come out in a timely manner:

From the Editors' offices: Patricia Duffey; Gregory K. Folkers; Andrew Josephson, MD; H. Clifford Lane, MD; Carol A. Langford, MD; Julie B. McCoy; Anita Ortiz; Elizabeth Robbins, MD; Marie E. Scurti; and Stephanie Tribuna.

From McGraw-Hill: James F. Shanahan, Kim J. Davis, and Catherine H. Saggese.

The Editors also wish to acknowledge contributors to past editions of this *Manual*, whose work formed the basis for many of the chapters herein: Tamar F. Barlam, MD; Gerhard P. Baumann, MD; Eugene Braunwald, MD; Punit Chadha, MD; Joseph B. Martin, MD, PhD; Michael Sneller, MD; Kenneth Tyler, MD; Sophia Vinogradov, MD; and Jean Wilson, MD.

1 Electrolytes/Acid-Base Balance

SODIUM

Disturbances of sodium concentration [Na^+] result in most cases from abnormalities of H_2O homeostasis, which change the relative ratio of Na^+ to H_2O. Disorders of Na^+ balance per se are, in contrast, associated with changes in extracellular fluid volume, either hypo- or hypervolemia. Maintenance of "arterial circulatory integrity" is achieved in large part by changes in urinary sodium excretion and vascular tone, whereas H_2O balance is achieved by changes in both H_2O intake and urinary H_2O excretion (Table 1-1). Confusion can result from the coexistence of defects in both H_2O and Na^+ balance. For example, a hypovolemic pt may have an appropriately low urinary Na^+ due to increased renal tubular reabsorption of filtered NaCl; a concomitant increase in circulating arginine vasopressin (AVP)—part of the defense of effective circulating volume (Table 1-1)—will cause the renal retention of ingested H_2O and the development of hyponatremia.

HYPONATREMIA

This is defined as a serum [Na^+] <135 mmol/L and is among the most common electrolyte abnormalities encountered in hospitalized pts. Symptoms include nausea, vomiting, confusion, lethargy, and disorientation; if severe (<120 mmol/L) and/or abrupt, seizures, central herniation, coma, or death may result (see Acute Symptomatic Hyponatremia, below). Hyponatremia is almost always the result of an increase

TABLE 1-1 OSMOREGULATION VERSUS VOLUME REGULATION

	Osmoregulation	Volume Regulation
What is sensed	Plasma osmolality	Arterial filling
Sensors	Hypothalamic osmoreceptors	Carotid sinus
		Afferent arteriole
		Atria
Effectors	AVP	Sympathetic nervous system
	Thirst	Renin-angiotensin-aldosterone system
		ANP/BNP
		AVP
What is affected	Urine osmolality	Urinary sodium excretion
	H_2O intake	Vascular tone

Note: See text for details.
Abbreviations: ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide.
Source: Adapted from Rose BD, Black RM (eds): *Manual of Clinical Problems in Nephrology*. Boston, Little Brown, 1988; with permission.

in circulating AVP and/or increased renal sensitivity to AVP; a notable exception is in the setting of low solute intake ("beer potomania"), wherein a markedly reduced urinary solute excretion is inadequate to support the excretion of sufficient free H_2O. The serum [Na^+] by itself does not yield diagnostic information regarding total-body Na^+ content; hyponatremia is primarily a disorder of H_2O homeostasis. Pts with hyponatremia are thus categorized diagnostically into three groups, depending on their clinical volume status: hypovolemic, euvolemic, and hypervolemic hyponatremia (Fig. 1-1). All three forms of hyponatremia share an exaggerated, "nonosmotic" increase in circulating AVP, in the setting of reduced serum osmolality. Notably, hyponatremia is often multifactorial; clinically important nonosmotic stimuli that can cause a release of AVP and increase the risk of hyponatremia include drugs, pain, nausea, and strenuous exercise.

Laboratory investigation of a pt with hyponatremia should include a measurement of serum osmolality to exclude "pseudohyponatremia" due to hyperlipidemia or hyperproteinemia. Serum glucose also should be measured; serum Na^+ falls by 1.4 m*M* for every 100-mg/dL increase in glucose, due to glucose-induced H_2O efflux from cells. Hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism; increased blood urea nitrogen (BUN) and creatinine may suggest a renal cause. Urine electrolytes and osmolality are also critical tests in the initial evaluation of hyponatremia. In particular, a urine Na^+ <20 meq/L is consistent with hypovolemic hyponatremia in the clinical absence of a "hypervolemic," Na^+-avid syndrome such as congestive heart failure (CHF) (Fig. 1-1). Urine osmolality <100 mosmol/kg is suggestive of polydipsia or, in rare cases, of decreased solute intake; urine osmolality >400 mosmol/kg suggests that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a component of polydipsia). Finally, in the right clinical setting, thyroid, adrenal, and pituitary function should also be tested.

Hypovolemic Hyponatremia

Hypovolemia from both renal and extrarenal causes is associated with hyponatremia. Renal causes of hypovolemia include primary adrenal insufficiency and hypoaldosteronism, salt-losing nephropathies (e.g., reflux nephropathy, nonoliguric acute tubular necrosis), diuretics, and osmotic diuresis. Random "spot" urine Na^+ is typically >20 meq/L in these cases but may be <20 meq/L in diuretic-associated hyponatremia if tested long after administration of the drug. Nonrenal causes of hypovolemic hyponatremia include GI loss (e.g., vomiting, diarrhea, tube drainage) and integumentary loss (sweating, burns); urine Na^+ is typically <20 meq/L in these cases.

Hypovolemia causes profound neurohumoral activation, inducing systems that preserve arterial circulatory integrity, such as the renin-angiotensin-aldosterone (RAA) axis, the sympathetic nervous system, and AVP (Table 1-1). The increase in circulating AVP serves to increase the retention of ingested free H_2O, leading to hyponatremia. The optimal treatment of hypovolemic hyponatremia is volume administration, generally as isotonic crystalloid, i.e., 0.9% NaCl ("normal saline"). If the history suggests that hyponatremia has been "chronic," i.e., present for 48 h, care should be taken to avoid overcorrection (see below), which can easily occur as AVP levels plummet in response to volume-resuscitation; if necessary, the administration of desmopressin (DDAVP) and free water can reinduce or arrest the correction of hyponatremia (see below).

Hypervolemic Hyponatremia

The edematous disorders (CHF, hepatic cirrhosis, and nephrotic syndrome) are often associated with mild to moderate degrees of hyponatremia ([Na^+] = 125–135 mmol/L); occasionally, pts with severe CHF or cirrhosis may present with serum [Na^+] <120 mmol/L. The pathophysiology is similar to that in hypovolemic hyponatremia, except that arterial filling and circulatory integrity are decreased due to the specific

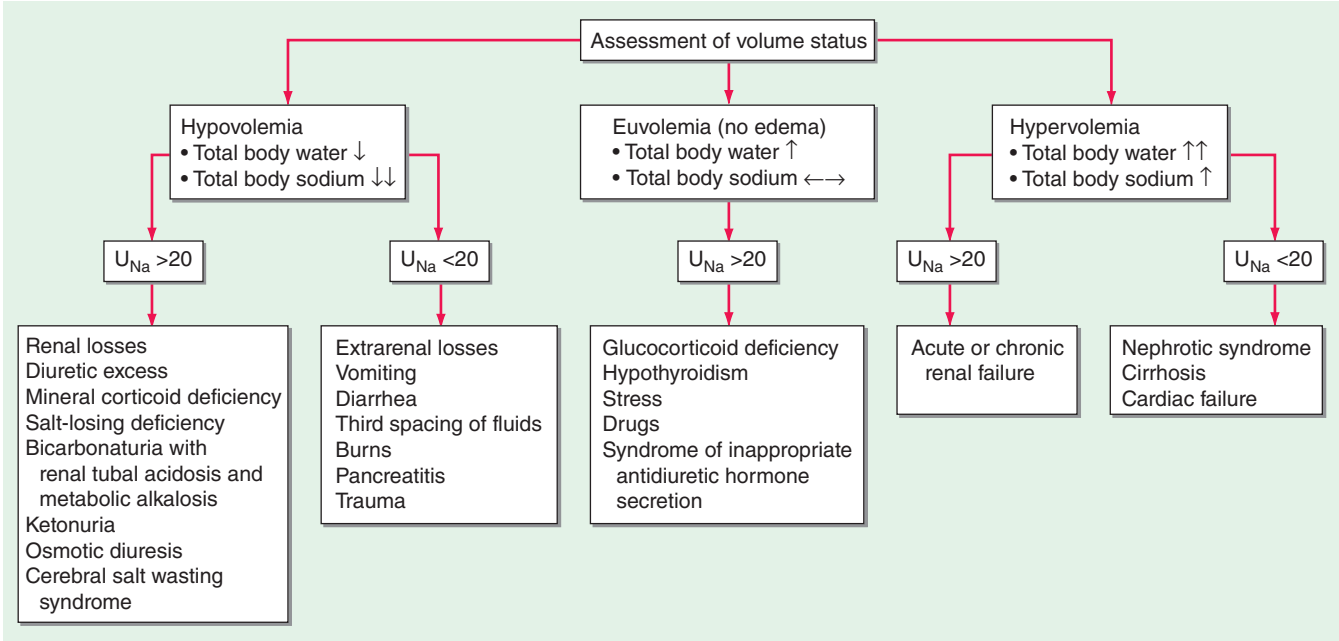


FIGURE 1-1 The diagnostic approach to hyponatremia. See text for details. *(From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)*

etiologic factors, i.e., cardiac dysfunction, peripheral vasodilation in cirrhosis, and hypoalbuminemia in nephrotic syndrome. The degree of hyponatremia is an indirect index of the associated neurohumoral activation (Table 1-1) and an important prognostic indicator in hypervolemic hyponatremia.

Management consists of treatment of the underlying disorder (e.g., afterload reduction in heart failure, large-volume paracentesis in cirrhosis, immunomodulatory therapy in some forms of nephrotic syndrome), Na^+ restriction, diuretic therapy, and, in some pts, H_2O restriction. Vasopressin antagonists (e.g., tolvaptan and conivaptan) are also effective in normalizing hyponatremia associated with both cirrhosis and CHF.

Euvolemic Hyponatremia

The syndrome of inappropriate ADH secretion (SIADH) characterizes most cases of euvolemic hyponatremia. Other causes of euvolemic hyponatremia include hypothyroidism and secondary adrenal insufficiency due to pituitary disease; notably, repletion of glucocorticoid levels in the latter may cause a rapid drop in circulating AVP levels and overcorrection of serum $[Na^+]$ (see below).

Common causes of SIADH include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis); SIADH also occurs with malignancies (e.g., small cell carcinoma of the lung) and drugs (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, nicotine, vincristine, chlorpropamide, carbamazepine, narcotic analgesics, antipsychotic drugs, cyclophosphamide, ifosfamide). Optimal treatment of euvolemic hyponatremia includes treatment of the underlying disorder. H_2O restriction to <1 L/d is a cornerstone of therapy, but may be ineffective or poorly tolerated. However, vasopressin antagonists are predictably effective in normalizing serum $[Na^+]$ in SIADH. Alternatives include the administration of loop diuretics to inhibit the countercurrent mechanism and reduce urinary concentration, combined with oral salt tablets to abrogate diuretic-induced salt loss and attendant hypovolemia.

Acute Symptomatic Hyponatremia

Acute symptomatic hyponatremia is a medical emergency; a sudden drop in serum $[Na^+]$ can overwhelm the capacity of the brain to regulate cell volume, leading to cerebral edema, seizures, and death. Women, particularly premenopausal women, are particularly prone to such sequelae; neurologic consequences are comparatively rare in male pts. Many of these pts develop hyponatremia from iatrogenic causes, including hypotonic fluids in the postoperative period, prescription of a thiazide diuretic, colonoscopy preparation, or intraoperative use of glycine irrigants. Polydipsia with an associated cause of increased AVP may also cause acute hyponatremia, as can increased H_2O intake in the setting of strenuous exercise, e.g., a marathon. The recreational drug Ecstasy (methylenedioxymethamphetamine [MDMA]) can cause acute hyponatremia, rapidly inducing both AVP release and increased thirst.

Severe symptoms may occur at relatively modest levels of serum $[Na^+]$, e.g., in the mid-120s. Nausea and vomiting are common premonitory symptoms of more severe sequelae. An important concomitant is respiratory failure, which may be hypercapnic due to CNS depression or normocapnic due to neurogenic, noncardiogenic pulmonary edema; the attendant hypoxemia amplifies the impact of hyponatremic encephalopathy.

TREATMENT HYPONATREMIA

Three considerations are critical in the therapy of hyponatremia. First, the presence, absence, and/or severity of symptoms determine the urgency of therapy (see above for acute symptomatic hyponatremia). Second, pts with hyponatremia that has been present for >48 h ("chronic hyponatremia") are at risk for osmotic demyelination syndrome, typically central pontine myelinolysis, if serum Na^+ is

corrected by >10–12 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions, such as hypertonic saline or vasopressin antagonists, can be highly unpredictable, such that frequent monitoring of serum Na^+ (initially every 2–4 h) is imperative.

Treatment of acute symptomatic hyponatremia should include hypertonic saline to acutely increase serum Na^+ by 1–2 m*M*/h to a total increase of 4–6 m*M*; this increase is typically sufficient to alleviate acute symptoms, after which corrective guidelines for "chronic" hyponatremia are appropriate (see below). A number of equations and algorithms have been developed to estimate the required rate of hypertonic solution; one popular approach is to calculate a "Na^+ deficit," where the Na^+ deficit = 0.6 × body weight × (target $[Na^+]$ – starting $[Na^+]$). Regardless of the method used to determine the rate of administered hypertonic saline, the increase in serum $[Na^+]$ can be highly unpredictable, due to rapid changes in the underlying physiology; serum $[Na^+]$ should be monitored every 2–4 h during and after treatment with hypertonic saline. The administration of supplemental O_2 and ventilatory support can also be critical in acute hyponatremia, if pts develop acute pulmonary edema or hypercapnic respiratory failure. IV loop diuretics will help treat associated acute pulmonary edema and will also increase free H_2O excretion by interfering with the renal countercurrent multiplier system. It is noteworthy that vasopressin antagonists do not have a role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<10–12 m*M* in the first 24 h and <18 m*M* in the first 48 h), so as to avoid osmotic demyelination syndrome. Vasopressin antagonists are highly effective in SIADH and in hypervolemic hyponatremia due to heart failure or cirrhosis. Abnormalities in liver function tests have been reported during the use of tolvaptan; hence, therapy with this agent should be restricted to 1–2 months with close monitoring of liver function. Should pts overcorrect serum $[Na^+]$ in response to vasopressin antagonists, hypertonic saline, or isotonic saline (in chronic hypovolemic hyponatremia), hyponatremia can be safely reinduced or stabilized by the administration of the vasopressin *agonist* DDAVP and the administration of free H_2O, typically IV D_5W; again, close monitoring of the response of serum $[Na^+]$ is essential to adjust therapy. Alternatively, the treatment of pts with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum $[Na^+]$ in a more controlled fashion, thus reducing upfront the risk of overcorrection.

HYPERNATREMIA

This is rarely associated with hypervolemia, where the association is typically iatrogenic, e.g., administration of hypertonic sodium bicarbonate. More commonly, hypernatremia is the result of a combined H_2O and volume deficit, with losses of H_2O in excess of Na^+. Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of hypernatremia due to decreased free H_2O intake. Common causes of renal H_2O loss are osmotic diuresis secondary to hyperglycemia, postobstructive diuresis, or drugs (radiocontrast, mannitol, etc.); H_2O diuresis occurs in central or nephrogenic diabetes insipidus (DI) (Chap. 168). In pts with hypernatremia due to renal loss of H_2O, it is critical to quantify *ongoing* daily losses in addition to calculation of the baseline H_2O deficit (Table 1-2).

TREATMENT HYPERNATREMIA

The approach to correction of hypernatremia is outlined in Table 1-2. As with hyponatremia, it is advisable to correct the H_2O deficit slowly to avoid neurologic compromise, decreasing the serum $[Na^+]$ over 48–72 h. Depending on the blood pressure or clinical volume status, it may be appropriate to initially treat

TABLE 1-2 CORRECTION OF HYPERNATREMIA

H_2O Deficit

1. Estimate TBW: 50–60% body weight (kg) depending on body composition
2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$
3. Administer deficit over 48–72 h

Ongoing H_2O Losses

4. Calculate free-water clearance, C_eH_2O:

$$C_eH_2O = V\left(1 - \frac{U_{Na} + U_K}{S_{Na}}\right)$$

where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and SNa is serum $[Na^+]$.

Insensible Losses

5. ~10 mL/kg per day: less if ventilated, more if febrile

Total

6. Add components to determine H_2O deficit and ongoing H_2O loss; correct the H_2O deficit over 48–72 h and replace daily H_2O loss.

Abbreviation: TBW, total-body water.

with hypotonic saline solutions (1/4 or 1/2 normal saline); blood glucose should be monitored in pts treated with large volumes of D_5W, should hyperglycemia ensue. Calculation of urinary electrolyte-free H_2O clearance is helpful to estimate daily, ongoing loss of free H_2O in pts with nephrogenic or central DI (Table 1-2). Other forms of therapy may be helpful in selected cases of hypernatremia. Pts with central DI may respond to the administration of intranasal DDAVP. Stable pts with nephrogenic DI may reduce their polyuria with hydrochlorothiazide (12.5–50 mg/d). This diuretic is thought to increase proximal H_2O reabsorption and decrease distal solute delivery, thus reducing polyuria. Pts with lithium-associated nephrogenic DI may respond to amiloride (2.5–10 mg/d), which decreases the entry of lithium into principal cells in the distal nephron by inhibiting the amiloride-sensitive epithelial sodium channel (ENaC). Notably, however, most pts with lithium-induced nephrogenic DI can adequately accommodate by increasing their H_2O intake. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors have also been used to treat polyuria associated with nephrogenic DI, reducing the negative effect of local prostaglandins on urinary concentration; however, the nephrotoxic potential of NSAIDs typically makes them a less attractive therapeutic option.

POTASSIUM

Because potassium (K^+) is the major intracellular cation, discussion of disorders of K^+ balance must take into consideration changes in the exchange of intra- and extracellular K^+ stores. (Extracellular K^+ constitutes <2% of total-body K^+ content.) Insulin, β_2-adrenergic agonists, and alkalosis tend to promote K^+ uptake by cells; acidosis, insulinopenia, or acute hyperosmolality (e.g., after treatment with mannitol or $D_{50}W$) promotes the efflux or reduced uptake of K^+. A corollary is that tissue necrosis and the attendant release of K^+ can cause severe hyperkalemia, particularly in the setting of acute kidney injury. Hyperkalemia due to rhabdomyolysis is thus particularly common, due to the enormous store of K^+ in muscle; hyperkalemia may also be prominent in tumor lysis syndrome.

The kidney plays a dominant role in K^+ excretion. Although K^+ is transported along the entire nephron, it is the principal cells of the connecting segment and cortical collecting duct that play a dominant role in K^+ excretion. Apical Na^+ entry into principal cells via the amiloride-sensitive epithelial Na^+ channel (ENaC) generates a lumen-negative potential difference, which drives passive K^+ exit through apical K^+ channels. *This relationship is key to the bedside understanding of potassium disorders.* For example, decreased distal delivery of Na^+ tends to blunt the ability to excrete K^+, leading to hyperkalemia. Abnormalities in the renin-angiotensin-aldosterone system (RAAS) can cause both hypo- and hyperkalemia; aldosterone has a major influence on potassium excretion, increasing the activity of ENaC channels and the basolateral Na+/K+-ATPase, thus amplifying the driving force for K^+ secretion across the luminal membrane of principal cells.

HYPOKALEMIA

Major causes of hypokalemia are outlined in Table 1-3. Atrial and ventricular arrhythmias are the most serious health consequences of hypokalemia. Pts with concurrent Mg deficit and/or digoxin therapy are at a particularly increased risk of arrhythmias. Hypokalemia can directly prolong the QT interval and is a significant cofactor in arrhythmias due to other causes of a prolonged QT interval. Other clinical manifestations include muscle weakness, which may be profound at serum [K^+]

TABLE 1-3 CAUSES OF HYPOKALEMIA

- I. Decreased intake
  - A. Starvation
  - B. Clay ingestion
- II. Redistribution into cells
  - A. Acid-base
    1. Metabolic alkalosis
  - B. Hormonal
    1. Insulin
    2. Increased β_2-adrenergic sympathetic activity: post–myocardial infarction, head injury, theophylline
    3. β_2-Adrenergic agonists: bronchodilators, tocolytics
    4. α-Adrenergic antagonists
    5. Thyrotoxic periodic paralysis
    6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine
  - C. Anabolic state
    1. Vitamin B_{12} or folic acid administration (red blood cell production)
    2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
    3. Total parenteral nutrition
  - D. Other
    1. Pseudohypokalemia
    2. Hypothermia
    3. Familial hypokalemic periodic paralysis
    4. Barium toxicity: systemic inhibition of "leak" K^+ channels

(*Continued*)

TABLE 1-3 CAUSES OF HYPOKALEMIA (*CONTINUED*)

III. Increased loss
- A. Nonrenal
  1. Gastrointestinal loss (diarrhea)
  2. Integumentary loss (sweat)
- B. Renal
  1. Increased distal flow and distal Na^+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
  2. Increased secretion of potassium
     a. Mineralocorticoid excess: primary hyperaldosteronism (APAs), PAH or UAH, IHA due to bilateral adrenal hyperplasia and adrenal carcinoma, familial hyperaldosteronism (FH-I, FH-II, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
     b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome (genetic activation of ENaC)
     c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
  3. Magnesium deficiency, amphotericin B, Liddle's syndrome

Abbreviations: APA, aldosterone-producing adenoma; ENaC, epithelial Na^+ channels; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia; UAH, unilateral adrenal hyperplasia.

<2.5 mmol/L, and, if hypokalemia is sustained, hypertension, ileus, polyuria, renal cysts, and even renal failure.

The cause of hypokalemia is usually obvious from history, physical examination, and/or basic laboratory tests. However, persistent hypokalemia may require a more thorough, systematic evaluation (Fig. 1-2). Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, and Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. Serum and urine osmolality are required for calculation of the transtubular K^+ gradient (TTKG), which should be <3 in the presence of hypokalemia (see also Hyperkalemia). Alternatively, a urinary K^+-to-creatinine ratio of >13-mmol/g creatinine (>1.5-mmol/mmol creatinine) is compatible with excessive K^+ excretion. Further tests such as urinary Mg^{2+} and Ca^{2+} and/or plasma renin and aldosterone levels may be necessary in specific cases.

TREATMENT HYPOKALEMIA

The goals of therapy in hypokalemia are to prevent life-threatening and/or serious chronic consequences, to replace the associated K^+ deficit, and to correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (cardiac disease, digoxin therapy, etc.), and the rate of decline in serum K^+. Pts with a

prolonged QT interval and/or other risk factors for arrhythmia should be monitored by continuous cardiac telemetry during repletion. Urgent but cautious K^+ replacement should be considered in pts with severe redistributive hypokalemia (plasma K^+ concentration <2.5 m*M*) and/or when serious complications ensue; however, this approach has a risk of rebound hyperkalemia following acute resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in thyrotoxic periodic paralysis, theophylline overdose, and acute head injury, high-dose propranolol (3 mg/kg) should be considered; this nonspecific β-adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia. It should be noted that hypokalemia is refractory to correction in the presence of Mg^{++} deficiency, which also should be corrected when present; renal wasting of both cations may be particularly prominent after renal tubular injury, e.g., from cisplatin nephrotoxicity.

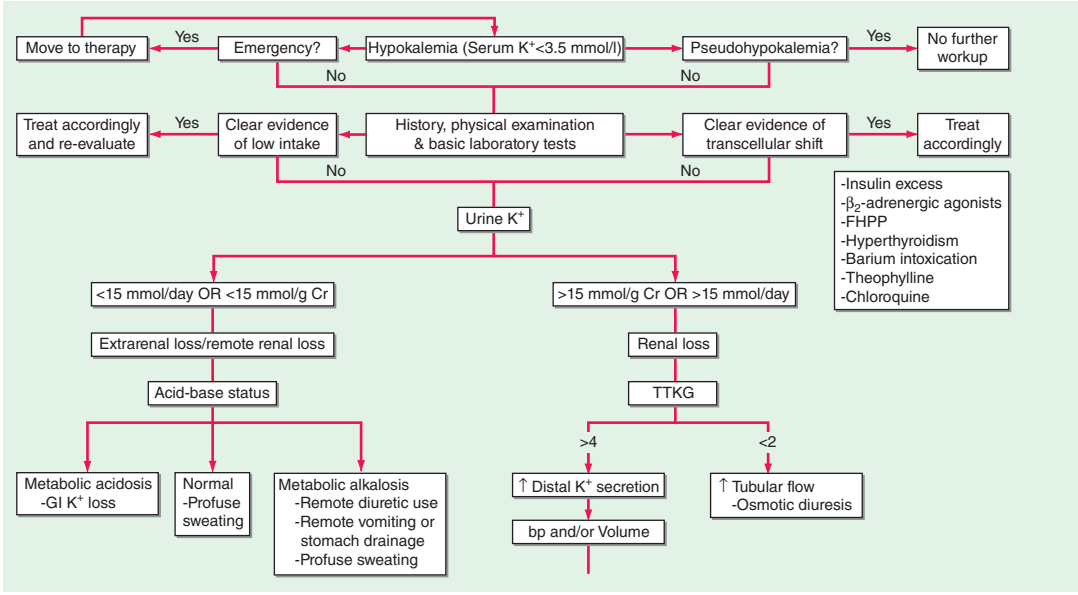
Oral replacement with K^+-Cl^- is the mainstay of therapy in hypokalemia. Potassium phosphate, oral or IV, may be appropriate in pts with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in pts with concomitant metabolic acidosis. The deficit of K^+ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should also be considered so as to gauge the risk of overcorrection. In the absence of abnormal K^+ redistribution, the total deficit correlates with serum K^+ such that serum K^+ drops by approximately 0.27 m*M* for every 100-mmol reduction in total-body stores. Notably, given the delay in redistributing potassium into intracellular compartments, this deficit must be replaced gradually over 24–48 h, with frequent monitoring of plasma K^+ concentration to avoid transient over-repletion and transient hyperkalemia if otherwise appropriate. If hypokalemia is severe (<2.5 mmol/L) and/or if oral supplementation is not feasible or tolerated, IV KCl can be administered through a central vein with cardiac monitoring in an intensive care setting, at rates that should not exceed 20 mmol/h. KCl should always be administered in saline solutions, rather than dextrose; the dextrose-induced increase in insulin can acutely exacerbate hypokalemia.

Strategies to minimize K^+ losses should also be considered. These measures may include minimizing the dose of non-K^+-sparing diuretics, restricting Na^+ intake, and using clinically appropriate combinations of non-K^+-sparing and K^+-sparing medications (e.g., loop diuretics with angiotensin-converting enzyme inhibitors).

HYPERKALEMIA

Causes are outlined in Table 1-4; in most cases, hyperkalemia is due to decreased renal K^+ excretion. However, increases in dietary K^+ intake can have a major effect in susceptible pts, e.g., diabetics with hyporeninemic hypoaldosteronism and chronic kidney disease (CKD). Drugs that impact on the RAA axis are also a major cause of hyperkalemia.

The first priority in the management of hyperkalemia is to assess the need for emergency treatment (ECG changes and/or K^+ ≥6.0 m*M*). This should be followed by a comprehensive workup to determine the cause (Fig. 1-3). History and physical examination should focus on medications (e.g., ACE inhibitors, NSAIDs, trimethoprim/sulfamethoxazole), diet and dietary supplements (e.g., salt substitute), risk factors for acute kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, and Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. A urine $[Na^+]$ <20 meq/L suggests that distal Na^+ delivery is a limiting factor in K^+ excretion;


Hypokalemia (Serum K+<3.5 mmol/l)
Emergency?
Yes
Move to therapy
Pseudohypokalemia?
Yes
No further workup
No
No
History, physical examination & basic laboratory tests
Clear evidence of low intake
Yes
Treat accordingly and re-evaluate
Clear evidence of transcellular shift
Yes
Treat accordingly
No
No
-Insulin excess
-β2-adrenergic agonists
-FHPP
-Hyperthyroidism
-Barium intoxication
-Theophylline
-Chloroquine
Urine K+
<15 mmol/day OR <15 mmol/g Cr
>15 mmol/g Cr OR >15 mmol/day
Extrarenal loss/remote renal loss
Renal loss
Acid-base status
TTKG
>4
<2
Metabolic acidosis
-GI K+ loss
Normal
-Profuse sweating
Metabolic alkalosis
-Remote diuretic use
-Remote vomiting or stomach drainage
-Profuse sweating
↑ Distal K+ secretion
↑ Tubular flow
-Osmotic diuresis
bp and/or Volume

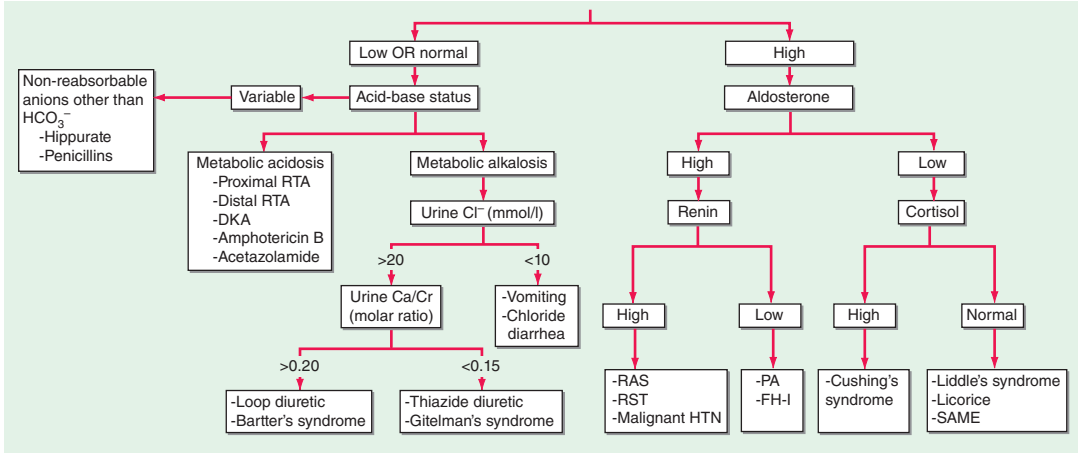


FIGURE 1-2 The diagnostic approach to hypokalemia. See text for details. bp, blood pressure; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. *(From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

TABLE 1-4 CAUSES OF HYPERKALEMIA

I. "Pseudo" hyperkalemia
   A. Cellular efflux: thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
   B. Hereditary defects in red cell membrane transport

II. Intra- to extracellular shift
   A. Acidosis
   B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
   C. β-Adrenergic antagonists (noncardioselective agents)
   D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
   E. Hyperkalemic periodic paralysis
   F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
   G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
   H. Rapid tumor lysis

III. Inadequate excretion
   A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination or at higher than recommended dosages
      1. ACE inhibitors
      2. Renin inhibitors: aliskiren (in combination with ACE inhibitors or ARBs)
      3. ARBs
      4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
      5. Blockade of ENaC: amiloride, triamterene, trimethoprim, pentamidine, nafamostat
   B. Decreased distal delivery
      1. Congestive heart failure
      2. Volume depletion
   C. Hyporeninemic hypoaldosteronism
      1. Tubulointerstitial diseases: SLE, sickle cell anemia, obstructive uropathy
      2. Diabetes, diabetic nephropathy
      3. Drugs: nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, β blockers, cyclosporine, tacrolimus
      4. Chronic kidney disease, advanced age
      5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
   D. Renal resistance to mineralocorticoid
      1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
      2. Hereditary: pseudohypoaldosteronism type I: defects in the mineralocorticoid receptor or ENaC

(*Continued*)

TABLE 1-4 CAUSES OF HYPERKALEMIA (*CONTINUED*)

E. Advanced renal insufficiency with low GFR
   1. Chronic kidney disease
   2. End-stage renal disease
   3. Acute oliguric kidney injury

F. Primary adrenal insufficiency
   1. Autoimmune: Addison's disease, polyglandular endocrinopathy
   2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
   3. Infiltrative: amyloidosis, malignancy, metastatic cancer
   4. Drug-associated: heparin, low-molecular-weight heparin
   5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
   6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

Abbreviations: ARB, angiotensin receptor blocker; COX-2, cyclooxygenase 2; ENaC, epithelial Na^+ channels.

volume repletion with 0.9% saline or treatment with furosemide may then be effective in reducing serum $[K^+]$ by increasing distal Na^+ delivery. Serum and urine osmolality are required for calculation of the TTKG. The expected values of the TTKG are largely based on historic data: <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia.

$$\text{TTKG} = \frac{[K^+]_{\text{urine}} \times \text{OSM}_{\text{serum}}}{[K^+]_{\text{serum}} \times \text{OSM}_{\text{urine}}}$$

TREATMENT HYPERKALEMIA

The most important consequence of hyperkalemia is altered cardiac conduction, with the risk of bradycardic cardiac arrest. **Figure 1-4** shows serial ECG patterns of hyperkalemia; ECG manifestations of hyperkalemia should be considered a true medical emergency and treated urgently. However, ECG changes of hyperkalemia are notoriously insensitive, particularly in pts with CKD; given these limitations, pts with significant hyperkalemia (K^+ ≥6–6.5 mmol/L) in the absence of ECG changes should also be aggressively managed.

Urgent management of hyperkalemia constitutes a 12-lead ECG, admission to the hospital, continuous cardiac monitoring, and immediate treatment. Treatment of hyperkalemia is divided into three categories: (1) antagonism of the cardiac effects of hyperkalemia, (2) rapid reduction in $[K^+]$ by redistribution into cells, and (3) removal of K^+ from the body. Treatment of hyperkalemia is summarized in **Table 1-5**.

ACID-BASE DISORDERS (FIG. 1-5)

Regulation of normal pH (7.35–7.45) depends on both the lungs and kidneys. By the Henderson-Hasselbalch equation, pH is a function of the ratio of HCO_3^- (regulated by the kidney) to PCO_2 (regulated by the lungs). The HCO_3/PCO_2 relationship is

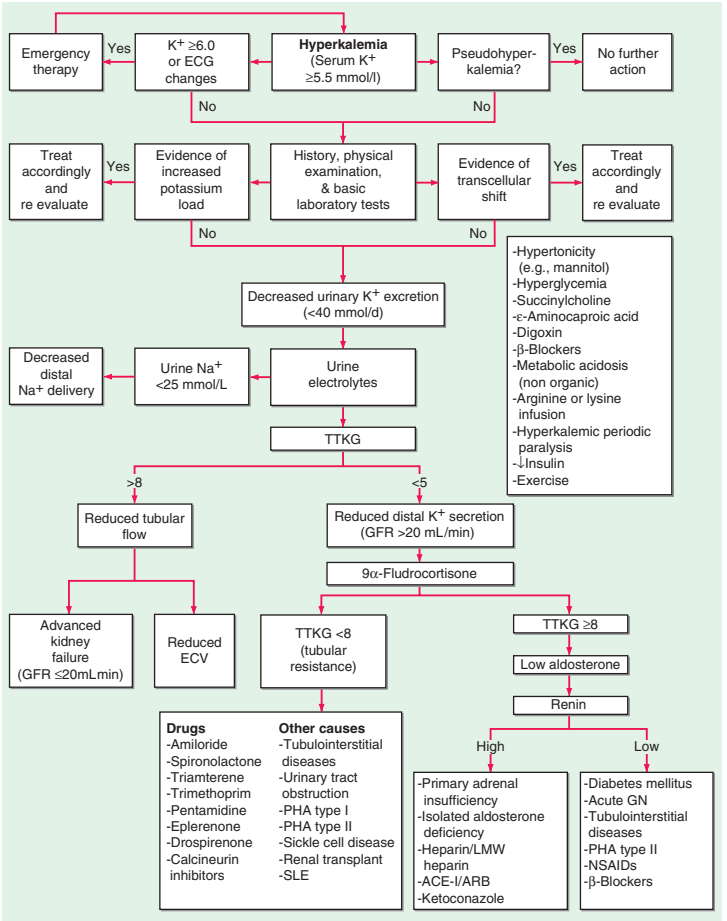


FIGURE 1-3 The diagnostic approach to hyperkalemia. See text for details. ACEI, angiotensin-converting enzyme inhibitor; acute GN, acute glomerulonephritis; ARB, angiotensin II receptor blocker; ECV, effective circulatory volume; LMW heparin, low-molecular-weight heparin; PHA, pseudohypoaldosteronism; TTKG, transtubular potassium gradient. *(From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

useful in classifying disorders of acid-base balance. Acidosis is due to gain of acid or loss of alkali; causes may be metabolic (fall in serum HCO_3^-) or respiratory (rise in PCO_2). Alkalosis is due to loss of acid or addition of base and is either metabolic (↑ serum $[HCO_3^-]$) or respiratory (↓ PCO_2).

To limit the change in pH, metabolic disorders evoke an immediate compensatory response in ventilation; full renal compensation for respiratory disorders is a slower process, such that "acute" compensations are of lesser magnitude than "chronic" compensations. Simple acid-base disorders consist of one primary disturbance and

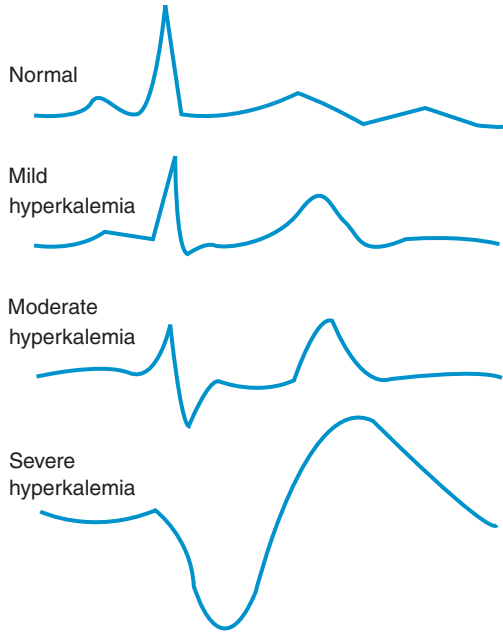


FIGURE 1-4 Diagrammatic ECGs at normal and high serum K. Peaked T waves (precordial leads) are followed by diminished R wave, wide QRS, prolonged P-R, loss of P wave, and ultimately a sine wave.

its compensatory response. In mixed disorders, a combination of primary disturbances is present.

The cause of simple acid-base disorders is usually obvious from history, physical examination, and/or basic laboratory tests. Initial laboratory evaluation depends on the dominant acid-base disorder, but for metabolic acidosis and alkalosis this should include electrolytes, BUN, creatinine, albumin, urinary pH, and urinary electrolytes. An arterial blood gas (ABG) is not always required for pts with a simple acid-base disorder, e.g., mild metabolic acidosis in the context of chronic renal failure. However, concomitant ABG and serum electrolytes are necessary to fully evaluate more complex acid-base disorders. The compensatory response should be estimated from the ABG; Winter's formula [$PaCO_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$] is particularly useful for assessing the respiratory response to metabolic acidosis. The anion gap should also be calculated; the anion gap = $[Na^+] - ([HCO_3^-] + [Cl^-])$ = unmeasured anions - unmeasured cations. The anion gap should be adjusted for changes in the concentration of albumin, a dominant unmeasured anion; the "adjusted anion gap" = anion gap + ~2.5 × (4 - albumin mg/dL). Other supportive tests will elucidate the specific form of anion-gap acidosis (see below).

METABOLIC ACIDOSIS

The low HCO_3^- in metabolic acidosis results from the addition of acids (organic or inorganic) or from a loss of HCO_3^-; causes of metabolic acidosis are classically categorized by presence or absence of an increase in the anion gap (Table 1-6). Increased anion-gap acidosis (>12 mmol/L) is due to addition of acid (other than HCl) and unmeasured anions to the body. Common causes include ketoacidosis

TABLE 1-5 TREATMENT OF HYPERKALEMIA

Mechanism	Therapy	Dose	Onset	Duration	Comments
Stabilize membrane potential	Calcium	10% Ca gluconate, 10 mL over 10 min	1–3 min	30–60 min	Repeat in 5 min if persistent electrocardiographic changes; avoid in digoxin toxicity.
Cellular K^+ uptake	Insulin	10 U R with 50 mL of D_{50}, if blood sugar <250	30 min	4–6 h	Can repeat in 15 min; initiate $D_{10}W$ IV at 50–75 mL/h to avoid rebound hypoglycemia.
	β_2-Agonist	Nebulized albuterol, 10–20 mg in 4-mL saline	30 min	2–4 h	Can be synergistic/additive to insulin; should not be used as sole therapy; use with caution in cardiac disease; may cause tachycardia/hyperglycemia.
K^+ removal	Kayexalate	30–60 g PO in 20% sorbitol	6 h	?	For sustained efficacy may need more than one dose. May cause fatal colonic necrosis, particularly in enema form and postoperative state.
	Furosemide	20–250 mg IV	15 min	4–6 h	Depends on adequate renal response/function.
	Hemodi-alysis		Immediate		Efficacy depends on pretreatment of hyperkalemia (with attendant decrease in serum K^+), the dialyzer used, blood flow and dialysate flow rates, duration, and serum to dialysate K^+ gradient.

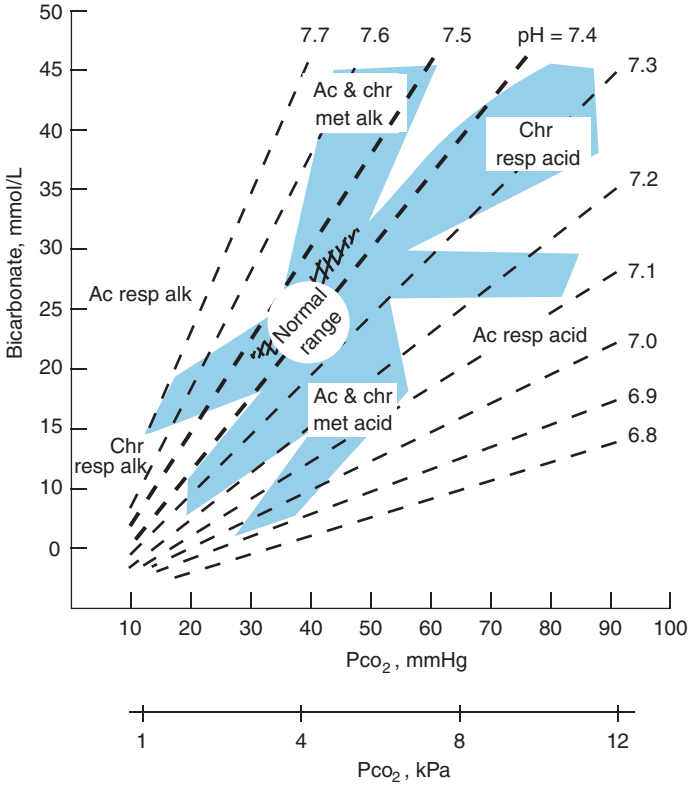


FIGURE 1-5 Nomogram showing bands for uncomplicated respiratory or metabolic acid-base disturbances in intact subjects. Each confidence band represents the mean ±2 SD for the compensatory response of normal subjects or pts to a given primary disorder. Ac, acute; acid, acidosis; alk, alkalosis; chr, chronic; met, metabolic; resp, respiratory. *(From Levinsky NG: HPIM-12, p. 290; modified from Arbus GS: Can Med Assoc J 109:291, 1973.)*

(diabetes mellitus [DKA], starvation, alcohol), lactic acidosis, poisoning (salicylates, ethylene glycol, and methanol), and renal failure.

Rare and newly appreciated causes of anion-gap acidosis include D-lactic acidosis, propylene glycol toxicity, and 5-oxoprolinuria (also known as pyroglutamic aciduria). D-Lactic acidosis (an increase in the D-enantiomer of lactate) can occur in pts with removal, disease, or bypass of the short bowel, leading to increased delivery of carbohydrates to colon. Intestinal overgrowth of organisms that metabolize carbohydrate to D-lactate results in D-lactic acidosis; a wide variety of neurologic symptoms can ensue, with resolution following treatment with appropriate antibiotics to change the intestinal flora. Propylene glycol is a common solvent for IV preparations of a number of drugs, most prominently lorazepam. Pts receiving high rates of these drugs may develop a hyperosmolar anion-gap metabolic acidosis, due mostly to increased lactate, often accompanied by acute kidney failure. Pyroglutamic aciduria (5-oxoprolinuria) is a high anion-gap acidosis caused by dysfunction of the γ-glutamyl cycle that replenishes intracellular glutathione; 5-oxoproline is an

TABLE 1-6 METABOLIC ACIDOSIS

Non-Anion-Gap Acidosis		Anion-Gap Acidosis	
Cause	**Clue**	**Cause**	**Clue**
Diarrhea enterostomy	Hx; ↑ K^+ drainage	DKA	Hyperglycemia, ketones
RF	Early chronic kidney disease	RF	Late chronic kidney disease
RTA		Lactic acidosis	Clinical setting + ↑ serum lactate
Proximal	↓ K^+, presence of other proximal tubular defects (Fanconi syndrome)	(L-lactate)	
		Alcoholic ketoacidosis	Hx; weak + ketones; + osm gap
Distal—hypokalemic	↓ K^+; hypercalciuria; UpH >5.5	Starvation	Hx; mild acidosis; + ketones
Distal—hyperkalemic	↑ K^+; nl PRA/aldo; UpH >5.5	Salicylates	Hx; tinnitus; high serum level; + ketones; + lactate
Distal—hyporeninemic hypoaldosteronism	↑ K^+; ↓ PRA/aldo; UpH <5.5	Methanol	Large AG; concomitant respiratory alkalosis; retinitis; + toxic screen; + osm gap
Dilutional	Massive volume expansion with saline		
Ureterosigmoidostomy	Obstructed ileal loop	Ethylene glycol	RF; CNS symptoms; + toxic screen; crystalluria; + osm gap
Hyperalimentation	Amino acid infusion	D-lactic acidosis	Small-bowel disease; prominent neuro symptoms
Acetazolamide, NH_4Cl, lysine HCl, arginine HCl, sevelamer-HCl	Hx of administration of these agents	Propylene glycol	IV infusions, e.g., lorazepam; + osm gap; RF
		Pyroglutamic aciduria, 5-oxoprolinuria	Large AG; chronic acetaminophen

Abbreviations: AG, anion gap; DKA, diabetic ketoacidosis; osm gap, osmolar gap; PRA, plasma renin activity; RF, renal failure; RTA, renal tubular acidosis; UpH, urinary pH.

intermediate product of the cycle. Hereditary defects in the γ-glutamyl cycle are associated with 5-oxoprolinuria; acquired defects occur in the context of acetaminophen therapy, due to derepression of the cycle by reduced glutathione and overproduction of 5-oxoproline. Resolution occurs after withdrawal of acetaminophen; treatment with *N*-acetyl cysteine to replenish glutathione stores may hasten recovery.

The differentiation of the various anion-gap acidoses depends on the clinical scenario and routine laboratory tests (Table 1-6) in conjunction with measurement of serum lactate, ketones, toxicology screens (if ethylene glycol or methanol ingestion are suspected), and serum osmolality. D-Lactic acidosis can be diagnosed by a specific assay for the D-enantiomer; 5-oxoprolinuria can be diagnosed by the clinical scenario and confirmed by gas chromatographic/mass spectroscopic (GC/MS) analysis of urine, a widely available pediatric screening test for inborn errors of metabolism (typically "urine for organic acids").

Pts with ethylene glycol, methanol, or propylene glycol toxicity may have an "osmolar gap," defined as a >10-mosmol/kg difference between calculated and measured serum osmolality. Calculated osmolality = $2 \times Na^+$ + glucose/18 + BUN/2.8. Of note, pts with alcoholic ketoacidosis and lactic acidosis may also exhibit a modest elevation in the osmolar gap; pts may alternatively metabolize ethylene glycol or methanol to completion by presentation, with an increased anion gap and no increase in the osmolar gap. However, the rapid availability of a measured serum osmolality may aid in the urgent assessment and management of pts with these medical emergencies.

Normal anion-gap acidosis can result from HCO_3^- loss from the GI tract. Diarrhea is by far the most common cause, but other GI conditions associated with external losses of bicarbonate-rich fluids may lead to large alkali losses—e.g., in ileus secondary to intestinal obstruction, in which liters of alkaline fluid may accumulate within the intestinal lumen. Various forms of kidney disease are associated with non-anion-gap acidosis due to reduced tubular reabsorption of filtered bicarbonate and/or reduced excretion of ammonium (NH_4^+). The early stages of progressive renal disease are frequently associated with a non-anion-gap acidosis, with development of an anion-gap component in more advanced renal failure. Non-anion-gap acidosis is also seen in renal tubular acidosis or in the context of tubulointerstitial injury, e.g., after acute tubular necrosis, allergic interstitial nephritis, or urinary tract obstruction. Finally, non-anion-gap acidosis due to exogenous acid loads may occur after rapid volume expansion with saline-containing solutions, the administration of NH_4Cl (a component of cough syrup), lysine HCl, or treatment with the phosphate binder sevelamer hydrochloride.

Calculation of the urinary anion gap may be helpful in the evaluation of hyperchloremic metabolic acidosis, along with a measurement of urine pH. The urinary anion gap is defined as urinary ($[Na^+] + [K^+]$) - ($[Cl^-]$ = [unmeasured anions] - [unmeasured cations]); the NH_4^+ ion is the major unmeasured urinary cation in metabolic acidosis, wherein the urinary anion gap should be strongly negative. A negative anion gap thus suggests GI losses of bicarbonate, with appropriate renal response and increased NH_4^+ excretion; a positive anion gap suggests altered urinary acidification, as seen in renal failure or distal renal tubular acidoses. An important caveat is that the rapid renal excretion of unmeasured anions in anion-gap acidosis, classically seen in DKA, may reduce the serum anion gap and generate a positive value for the urinary anion gap, despite the adequate excretion of urinary NH_4^+; this may lead to misdiagnosis as a renal tubular acidosis.

TREATMENT METABOLIC ACIDOSIS

Treatment of metabolic acidosis depends on the cause and severity. DKA responds to insulin therapy and aggressive hydration; close attention to serum $[K^+]$ and administration of KCl is essential, given that the correction of insulinopenia can

cause profound hypokalemia. The administration of alkali in anion-gap acidoses is controversial and is rarely appropriate in DKA. It is reasonable to treat severe lactic acidosis with IV HCO_3^- at a rate sufficient to maintain a pH >7.20; treatment of moderate lactic acidosis with HCO_3^- is controversial. IV HCO_3^- is however appropriate to reduce acidosis in D-lactic acidosis, ethylene glycol and methanol toxicity, and 5-oxoprolinuria.

Chronic metabolic acidosis should be treated when HCO_3^- is <18–20 mmol/L. In pts with CKD, there is some evidence that acidosis promotes protein catabolism and may worsen bone disease. There is also evidence that correction of metabolic acidosis in CKD leads to a reduced rate of progression to end-stage renal disease (ESRD). Sodium citrate may be more palatable than oral $NaHCO_3$. Oral therapy with $NaHCO_3$ usually begins with 650 mg tid and is titrated upward to maintain serum [HCO_3^-].

METABOLIC ALKALOSIS

Metabolic alkalosis is due to a primary increase in serum [HCO_3^-], distinguished from chronic respiratory acidosis—with a compensatory increase in renal HCO_3^- reabsorption—by the associated increase in arterial pH (normal or decreased in chronic respiratory acidosis). Administered, exogenous alkali (HCO_3^-, acetate, citrate, or lactate) may cause alkalosis if the normal capacity to excrete HCO_3^- is reduced or if renal HCO_3^- reabsorption is enhanced. A recently resurgent problem is "milk alkali syndrome," a triad of hypercalcemia, metabolic alkalosis, and acute renal failure due to ingested calcium carbonate, typically taken for the treatment or prevention of osteoporosis or for symptomatic relief of peptic ulcer disease.

Metabolic alkalosis is primarily caused by renal retention of HCO_3^- and is due to a variety of underlying mechanisms. Pts are typically separated into two major subtypes: Cl^- responsive and Cl^- resistant. Measurement of urine Cl^- affords this separation in the clinical setting (Fig. 1-6). The quintessential causes of Cl^--responsive alkalosis are GI induced from vomiting or gastric aspiration through a nasogastric tube, and renal induced from diuretic therapy. Hypovolemia, chloride deficiency, activation of the RAA axis, and hypokalemia play interrelated roles in the maintenance of this hypochloremic or "contraction" alkalosis. The various syndromes of true or apparent mineralocorticoid excess cause Cl^--resistant metabolic alkalosis (Fig. 1-6); most of these pts are hypokalemic, volume expanded, and/or hypertensive.

Common forms of metabolic alkalosis are generally diagnosed from the history, physical examination, and/or basic laboratory tests. ABGs will help determine whether an elevated [HCO_3^-] is reflective of metabolic alkalosis or chronic respiratory acidosis; ABGs are required for the diagnosis of mixed acid-base disorders. Measurement of urinary electrolytes will aid in separating Cl^--responsive and Cl^--resistant forms. Urinary [Na^+] may thus be >20 meq/L in Cl^--responsive alkalosis despite the presence of hypovolemia; however, urinary [Cl^-] will typically be very low, except in pts with severe hypokalemia. Notably, urinary [Cl^-] may be variable in pts with diuretic-associated alkalosis, depending on the temporal relationship to diuretic administration. Other diagnostic tests—e.g., plasma renin, aldosterone, cortisol—may be appropriate in Cl^--resistant forms with high urinary [Cl^-] (Fig. 1-6).

TREATMENT METABOLIC ALKALOSIS

The acid-base disorder in Cl^--responsive alkalosis will typically respond to saline infusion; however, the associated hypokalemia should also be corrected. Pts with true or apparent mineralocorticoid excess require specific treatment of the underlying disorder. For example, hyperactive amiloride-sensitive ENaC channels cause Liddle's syndrome, which can respond to therapy with amiloride and related drugs; pts with hyperaldosteronism may in turn respond to blockade of

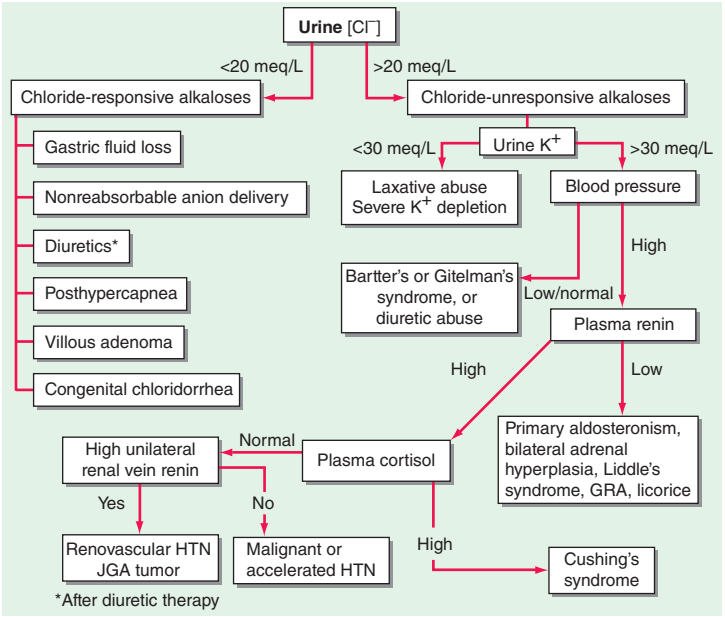


FIGURE 1-6 The diagnostic approach to metabolic alkalosis. See text for details. GRA, glucocorticoid-remediable aldosteronism; HTN, hypertension; JGA, juxtaglomerular apparatus. *(Modified from Dubose TD: Disorders of acid-base balance, in The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, Saunders, 2008; with permission.)*

the mineralocorticoid receptor with spironolactone or eplerenone. Finally, severe alkalosis in the critical care setting may require treatment with acidifying agents such as acetazolamide.

RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by CO_2 retention due to ventilatory failure. Causes include sedatives, stroke, chronic pulmonary disease, airway obstruction, severe pulmonary edema, neuromuscular disorders, and cardiopulmonary arrest. Symptoms include confusion, asterixis, and obtundation.

TREATMENT RESPIRATORY ACIDOSIS

The goal is to improve ventilation through pulmonary toilet and reversal of bronchospasm. Intubation or noninvasive positive pressure ventilation (NPPV) may be required in severe acute cases. Acidosis due to hypercapnia is usually mild; however, combined respiratory and metabolic acidosis may cause a profound reduction in pH. Respiratory acidosis may accompany low tidal volume ventilation in ICU pts and may require metabolic "overcorrection" to maintain a neutral pH.

RESPIRATORY ALKALOSIS

Excessive ventilation causes a primary reduction in CO_2 and ↑ pH in pneumonia, pulmonary edema, interstitial lung disease, and asthma. Pain and psychogenic causes

are common; other etiologies include fever, hypoxemia, sepsis, delirium tremens, salicylates, hepatic failure, mechanical overventilation, and CNS lesions. Pregnancy is associated with a mild respiratory alkalosis. Severe respiratory alkalosis may acutely cause seizures, tetany, cardiac arrhythmias, or loss of consciousness.

TREATMENT **RESPIRATORY ALKALOSIS**

Treatment should be directed at the underlying disorders. In psychogenic cases, sedation or a rebreathing bag may be required.

"MIXED" DISORDERS

In many circumstances, more than a single acid-base disturbance exists. Examples include combined metabolic and respiratory acidosis with cardiogenic shock; metabolic alkalosis and anion-gap acidosis in pts with vomiting and diabetic ketoacidosis; and anion-gap metabolic acidosis with respiratory alkalosis in pts with salicylate toxicity. The diagnosis may be clinically evident and/or suggested by relationships between the PCO_2 and $[HCO_3^-]$ that diverge from those found in simple disorders. For example, the PCO_2 in a pt with metabolic acidosis and respiratory alkalosis will be considerably less than that predicted from the $[HCO_3^-]$ and Winter's formula $[PaCO_2 = (1.5 \times [HCO_3^-]) + 8 + 2]$.

In "simple" anion-gap acidosis, the anion gap increases in proportion to the fall in $[HCO_3^-]$. A lesser drop in serum $[HCO_3^-]$ than in the anion gap suggests a coexisting metabolic alkalosis. Conversely, a proportionately *larger* drop in $[HCO_3^-]$ than in the anion gap suggests the presence of a mixed anion-gap and non-anion-gap metabolic acidosis. Notably, however, these interpretations assume 1:1 relationships between unmeasured anions and the fall in $[HCO_3^-]$, which are not uniformly present in individual pts or as acidoses evolve. For example, volume resuscitation of pts with DKA will typically increase glomerular filtration and the urinary excretion of ketones, resulting in a decrease in the anion gap in the absence of a supervening non-anion-gap acidosis.



For a more detailed discussion, see Mount DB: Fluid and Electrolyte Disturbances, Chap. 63, p. 295; and DuBose TD Jr: Acidosis and Alkalosis, Chap. 66, p. 315, in HPIM-19. See also Mount DB, Zandi-Nejad K: Disorders of potassium balance, in The Kidney, 9th ed, BM Brenner (ed). Philadelphia, Saunders, 2011; and Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007; Perianayagam A et al: DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol 3:331, 2008; Sood L et al: Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. Am J Kidney Dis 61:571-578, 2013.

2 Diagnostic Imaging in Internal Medicine

Clinicians have a wide array of radiologic modalities at their disposal to aid them in noninvasive diagnosis. Despite the introduction of highly specialized imaging modalities, radiologic tests such as chest radiographs and ultrasound continue to serve a vital role in the diagnostic approach to pt care. At most institutions, CT is available on an emergent basis and is invaluable for initial evaluation of pts with trauma, suspected CNS hemorrhage, or ischemic stroke. MRI and related techniques (MR angiography, functional MRI, MR spectroscopy) provide remarkable resolution of many tissues including the brain, vascular system, joints, and most large organs. Radionuclide scans including positron emission tomography (PET) can provide functional assessment of organs or specific regions within organs. Combination of PET with MRI or CT scanning provides highly informative images of the location and configuration of metabolically active lesions, such as cancers. Increasingly, internists are being trained in the use of ultrasound to assist with line placement, thyroid nodules, cardiac sounds, and abdominal abnormalities.

This chapter will review the indications and utility of the most commonly utilized radiologic studies used by internists.

CHEST RADIOGRAPHY (FIG. 2-1)

- Can be obtained quickly and should be part of the standard evaluation for pts with cardiopulmonary complaints.
- Is able to identify life-threatening conditions such as pneumothorax, intraperitoneal air, pulmonary edema, pneumonia, and aortic dissection.
- Is most often normal in a pt with an acute pulmonary embolus.
- Should be repeated in 4–6 weeks in a pt with an acute pneumonic process to document resolution of the radiographic infiltrate.
- Is used in conjunction with the physical examination to support the diagnosis of congestive heart failure. Radiographic findings supporting the diagnosis of heart failure include cardiomegaly, cephalization, Kerley B lines, and pleural effusions.
- Should be repeated frequently in intubated pts to examine endotracheal tube position and the possibility of barotrauma.
- Helps to identify alveolar or airspace disease. Radiographic features of such diseases include inhomogeneous, patchy opacities and air-bronchograms.
- Helps to document the free-flowing nature of pleural effusions. Decubitus views should be obtained to exclude loculated pleural fluid prior to attempts to extract such fluid.

ABDOMINAL RADIOGRAPHY

- Should be the initial imaging modality in a pt with suspected bowel obstruction. Signs of small-bowel obstruction on plain radiographs include multiple air-fluid levels, absence of colonic distention, and a "stepladder" appearance of small-bowel loops.
- Should not be performed with barium enhancement when perforated bowel, portal venous gas, or toxic megacolon is suspected.
- Is used to evaluate the size of bowel:
  1. Normal small bowel is <3 cm in diameter.
  2. Normal caliber of the cecum is up to 9 cm, with the rest of the large bowel up to 6 cm in diameter.

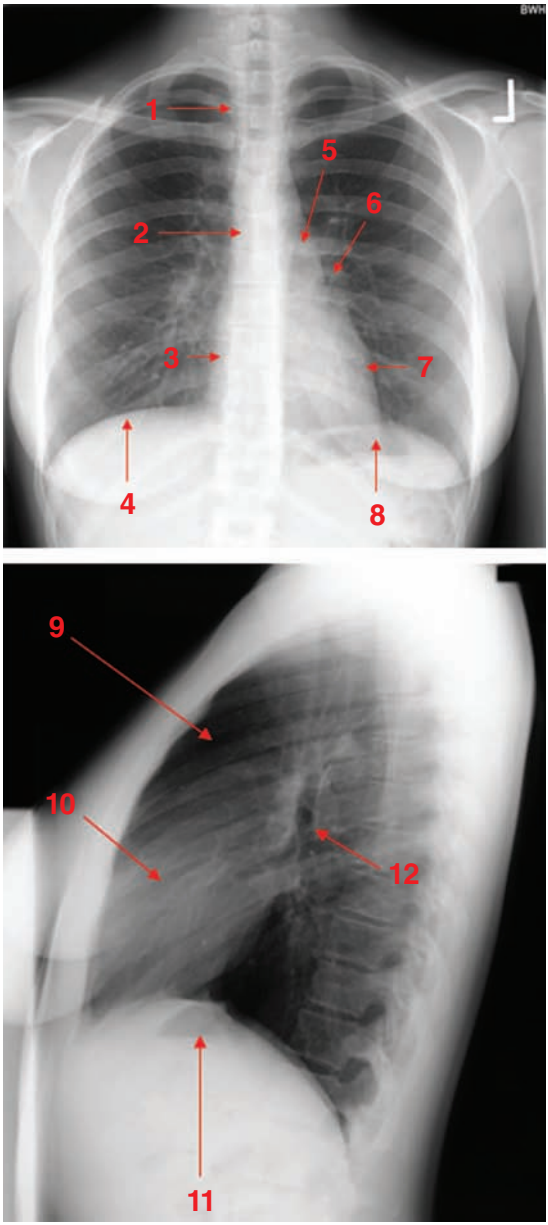


FIGURE 2-1 Normal chest radiograph-review of anatomy. **1.** Trachea. **2.** Carina. **3.** Right atrium. **4.** Right hemidiaphragm. **5.** Aortic knob. **6.** Left hilum. **7.** Left ventricle. **8.** Left hemidiaphragm (with stomach bubble). **9.** Retrosternal clear space. **10.** Right ventricle. **11.** Left hemidiaphragm (with stomach bubble). **12.** Left upper lobe bronchus.

ULTRASOUND

- Is more sensitive and specific than CT scanning in evaluating for the presence of gallstone disease.
- Can be used to assist with central line placement and with peripheral access when challenging.
- Can readily identify the size of the kidneys in a pt with renal insufficiency and can exclude the presence of hydronephrosis.
- Can expeditiously evaluate for the presence of peritoneal fluid in a pt with blunt abdominal trauma.
- Is used in conjunction with Doppler studies to evaluate for the presence of arterial atherosclerotic disease.
- Is used to evaluate cardiac valves and wall motion.
- Should be used to localize loculated pleural and peritoneal fluid prior to draining such fluid.
- Can determine the size of thyroid nodules and guide fine-needle aspiration biopsy.
- Can determine the size and location of enlarged lymph nodes, especially in superficial locations such as in the neck.
- Is the modality of choice for assessing known or suspected scrotal pathology.
- Should be the first imaging modality utilized when evaluating the ovaries.

COMPUTED TOMOGRAPHY

- CT delivers a substantially higher radiation dose than conventional radiography; it should therefore be used judiciously.
- CT of the brain should be the initial radiographic modality in evaluating a pt with a potential stroke.
- Is highly sensitive for diagnosing an acute subarachnoid hemorrhage and, in the acute setting, is more sensitive than MRI.
- CT of the brain is an essential test in evaluating a pt with mental status changes to exclude entities such as intracranial bleeding, mass effect, subdural or epidural hematomas, and hydrocephalus.
- Is better than MRI for evaluating osseous lesions of the skull and spine.
- CT of the chest should be considered in the evaluation of a pt with chest pain to rule out entities such as pulmonary embolus or aortic dissection.
- CT of the chest is essential for evaluating lung nodules to assess for the presence of thoracic lymphadenopathy.
- CT, with high-resolution cuts through the lungs, is the imaging modality of choice for evaluating the lung interstitium in a pt with interstitial lung disease.
- Can be used to evaluate for the presence of pleural and pericardial fluid and to localize loculated effusions.
- Is useful in a pt with unexplained abdominal pain to evaluate for conditions such as appendicitis, mesenteric ischemia or infarction, diverticulitis, or pancreatitis.
- CT of the abdomen is also the test of choice for evaluating for nephrolithiasis in a pt with renal colic.
- Is the test of choice for evaluating for the presence of an abscess in the chest or abdomen.
- In conjunction with abdominal radiography, CT can help identify the cause of bowel obstruction.
- Can identify abdominal conditions such as intussusception and volvulus in a pt with abdominal pain.
- Is the imaging modality of choice for evaluating the retroperitoneum.
- Should be obtained expeditiously in a pt with abdominal trauma to evaluate for the presence of intraabdominal hemorrhage and to assess injury to abdominal organs.

MAGNETIC RESONANCE IMAGING

- Is more useful than CT in the evaluation of ischemic infarction, dementia, mass lesions, demyelinating diseases, and most nonosseous spinal disorders.
- Provides excellent imaging of large joints including the knee, hip, and shoulder.
- Can be used, often with CT or angiography, to assess possible dissecting aortic aneurysms and congenital anomalies of the cardiovascular system.
- Cardiac MRI is proving useful to evaluate cardiac wall motion and for assessing cardiac muscle viability in ischemic heart disease.
- Is preferable to CT for evaluating adrenal masses such as pheochromocytoma and for helping to distinguish benign and malignant adrenal masses.
- Is preferable to CT for evaluating pituitary lesions and parasellar pathology.

RADIONUCLIDE IMAGING

- Radionuclides can be used in the form of radioactive ions (iodide, gallium, thallium) or radiolabeled substances with affinity for specific tissues (radiopharmaceuticals, e.g., bisphosphonates, sestamibi, octreotide, metaiodobenzylguanidine [MIBG], iodocholesterol, etc.), or in the form of fluorodeoxyglucose for PET scanning.
- Radionuclide scintigraphy can be combined/merged with CT or MRI for precise anatomic localization of the radionuclide-imaged tissue.
- Tomographic radionuclide scintigraphy (single-photon emission computed tomography [SPECT]) is analogous to CT, using radionuclide emissions instead of x-rays. It permits visualization of sequential slices that can be computer manipulated to yield a three-dimensional reconstruction.
- PET is very useful for detection of metabolically active tissues, such as cancers and their metastases, and has largely supplanted older modalities of radionuclide scanning (e.g., gallium scintigraphy).
- Radionuclide scans frequently ordered by the general internist are: (1) bone scans to identify metastatic disease in bone or osteomyelitis, (2) sestamibi scans for preoperative localization of parathyroid adenomas, (3) thyroid scans (technetium or iodine) to identify hot or cold thyroid nodules.
- Specialized radionuclide scans include thallium or sestamibi myocardial perfusion scans, pulmonary ventilation/perfusion scans, octreotide scans for neuroendocrine tumors, MIBG scans for pheochromocytoma, iodocholesterol scans for adrenocortical adenomas, and whole-body radioiodine scans for disseminated thyroid cancer.
- Radioiodine scanning of the thyroid can be used to obtain quantitative information on iodine uptake by the thyroid, which is useful to differentiate subacute thyroiditis from Graves' disease.

3 Procedures Commonly Performed by Internists

Internists perform a wide range of medical procedures, although practices vary widely among institutions and by specialty. Internists, nurses, or other ancillary health care professionals perform venipuncture for blood testing, arterial puncture for blood gases, endotracheal intubation, and flexible sigmoidoscopy, and insert IV lines, nasogastric (NG) tubes, and urinary catheters. These procedures are not

covered here, but require skill and practice to minimize pt discomfort and potential complications. Here, we review more invasive diagnostic and therapeutic procedures performed by internists—thoracentesis, lumbar puncture, and paracentesis. Many additional procedures are performed by specialists and require additional training and credentialing, including the following:

- Allergy: skin testing, rhinoscopy
- Cardiology: stress testing, echocardiograms, coronary catheterization, angioplasty, stent insertion, pacemakers, electrophysiology testing and ablation, implantable defibrillators, cardioversion
- Endocrinology: thyroid biopsy, dynamic hormone testing, bone densitometry
- Gastroenterology: upper and lower endoscopy, esophageal manometry, endoscopic retrograde cholangiopancreatography, stent insertion, endoscopic ultrasound, liver biopsy
- Hematology/oncology: bone marrow biopsy, stem cell transplant, lymph node biopsy, plasmapheresis
- Pulmonary: intubation and ventilator management, bronchoscopy
- Renal: kidney biopsy, dialysis
- Rheumatology: joint aspiration

Increasingly, ultrasound, CT, and MRI are being used to guide invasive procedures, and flexible fiberoptic instruments are extending the reach into the body. For most invasive medical procedures, including those reviewed below, informed consent should be obtained in writing before beginning the procedure.

THORACENTESIS

Drainage of the pleural space can be performed at the bedside. Indications for this procedure include diagnostic evaluation of pleural fluid, removal of pleural fluid for symptomatic relief, and instillation of sclerosing agents in pts with recurrent, usually malignant pleural effusions.

PREPARATORY WORK

Familiarity with the components of a thoracentesis tray is a prerequisite to performing a thoracentesis successfully. Recent posterior-anterior (PA) and lateral chest radiographs with bilateral decubitus views should be obtained to document the free-flowing nature of the pleural effusion. Loculated pleural effusions should be localized by ultrasound or CT prior to drainage. Management should be individualized in pts with a coagulopathy of thrombocytopenia. Thoracentesis is more challenging in pts with mechanical ventilation and should be performed with ultrasound guidance if possible.

TECHNIQUE

A posterior approach is the preferred means of accessing pleural fluid. Comfortable positioning is a key to success for both pt and physician. The pt should sit on the edge of the bed, leaning forward with the arms abducted onto a pillow on a bedside stand. Pts undergoing thoracentesis frequently have severe dyspnea, and it is important to assess if they can maintain this positioning for at least 10 min. The entry site for the thoracentesis is based on the physical examination and radiographic findings. Percussion of dullness is utilized to ascertain the extent of the pleural effusion with the site of entry being the first or second highest interspace in this area. The entry site for the thoracentesis is at the superior aspect of the rib, thus avoiding the intercostal nerve, artery, and vein, which run along the inferior aspect of the rib (Fig. 3-1).

The site of entry should be marked with a pen to guide the thoracentesis. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is used to anesthetize the skin, and a larger-gauge needle is used to anesthetize down to the superior aspect of the rib. The

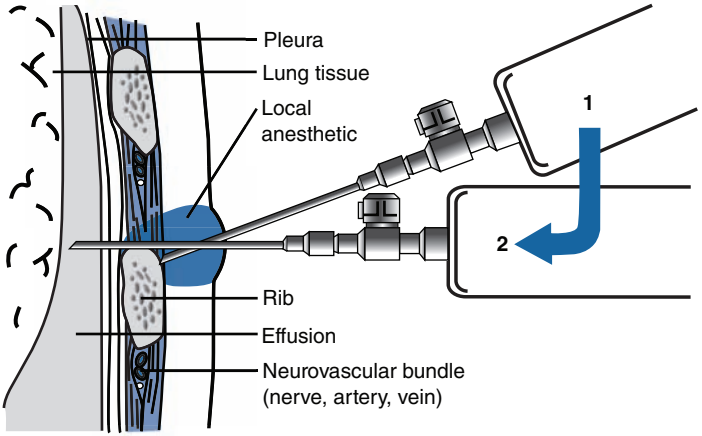


FIGURE 3-1 In thoracentesis, the needle is passed over the top of the rib to avoid the neurovascular bundle. *(From LG Gomella, SA Haist: Clinician's Pocket Reference, 11th ed. New York, McGraw-Hill, 2007.)*

needle should then be directed over the upper margin of the rib to anesthetize down to the parietal pleura. The pleural space should be entered with the anesthetizing needle, all the while using liberal amounts of lidocaine.

A dedicated thoracentesis needle with an attached syringe should next be utilized to penetrate the skin. This needle should be advanced to the superior aspect of the rib. While maintaining gentle negative pressure, the needle should be slowly advanced into the pleural space. If a diagnostic tap is being performed, aspiration of only 30–50 mL of fluid is necessary before termination of the procedure. If a therapeutic thoracentesis is being performed, a three-way stopcock is utilized to direct the aspirated pleural fluid into collection bottles or bags. No more than 1 L of pleural fluid should be withdrawn at any given time, because quantities >1–1.5 L can result in re-expansion pulmonary edema.

After all specimens have been collected, the thoracentesis needle should be withdrawn and the needle site occluded for at least 1 min.

SPECIMEN COLLECTION

The diagnostic evaluation of pleural fluid depends on the clinical situation. All pleural fluid samples should be sent for cell count and differential, Gram stain, and bacterial cultures. LDH and protein determinations should also be made to differentiate between exudative and transudative pleural effusions. The pH should be determined if empyema is a diagnostic consideration. Other studies on pleural fluid include mycobacterial and fungal cultures, glucose, triglyceride level, amylase, and cytologic determination.

POSTPROCEDURE

A postprocedural chest radiograph should be obtained to evaluate for a pneumothorax, and the pt should be instructed to notify the physician if new shortness of breath develops.

LUMBAR PUNCTURE

Evaluation of CSF is essential for the diagnosis of suspected meningeal infection, subarachnoid hemorrhage, leptomeningeal neoplastic disease, and noninfectious meningitis. Relative contraindications to LP include local skin infection in the

lumbar area, suspected spinal cord mass lesion, and a suspected intracranial mass lesion. Any bleeding diathesis should also be corrected prior to performing LP to prevent the possible occurrence of an epidural hematoma. A functional platelet count >50,000/μL and an international normalized ratio (INR) <1.5 are advisable to perform LP safely.

In pts with an altered level of consciousness, focal neurologic deficits, or evidence of papilledema, an imaging study should generally be obtained prior to performing LP.

TECHNIQUE

Proper positioning of the pt is essential; either the lateral decubitus or the sitting position can be used. Most routine LPs should be performed using the lateral decubitus position (Fig. 3-2). The sitting position may be preferable in obese pts. With either position, the pt should be instructed to flex the spine as much as possible. In the lateral decubitus position, the pt assumes a fetal position with the knees flexed toward the abdomen; the shoulders and pelvis should be vertically aligned without forward or backward tilt. In the sitting position, the pt should bend over a bedside table with the head resting on folded arms.

The entry site for an LP is below the level of the conus medullaris, which extends to L1–L2 in most adults. Thus, either the L3–L4 or L4–L5 interspace can be utilized as the entry site. The posterior superior iliac crest should be identified and the spine palpated at this level. This represents the L3–L4 interspace, with the other interspaces referenced from this landmark. The midpoint of the interspace between the spinous processes represents the entry point for the spinal needle. For elective LPs, topical anaesthesia can be achieved by application of lidocaine 4% cream 30 min prior to the procedure. The skin is then prepped and draped in a sterile fashion with the operator observing sterile technique at all times. A small-gauge needle is then used to anesthetize the skin and subcutaneous tissue; this is usually performed with multiple small (0.5–1 mL), serial injections of 1% lidocaine as the needle is progressively advanced. The spinal needle should be introduced perpendicular to the skin in the midline and advanced slowly. The needle stylet can be withdrawn periodically as the spinal needle is advanced to assess if the subarachnoid space has been reached. As the needle enters the subarachnoid space, a "popping" sensation can sometimes be felt. If bone is encountered, the needle should be withdrawn to just below the skin and then redirected more caudally. Once CSF begins to flow, the opening pressure should be measured in the lateral decubitus position with the pt shifted to this position if the

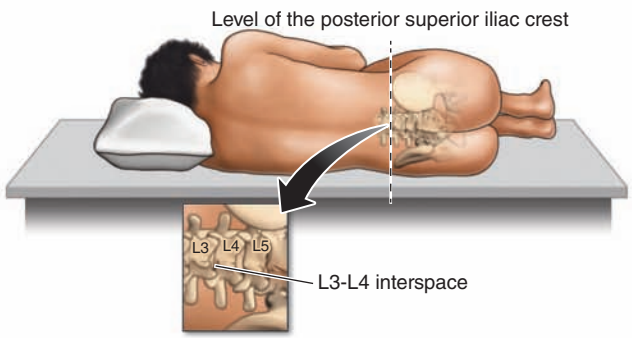


FIGURE 3-2 Proper positioning of a pt in the lateral decubitus position. Note that the shoulders and hips are in a vertical plane; the torso is perpendicular to the bed. *(From RP Simon et al [eds]: Clinical Neurology, 7th ed. New York, McGraw-Hill, 2009.)*

procedure was begun in the sitting position. The CSF can then be collected in a series of specimen tubes. A minimum of 10–15 mL of CSF is usually obtained. The stylet is then replaced and the spinal needle removed.

SPECIMEN COLLECTION

Diagnostic evaluation of CSF is based on the clinical scenario. In general, spinal fluid should always be sent for cell count with differential, protein, and glucose. Other studies that can be obtained on CSF include bacterial mycobacterial fungal, viral cultures, polymerase chain reaction (PCR) tests for microorganisms, smears (Gram and acid-fast stains), VDRL, cryptococcal antigen, gamma globulins, oligoclonal bands, and cytology.

POSTPROCEDURE

The pt is often instructed to lie in the recumbent position for 30–60 min, although this practice does not appear to reduce the risk (estimated at 10–30%) of post-LP headache, caused by a fall in CSF pressure. The post-LP headache is dramatically positional; it begins when the pt sits or stands upright and is relieved upon reclining. Bedrest, hydration, and oral analgesics are often helpful; IV caffeine (500 mg in 500-mL saline given over 2 h) is sometimes tried. For post-LP headaches lasting more than a few days, consultation with an anesthesiologist should be considered for placement of an epidural blood patch; this usually provides rapid relief.

PARACENTESIS

Removal and analysis of peritoneal fluid is invaluable in evaluating pts with new-onset ascites or ascites of unknown etiology. It is also indicated in pts with known ascites who have a decompensation in their clinical status. Relative contraindications include bleeding diathesis, prior abdominal surgery, distended bowel, or known loculated ascites.

PREPARATORY WORK

Prior to performing a paracentesis, any severe bleeding diathesis should be corrected. Bowel distention should also be relieved by placement of a NG tube, and the bladder should also be emptied before beginning the procedure. If a large-volume paracentesis is being performed, large vacuum bottles with the appropriate connecting tubing should be obtained.

TECHNIQUE

Proper pt positioning greatly improves the ease with which a paracentesis can be performed. The pt should be instructed to lie supine with the head of the bed elevated to 45°. This position should be maintained for ~15 min to allow ascitic fluid to accumulate in the dependent portion of the abdomen. Although not generally needed, ultrasound can be helpful for documenting ascites and identifying the locations of peritoneal fluid.

The preferred entry site for paracentesis is a midline puncture halfway between the pubic symphysis and the umbilicus; this correlates with the location of the relatively avascular linea alba. The midline puncture should be avoided if there is a previous midline surgical scar, because neovascularization may have occurred. Alternative sites of entry include the lower quadrants, lateral to the rectus abdominis, but caution should be used to avoid collateral blood vessels that may have formed in pts with portal hypertension.

The skin is prepped and draped in a sterile fashion. The skin, the subcutaneous tissue, and the abdominal wall down to the peritoneum should be infiltrated with an anesthetic agent. The paracentesis needle with an attached syringe is then introduced in the midline perpendicular to the skin. To prevent leaking of ascitic fluid, "Z-tracking" can sometimes be helpful: After penetrating the skin, the needle

is inserted 1–2 cm before advancing further. The needle is then advanced slowly while continuous aspiration is performed. As the peritoneum is pierced, the needle will "give" noticeably. Fluid should flow freely into the syringe soon thereafter. For a diagnostic paracentesis, removal of 50 mL of ascitic fluid is adequate. For a large-volume paracentesis, direct drainage into large vacuum containers using connecting tubing is a commonly utilized option.

After all samples have been collected, the paracentesis needle should be removed and firm pressure applied to the puncture site.

SPECIMEN COLLECTION

Peritoneal fluid should be sent for cell count with differential, Gram stain, and bacterial cultures. Albumin measurement of ascitic fluid is also necessary for calculating the serum–ascitic albumin gradient. Depending on the clinical scenario, other studies that can be obtained include mycobacterial cultures, amylase, adenosine deaminase, triglycerides, and cytology.

POSTPROCEDURE

The pt should be monitored carefully after paracentesis and should be instructed to lie supine in bed for several hours. If persistent fluid leakage occurs, continued bedrest with pressure dressings at the puncture site can be helpful. For pts with hepatic dysfunction undergoing large-volume paracentesis, the sudden reduction in intravascular volume can precipitate hepatorenal syndrome. Administration of 25-g IV albumin following large-volume paracentesis has been shown to decrease the incidence of postprocedure renal failure. Finally, if the ascites fluid analysis shows evidence of spontaneous bacterial peritonitis, then antibiotics (directed toward gram-negative gut bacteria) and IV albumin should be administered as soon as possible.



For a more detailed discussion, see Robbins E, Hauser SL: Technique of Lumbar Puncture, Chap. 443e, and the Clinical Procedure Tutorial videos in Chaps. 481e-486e in HPIM-19.

4 Principles of Critical Care Medicine

INITIAL EVALUATION OF THE CRITICALLY ILL PATIENT

Initial care of critically ill pts must often be performed rapidly and before a thorough medical history has been obtained. Physiologic stabilization begins with the principles of advanced cardiovascular life support and frequently involves invasive techniques such as mechanical ventilation and renal replacement therapy to support organ systems that are failing. A variety of severity-of-illness scoring systems, such as APACHE (acute physiology and chronic health evaluation), have been developed. Although these tools are useful for ensuring similarity among groups of pts involved in clinical trials, guiding resource allocation, or monitoring quality assurance, their

relevance to individual pts is less clear. These scoring systems are not typically used to guide clinical management.

SHOCK

Shock, which is characterized by multisystem end-organ hypoperfusion and tissue hypoxia, is a frequent problem requiring ICU admission. A variety of clinical indicators of shock exist, including reduced mean arterial pressure, tachycardia, tachypnea, cool extremities, altered mental status, oliguria, and lactic acidosis. Although hypotension is usually observed in shock, there is not a specific blood pressure threshold that is used to define it. Shock can result from decreased cardiac output, decreased systemic vascular resistance, or both. The three main categories of shock are hypovolemic, cardiogenic, and high cardiac output/low systemic vascular resistance. Clinical evaluation can be useful to assess the adequacy of cardiac output, with narrow pulse pressure, cool extremities, and delayed capillary refill suggestive of reduced cardiac output. Indicators of high cardiac output (e.g., widened pulse pressure, warm extremities, and rapid capillary refill) associated with shock suggest reduced systemic vascular resistance. Reduced cardiac output can be due to intravascular volume depletion (e.g., hemorrhage) or cardiac dysfunction. Intravascular volume depletion can be assessed through changes in right atrial pressure with spontaneous respirations or changes in pulse pressure during positive pressure mechanical ventilation. Reduced systemic vascular resistance is often caused by sepsis, but high cardiac output hypotension is also seen in pancreatitis, liver failure, burns, anaphylaxis, peripheral arteriovenous shunts, and thyrotoxicosis. Early resuscitation of septic and cardiogenic shock may improve survival; objective assessments such as echocardiography and/or invasive vascular monitoring should be used to complement clinical evaluation and minimize end-organ damage. The approach to the pt in shock is outlined in Fig. 4-1.

MECHANICAL VENTILATORY SUPPORT

Critically ill pts often require mechanical ventilation. During initial resuscitation, standard principles of advanced cardiovascular life support should be followed. Mechanical ventilation should be considered for acute hypoxemic respiratory failure, which may occur with cardiogenic shock, pulmonary edema (cardiogenic or noncardiogenic), or pneumonia. Mechanical ventilation should also be considered for treatment of ventilatory failure, which can result from an increased load on the respiratory system—often manifested by lactic acidosis or decreased lung compliance. Mechanical ventilation may decrease respiratory work, improve arterial oxygenation with improved tissue O_2 delivery, and reduce acidosis. Reduction in mean arterial pressure after institution of mechanical ventilation commonly occurs due to reduced venous return from positive pressure ventilation, reduced endogenous catecholamine secretion, and administration of drugs used to facilitate intubation (such as propofol and opiates). Because hypovolemia often contributes to post-intubation hypotension, IV volume administration should be considered. The major types of respiratory failure are discussed in Chap. 15.

TREATMENT THE MECHANICALLY VENTILATED PATIENT

Many pts receiving mechanical ventilation require treatment for pain (typically with opiates) and for anxiety (typically with benzodiazepines, which also have the benefit of providing amnesia). Protocol-driven approaches to sedation or daily interruption of sedative infusions can prevent excessive sedative drug accumulation. Less commonly, neuromuscular blocking agents are required to facilitate ventilation when there is extreme dyssynchrony between the pt's respiratory efforts and the ventilator that cannot be corrected with manipulation of the ventilator settings; aggressive sedation is required during treatment with

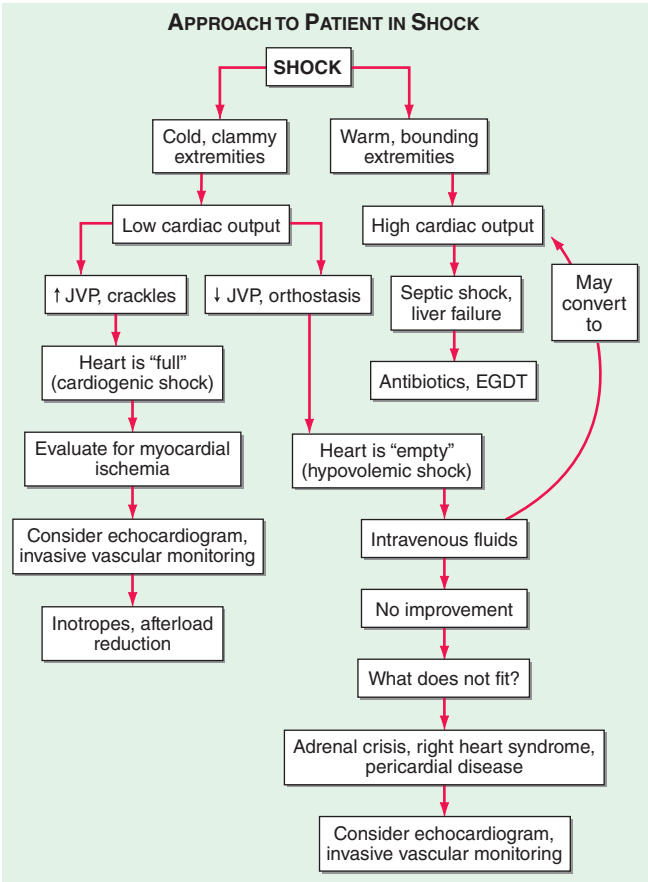


FIGURE 4-1 Approach to pt in shock. EGDT, early goal-directed therapy; JVP, jugular venous pulse.

neuromuscular blockers. Neuromuscular blocking agents should be used with caution because a myopathy associated with prolonged weakness can result.

Weaning from mechanical ventilation should be considered when the disease process prompting intubation has improved. Daily screening of intubated pts for weaning potential should be performed. Stable oxygenation (with oxygen supplementation levels that are achievable off of mechanical ventilation and at low positive end-expiratory pressure [PEEP] levels), intact cough and airway reflexes, and lack of requirement for vasopressor agents are required before considering a trial of weaning from mechanical ventilation. The most effective approach for weaning is usually a spontaneous breathing trial, which involves 30–120 min of breathing without significant ventilatory support. Either an open T-piece breathing system or minimal amounts of ventilatory support (pressure support to overcome resistance of the endotracheal tube and/or low levels of continuous positive airway pressure [CPAP]) can be used. Failure of a spontaneous breathing trial has occurred if tachypnea (respiratory rate >35 breaths/min for >5 min),

hypoxemia (O_2 saturation <90%), tachycardia (>140 beats/min or 20% increase from baseline), bradycardia (20% reduction from baseline), hypotension (<90 mmHg), hypertension (>180 mmHg), increased anxiety, or diaphoresis develops. At the end of the spontaneous breathing trial, the *rapid shallow breathing index* (RSBI or f/VT), which is calculated as respiratory rate in breaths/min divided by tidal volume in liters, can be used to predict weanability. A f/VT value <105 at the end of the spontaneous breathing test warrants a trial of extubation. Daily interruption of sedative infusions in conjunction with spontaneous breathing trials can limit excessive sedation and shorten the duration of mechanical ventilation. Despite careful weaning protocols, up to 10% of pts develop respiratory distress after extubation and may require reintubation.

MULTIORGAN SYSTEM FAILURE

Multiorgan system failure is a syndrome defined by the simultaneous dysfunction or failure of two or more organs in pts with critical illness. Multiorgan system failure is a common consequence of systemic inflammatory conditions (e.g., sepsis, pancreatitis, and trauma). To meet the criteria for multiorgan system failure, organ failure must persist for >24 h. Prognosis worsens with increased duration of organ failure and increased number of organ systems involved.

MONITORING IN THE ICU

With critical illness, close and often continuous monitoring of multiple organ systems is required. In addition to pulse oximetry, frequent arterial blood gas analysis can reveal evolving acid-base disturbances and assess the adequacy of ventilation. Intra-arterial pressure monitoring is frequently performed to follow blood pressure and to provide arterial blood gases and other blood samples. Pulmonary artery (Swan-Ganz) catheters can provide pulmonary artery pressure, cardiac output, systemic vascular resistance, and oxygen delivery measurements. However, no morbidity or mortality benefit from pulmonary artery catheter use has been demonstrated, and rare but significant complications from placement of central venous access (e.g., pneumothorax, infection) or the pulmonary artery catheter (e.g., cardiac arrhythmias, pulmonary artery rupture) can result. Thus, routine pulmonary artery catheterization in critically ill pts is not recommended.

For intubated pts receiving volume-controlled modes of mechanical ventilation, respiratory mechanics can be followed easily. The peak airway pressure is regularly measured by mechanical ventilators, and the plateau pressure can be assessed by including an end-inspiratory pause. The inspiratory airway resistance is calculated as the difference between the peak and plateau airway pressures (with adjustment for flow rate). Increased airway resistance can result from bronchospasm, respiratory secretions, or a kinked endotracheal tube. Static compliance of the respiratory system is calculated as the tidal volume divided by the gradient in airway pressure (plateau pressure minus PEEP). Reduced respiratory system compliance can result from pleural effusions, pneumothorax, pneumonia, pulmonary edema, or auto-PEEP (elevated end-expiratory pressure related to insufficient time for alveolar emptying before the next inspiration).

PREVENTION OF CRITICAL ILLNESS COMPLICATIONS

Critically ill pts are prone to a number of complications, including the following:

- Sepsis: Often nosocomial infections related to the invasive monitoring devices used in critically ill pts.
- Anemia: Usually due to chronic inflammation as well as iatrogenic blood loss. A conservative approach to providing blood transfusions is recommended unless pts have active hemorrhage.

- Deep-vein thrombosis: May occur despite standard prophylaxis with subcutaneous (SC) heparin or lower extremity sequential compression devices and may occur at the site of central venous catheters. Low-molecular-weight heparins (e.g., enoxaparin) are more effective for high-risk pts than unfractionated heparin.
- GI bleeding: Stress ulcers of the gastric mucosa frequently develop in pts with bleeding diatheses, shock, or respiratory failure, necessitating prophylactic acid neutralization in such pts.
- Acute renal failure: A frequent occurrence in ICU pts, exacerbated by nephrotoxic medications and hypoperfusion. The most common etiology is acute tubular necrosis. Low-dose dopamine treatment does not protect against the development of acute renal failure.
- Inadequate nutrition and hyperglycemia: Enteral feeding, when possible, is preferred over parenteral nutrition, because the parenteral route is associated with multiple complications including hyperglycemia, cholestasis, and sepsis. The utility of tight glucose control in the ICU is controversial.
- ICU-acquired weakness: Neuropathies and myopathies have been described—typically after at least 1 week of ICU care. These complications are especially common in sepsis.

NEUROLOGIC DYSFUNCTION IN CRITICALLY ILL PATIENTS

A variety of neurologic problems can develop in critically ill pts. Most ICU pts develop delirium, which is characterized by acute changes in mental status, inattention, disorganized thinking, and an altered level of consciousness. Use of dexmedetomidine was associated with less ICU delirium than midazolam, one of the conventional sedatives. Less common but important neurologic complications include anoxic brain injury, stroke, and status epilepticus.

LIMITATION OR WITHDRAWAL OF CARE

Withholding or withdrawing care commonly occurs in the ICU. Technological advances have allowed many pts to be maintained in the ICU with little or no chance of recovery. Increasingly, pts, families, and caregivers have acknowledged the ethical validity to withhold or withdraw care when the pt or surrogate decision-maker determines that the pt's goals for care are no longer achievable with the clinical situation.

For a more detailed discussion, see Kress JP, Hall JB: Approach to the Patient with Critical Illness, Chap. 321, p. 1729, in HPIM-19.

5 Pain and Its Management

APPROACH TO THE PATIENT: **Pain**

Pain is the most common symptom that brings a pt to a physician's attention. Management depends on determining its cause, alleviating triggering and potentiating factors, and providing rapid relief whenever possible. Pain may be of

somatic (skin, joints, muscles), visceral, or neuropathic (injury to nerves, spinal cord pathways, or thalamus) origin. Characteristics of each are summarized in Table 5-1.

Neuropathic Pain Due to damage of peripheral or central nociceptive pathways. Definitions: *neuralgia*: pain in the distribution of a single nerve, as in trigeminal neuralgia; *dysesthesia*: spontaneous, unpleasant, abnormal sensation; *hyperalgesia* and *hyperesthesia*: exaggerated responses to nociceptive or touch stimulus, respectively; *allodynia*: perception of light mechanical stimuli as painful, as when vibration evokes painful sensation. Reduced pain perception is called *hypalgesia* or, when absent, *analgesia*. *Causalgia* is continuous severe burning pain with indistinct boundaries and accompanying sympathetic nervous system dysfunction (sweating; vascular, skin, and hair changes—sympathetic dystrophy) that occurs after injury to a peripheral nerve.

Sensitization refers to a lowered threshold for activating primary nociceptors following repeated stimulation in damaged or inflamed tissues; inflammatory mediators play a role. Sensitization contributes to tenderness, soreness, and hyperalgesia (as in sunburn).

Referred pain results from the convergence of sensory inputs from skin and viscera on single spinal neurons that transmit pain signals to the brain. Because of this convergence, input from deep structures is mislocalized to a region of skin innervated by the same spinal segment.

Chronic Pain The problem is often difficult to diagnose with certainty, and pts may appear emotionally distraught. Several factors can cause, perpetuate, or exacerbate chronic pain: (1) painful disease for which there is no cure (e.g., arthritis, cancer, chronic daily headaches, diabetic neuropathy); (2) perpetuating factors initiated by a bodily disease that persist after the disease has resolved (e.g., damaged sensory or sympathetic nerves); (3) psychological conditions. Pay special attention to the medical history and to depression. Major depression is common, treatable, and potentially fatal (suicide).

TABLE 5-1 CHARACTERISTICS OF SOMATIC AND NEUROPATHIC PAIN

Somatic pain
Nociceptive stimulus usually evident
Usually well localized
Similar to other somatic pains in pt's experience
Relieved by anti-inflammatory or narcotic analgesics
Visceral pain
Most commonly activated by inflammation
Pain poorly localized and usually referred
Associated with diffuse discomfort, e.g., nausea, bloating
Relieved by narcotic analgesics
Neuropathic pain
No obvious nociceptive stimulus
Associated evidence of nerve damage, e.g., sensory impairment, weakness
Unusual, dissimilar from somatic pain, often shooting or electrical quality
Only partially relieved by narcotic analgesics; may respond to antidepressants or anticonvulsants

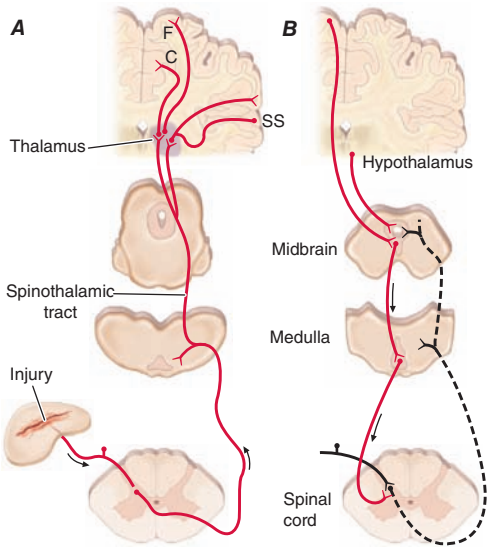


FIGURE 5-1 Pain transmission and modulatory pathways. **A.** Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). **B.** Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

PATHOPHYSIOLOGY: ORGANIZATION OF PAIN PATHWAYS

Pain-producing (nociceptive) sensory stimuli in skin and viscera activate peripheral nerve endings of primary afferent neurons, which synapse on second-order neurons in spinal cord or medulla (Fig. 5-1). These second-order neurons form crossed ascending pathways that reach the thalamus and project to the somatosensory cortex. Parallel ascending neurons, connecting with brainstem and thalamic nuclei, project to the limbic system and underlie the emotional aspect of pain. Pain transmission is regulated at the dorsal horn level by descending bulbospinal pathways that utilize serotonin, norepinephrine, and several neuropeptides as neurotransmitters.

Agents that modify pain perception may act by reducing tissue inflammation (NSAIDs, prostaglandin synthesis inhibitors), interfering with pain transmission (narcotics), or enhancing descending modulation (narcotics and antidepressants). Anticonvulsants (gabapentin, carbamazepine) may be effective for aberrant pain sensations arising from peripheral nerve injury.

TREATMENT PAIN (TABLE 5-2)

ACUTE SOMATIC PAIN

- Mild to moderate pain: Usually treated effectively with nonnarcotic analgesics, e.g., aspirin, acetaminophen, and NSAIDs, which inhibit cyclooxygenase (COX)

TABLE 5-2 DRUGS FOR RELIEF OF PAIN

Generic Name	Dose, mg	Interval	Comments
Nonnarcotic analgesics: usual doses and intervals			
Acetylsalicylic acid	650 PO	q4h	Enteric-coated preparations available
Acetaminophen	650 PO	q4h	Side effects uncommon
Ibuprofen	400 PO	q4–6h	Available without prescription
Naproxen	250–500 PO	q12h	Delayed effects may be due to long half-life
Fenoprofen	200 PO	q4–6h	Contraindicated in renal disease
Indomethacin	25–50 PO	q8h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q4–6h	Available for parenteral use
Celecoxib	100–200 PO	q12–24h	Useful for arthritis
Valdecoxib	10–20 PO	q12–24h	Removed from U.S. market in 2005
Generic Name	**Parenteral Dose, mg**	**PO Dose, mg**	**Comments**
Narcotic analgesics: usual doses and intervals			
Codeine	30–60 q4h	30–60 q4h	Nausea common
Oxycodone	—	5–10 q4–6h	Usually available with acetaminophen or aspirin
Morphine	5 q4h	30 q4h	
Morphine sustained release	—	15–60 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q4h	2–4 q4h	Shorter acting than morphine sulfate
Levorphanol	2 q6–8h	4 q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	5–10 q6–8h	5–20 q6–8h	Delayed sedation due to long half-life; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days

Meperidine	50–100 q3–4h	300 q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	—	1–2 q4h	Intranasal spray
Fentanyl	25–100 µg/h	—	72-h transdermal patch
Buprenorphine	5–20 µg/h		7-day transdermal patch
Buprenorphine	0.3 q6–8h		Parenteral administration
Tramadol	—	50–100 q4–6h	Mixed opioid/adrenergic action

	Uptake Blockade		Sedative	Anticholinergic	Orthostatic	Cardiac	Average Dose,	Range,
Generic Name	**5-HT**	**NE**	**Potency**	**Potency**	**Hypotension**	**Arrhythmia**	**mg/d**	**mg/d**
Antidepressants[a]								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60

Generic Name	**PO Dose, mg**	**Interval**	**Generic Name**	**PO Dose, mg**	**Interval**
Anticonvulsants and antiarrhythmics[a]					
Phenytoin	300	daily/qhs	Clonazepam	1	q6h
Carbamazepine	200–300	q6h	Gabapentin[b]	600–1200	q8h
Oxcarbazepine	300	bid	Pregabalin	150–600	bid

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.
[b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.
Abbreviations: 5-HT, serotonin; NE, norepinephrine.

and, except for acetaminophen, have anti-inflammatory actions, especially at high dosages. Particularly effective for headache and musculoskeletal pain.

- Parenteral NSAIDs: Ketorolac and diclofenac are sufficiently potent and rapid in onset to supplant opioids for many pts with acute severe pain.
- Narcotic analgesics in oral or parenteral form can be used for more severe pain. These are the most effective drugs available; the opioid antagonist naloxone should be readily available when narcotics are used in high doses or in unstable pts.
- Pt-controlled analgesia (PCA) permits infusion of a baseline dose plus self-administered boluses (activated by press of a button) as needed to control pain.

CHRONIC PAIN

- Develop an explicit treatment plan including specific and realistic goals for therapy, e.g., getting a good night's sleep, being able to go shopping, or returning to work.
- A multidisciplinary approach that utilizes medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve quality of life.
- Psychological evaluation is key; behaviorally based treatment paradigms are frequently helpful.
- Some pts may require referral to a pain clinic; for others, pharmacologic management alone can provide significant help.
- Tricyclic antidepressants are useful in management of chronic pain from many causes, including headache, diabetic neuropathy, postherpetic neuralgia, chronic low back pain, cancer, and central post-stroke pain.
- Anticonvulsants or antiarrhythmics benefit pts with neuropathic pain (e.g., diabetic neuropathy, trigeminal neuralgia).
- The long-term use of opioids is accepted for pain due to malignant disease, but is controversial for chronic pain of nonmalignant origin.

For a more detailed discussion, see Rathmell HP, Fields HL: Pain: Pathophysiology and Management, Chap. 18, p. 87, in HPIM-19.

6 Assessment of Nutritional Status

Stability of body weight requires that energy intake and expenditures are balanced over time. The major categories of energy output are resting energy expenditure (REE) and physical activity; minor sources include the energy cost of metabolizing food (thermic effect of food or specific dynamic action) and shivering thermogenesis. The average energy intake is about 2600 kcal/d for men and about 1800 kcal/d for women, though these estimates vary with age, body size, and activity level. Basal energy expenditure (BEE), measured in kcal/d, may be estimated by the Harris and Benedict formula (Fig. 6-1).

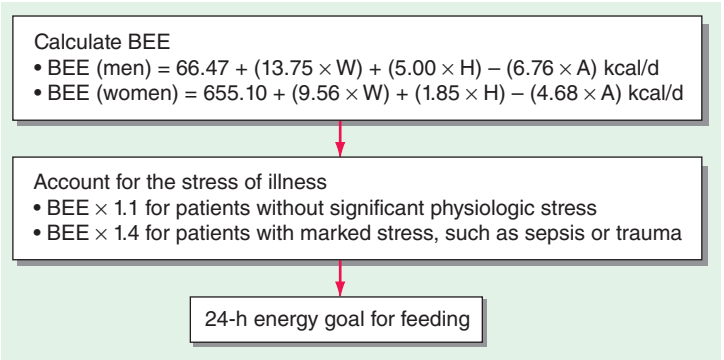


FIGURE 6-1 Basal energy expenditure (BEE) calculation in kcal/d, estimated by the Harris and Benedict formula. A, age in years; H, height in cm; W, Weight in kg.

Dietary reference intakes (DRIs) and recommended dietary allowances (RDAs) have been defined for many nutrients, including 9 essential amino acids, 4 fat-soluble and 10 water-soluble vitamins, several minerals, fatty acids, choline, and water (see Tables 95e-1 and 95e-2 in HPIM-19). The usual water requirements are 1.0–1.5 mL/kcal energy expenditure in adults, with adjustments for excessive losses. The RDA for protein is 0.6-g/kg ideal body weight, representing 10-15% of total caloric intake. Fat should constitute ≤30% of calories, and saturated fat should be <10% of calories. At least 55% of calories should be derived from carbohydrates.

MALNUTRITION

Malnutrition results from inadequate intake or abnormal GI assimilation of dietary calories, excessive energy expenditure, or altered metabolism of energy supplies by an intrinsic disease process.

Both outpatients and inpatients are at risk for malnutrition if they meet one or more of the following criteria:

- Unintentional loss of >10% of usual body weight in the preceding 3 months
- Body weight <90% of ideal for height (Table 6-1)
- Body mass index (BMI: weight/height^2 in kg/m^2) <18.5

Two forms of severe malnutrition can be seen: *marasmus*, which refers to generalized starvation that occurs in the setting of chronically decreased energy intake without systemic inflammation, and *kwashiorkor*, which refers to selective protein malnutrition due to decreased protein intake and catabolism in the setting of acute, life-threatening illnesses or chronic inflammatory disorders. Aggressive nutritional support is indicated in kwashiorkor to prevent infectious complications and poor wound healing.

Etiology

The major etiologies of malnutrition are starvation, stress from surgery or severe illness, and mixed mechanisms. Starvation results from decreased dietary intake (from poverty, chronic alcoholism, anorexia nervosa, fad diets, severe depression, neurodegenerative disorders, dementia, or strict vegetarianism; abdominal pain from intestinal ischemia or pancreatitis; or anorexia associated with AIDS, disseminated cancer, heart failure, or renal failure) or decreased assimilation of the diet (from pancreatic insufficiency; short bowel syndrome; celiac disease; or esophageal, gastric,

TABLE 6-1 IDEAL WEIGHT FOR HEIGHT

Men				Women			
Height[a]	Weight[a]	Height	Weight	Height	Weight	Height	Weight
145	51.9	166	64.0	140	44.9	161	56.9
146	52.4	167	64.6	141	45.4	162	57.6
147	52.9	168	65.2	142	45.9	163	58.3
148	53.5	169	65.9	143	46.4	164	58.9
149	54.0	170	66.6	144	47.0	165	59.5
150	54.5	171	67.3	145	47.5	166	60.1
151	55.0	172	68.0	146	48.0	167	60.7
152	55.6	173	68.7	147	48.6	168	61.4
153	56.1	174	69.4	148	49.2	169	62.1
154	56.6	175	70.1	149	49.8		
155	57.2	176	70.8	150	50.4		
156	57.9	177	71.6	151	51.0		
157	58.6	178	72.4	152	51.5		
158	59.3	179	73.3	153	52.0		
159	59.9	180	74.2	154	52.5		
160	60.5	181	75.0	155	53.1		
161	61.1	182	75.8	156	53.7		
162	61.7	183	76.5	157	54.3		
163	62.3	184	77.3	158	54.9		
164	62.9	185	78.1	159	55.5		
165	63.5	186	78.9	160	56.2		

[a]Values are expressed in cm for height and kg for weight. To obtain height in inches, divide by 2.54. To obtain weight in pounds, multiply by 2.2.
Source: Adapted from GL Blackburn et al: Nutritional and metabolic assessment of the hospitalized patient. *J Parenter Enteral Nutr* 1:11, 1977; with permission.

or intestinal obstruction). Contributors to physical stress include fever, acute trauma, major surgery, burns, acute sepsis, hyperthyroidism, and inflammation as occurs in pancreatitis, collagen vascular diseases, and chronic infectious diseases such as tuberculosis or AIDS opportunistic infections. Mixed mechanisms occur in AIDS, disseminated cancer, chronic obstructive pulmonary disease, chronic liver disease, Crohn's disease, ulcerative colitis, and renal failure.

Clinical Features

- *General:* weight loss, temporal and proximal muscle wasting, decreased skin-fold thickness
- *Skin, hair, and nails:* easily plucked hair (protein); sparse hair (protein, biotin, zinc); coiled hair, easy bruising, petechiae, and perifollicular hemorrhages (vit. C); "flaky paint" rash of lower extremities (zinc); hyperpigmentation of skin in exposed areas (niacin, tryptophan); spooning of nails (iron)
- *Eyes:* conjunctival pallor (anemia); night blindness, dryness, and Bitot spots (vit. A); ophthalmoplegia (thiamine)
- *Mouth and mucous membranes:* glossitis and/or cheilosis (riboflavin, niacin, vit. B_{12}, pyridoxine, folate), diminished taste (zinc), inflamed and bleeding gums (vit. C)

- *Neurologic:* disorientation (niacin, phosphorus); confabulation, cerebellar gait, or past pointing (thiamine); peripheral neuropathy (thiamine, pyridoxine, vit. E); lost vibratory and position sense (vit. B_{12})
- *Other:* edema (protein, thiamine), heart failure (thiamine, phosphorus), hepatomegaly (protein)

Laboratory findings in protein malnutrition include a low serum albumin, low total iron-binding capacity, and anergy to skin testing. Specific vitamin deficiencies also may be present.

For a more detailed discussion, see Dwyer J: Nutritional Requirements and Dietary Assessment, Chap. 95e; Russell RM and Suter PM: Vitamin and Trace Mineral Deficiency and Excess, Chap. 96e; and Heimberger DC: Malnutrition and Nutritional Assessment, Chap. 97, p. 459 in HPIM-19.

7 Enteral and Parenteral Nutrition

Nutritional support should be initiated in pts with malnutrition or in those at risk for malnutrition (e.g., conditions that preclude adequate oral feeding or pts in catabolic states, such as sepsis, burns, major surgery, or trauma). An approach for deciding when to use various types of specialized nutrition support (SNS) is summarized in Fig. 7-1.

Enteral therapy refers to feeding via the gut, using oral supplements or infusion of formulas via various feeding tubes (nasogastric, nasoduodenal, gastrostomy, jejunostomy, or combined gastrojejunostomy). *Parenteral therapy* refers to the infusion of nutrient solutions into the bloodstream via a peripherally inserted central catheter (PICC), a centrally inserted externalized catheter, or a centrally inserted tunneled catheter or subcutaneous port. When feasible, enteral nutrition is the preferred route because it sustains the digestive, absorptive, and immunologic functions of the GI tract, and because it minimizes the risk of fluid and electrolyte imbalance. Parenteral nutrition is often indicated in severe pancreatitis, necrotizing enterocolitis, prolonged ileus, and distal bowel obstruction.

ENTERAL NUTRITION

The components of a standard enteral formula are as follows:

- Caloric density: 1 kcal/mL
- Protein: ~14% cals; caseinates, soy, lactalbumin
- Fat: ~30% cals; corn, soy, safflower oils
- Carbohydrate: ~60% cals; hydrolyzed corn starch, maltodextrin, sucrose
- Recommended daily intake of all minerals and vitamins in ≥1500 kcal/d
- Osmolality (mosmol/kg): ~300

However, modification of the enteral formula may be required based on various clinical indications and/or associated disease states. After elevation of the head of the

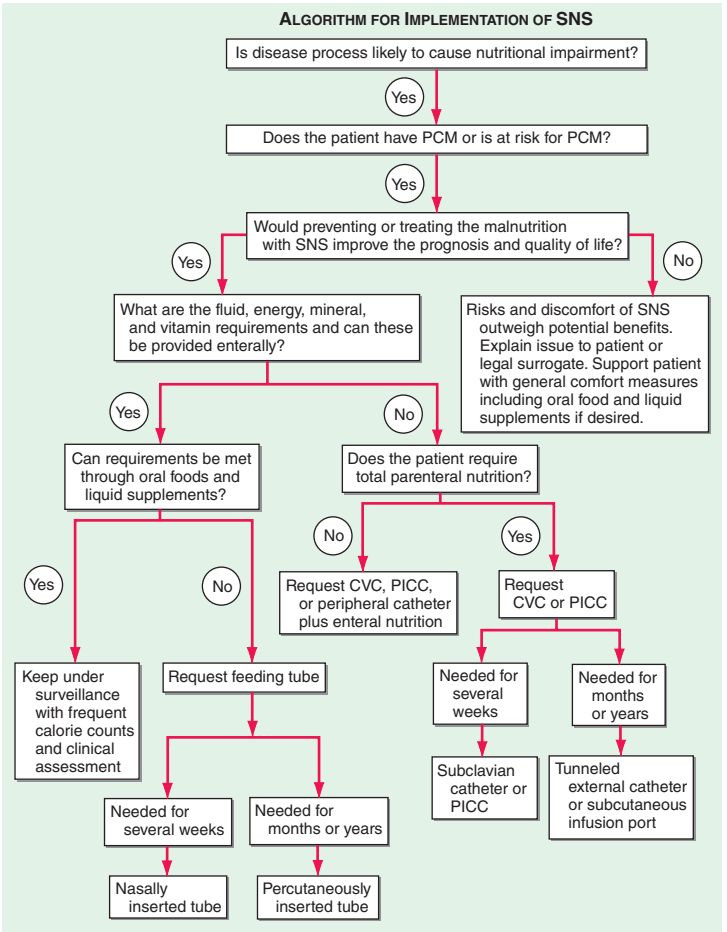


FIGURE 7-1 Decision-making for the implementation of specialized nutrition support (SNS). CVC, central venous catheter; PCM, protein-calorie malnutrition; PICC, peripherally inserted central catheter. *(Adapted from chapter in Harrison's Principles of Internal Medicine, 16e, by Lyn Howard, MD.)*

bed and confirmation of correct tube placement, continuous gastric infusion is initiated using a half-strength diet at a rate of 25–50 mL/h. This can be advanced to full strength as tolerated to meet the energy target. The major risks of enteral tube feeding are aspiration, diarrhea, electrolyte imbalance, warfarin resistance, sinusitis, and esophagitis.

PARENTERAL NUTRITION

The components of parenteral nutrition include adequate fluid (30-mL/kg body weight/24 h for adults, plus any abnormal loss); energy from glucose, amino acids, and lipid solutions; nutrients essential in severely ill pts, such as glutamine, nucleotides, and products of methionine metabolism; and electrolytes, vitamins, and minerals. The risks of parenteral therapy include mechanical complications from insertion of the infusion catheter, catheter sepsis, fluid overload, hyperglycemia, hypophosphatemia, hypokalemia, acid-base and electrolyte imbalance, cholestasis, metabolic bone disease, and micronutrient deficiencies.

TABLE 7-1 THERAPY FOR COMMON VITAMIN AND MINERAL DEFICIENCIES

Nutrient	Therapy
Vitamin A[a,b,c]	60 mg PO, repeated 1 and 14 days later if ocular changes; 30 mg for ages 6–11 months
	15 mg PO qd × 1 month if chronic malabsorption
Vitamin C	200 mg PO qd
Vitamin D[a,d]	Encourage sun exposure if possible
	50,000 units PO once weekly for 4–8 weeks, then 400–800 units PO qd
	Substantially higher dose may be required in chronic malabsorption
Folic acid	0.4 mg PO qd prenatally and during pregnancy
	Confirm normal B_{12} levels in pts with megaloblastic anemia
Vitamin B_{12}	1000 µg IM x 6 doses to replenish stores, then 1000 µg IM monthly
Vitamin E[a]	800–1200 mg PO qd
Vitamin K[a]	10 mg IV × 1
	1–2 mg PO qd or 1–2 mg IV weekly in chronic malabsorption
Thiamine[b]	300 mg IV qd × 3 days, followed by 10 mg PO qd until recovery
Niacin	100–200 mg PO tid for 5 days
Pyridoxine	50 mg PO qd, 100–200 mg PO qd if deficiency related to medications
Zinc[b,c]	60 mg PO bid

[a]Associated with fat malabsorption.
[b]Associated with chronic alcoholism; always replete thiamine before carbohydrates in alcoholics to avoid precipitation of acute thiamine deficiency.
[c]Associated with protein-calorie malnutrition.
[d]Therapy must be monitored by serum calcium measurements.

The following parameters should be monitored in all pts receiving supplemental nutrition, whether enteral or parenteral:

- Fluid balance (weight, intake vs. output)
- Glucose, electrolytes, BUN (daily until stable, then 2× per week)
- Serum creatinine, albumin, phosphorus, calcium, magnesium, Hb/Hct, WBC (baseline, then 2× per week)
- International normalized ratio (INR) (baseline, then weekly)
- Micronutrient tests as indicated

SPECIFIC MICRONUTRIENT DEFICIENCY

Appropriate therapies for micronutrient deficiencies are outlined in Table 7-1.



For a more detailed discussion, see Russell RM and Suter PM: Vitamin and Trace Mineral Deficiency and Excess, Chap. 96e; and Bistrian BR, Hoffer LJ, and Driscoll DF: Enteral and Parenteral Nutrition Therapy, Chap. 98e, HPIM-19.

8 Transfusion and Pheresis Therapy

TRANSFUSIONS

WHOLE BLOOD TRANSFUSION

Indicated when acute blood loss is sufficient to produce hypovolemia, whole blood provides both oxygen-carrying capacity and volume expansion. In acute blood loss, hematocrit may not accurately reflect degree of blood loss for 48 h until fluid shifts occur.

RED BLOOD CELL TRANSFUSION

Indicated for symptomatic anemia unresponsive to specific therapy or requiring urgent correction. Packed red blood cell (RBC) transfusions may be indicated in pts who are symptomatic from cardiovascular or pulmonary disease when Hb is between 70 and 90 g/L (7 and 9 g/dL). Transfusion is usually necessary when Hb is <70 g/L (<7 g/dL). One unit of packed RBCs raises the Hb by ~10 g/L (1 g/dL). In the setting of acute hemorrhage, packed RBCs, fresh frozen plasma (FFP), and platelets in an approximate ratio of 3:1:10 units are an adequate replacement for whole blood. Removal of leukocytes reduces risk of alloimmunization and transmission of cytomegalovirus. Washing to remove donor plasma reduces risk of allergic reactions. Irradiation prevents graft-versus-host disease in immunocompromised recipients by killing alloreactive donor lymphocytes. Avoid related donors.

Other Indications

(1) *Hypertransfusion therapy* to block production of defective cells, e.g., thalassemia, sickle cell anemia; (2) *exchange transfusion*—hemolytic disease of newborn, sickle cell crisis; (3) *transplant recipients*—decreases rejection of cadaveric kidney transplants.

Complications (Table 8-1)

(1) *Transfusion reaction*—immediate or delayed, seen in 1–4% of transfusions; IgA-deficient pts at particular risk for severe reaction; (2) *infection*—bacterial (rare); hepatitis C, 1 in 1,800,000 transfusions; HIV transmission, 1 in 2,300,000; (3) *circulatory overload*; (4) *iron overload*—each unit contains 200- to 250-mg iron; hemochromatosis may develop after 100 U of RBCs (less in children), in absence of blood loss; iron chelation therapy with deferoxamine indicated; (5) *graft-versus-host disease*; (6) *alloimmunization*.

AUTOLOGOUS TRANSFUSION

Use of pt's own stored blood avoids hazards of donor blood; also useful in pts with multiple RBC antibodies. Pace of autologous donation may be accelerated using erythropoietin (50–150 U/kg SC three times a week) in the setting of normal iron stores.

RED CELL EXCHANGE

The main goal of red cell exchange transfusions is to remove sickle cells and replace them with normal red cells to interrupt the vicious cycle of sickling, stasis, vasoocclusion, and hypoxemia that propagate sickle cell crises. The usual target is 70% hemoglobin A.

TABLE 8-1 RISKS OF TRANSFUSION COMPLICATIONS

	Frequency, Episodes: Unit
Reactions	
Febrile (FNHTR)	1–4:100
Allergic	1–4:100
Delayed hemolytic	1:1000
TRALI	1:5000
Acute hemolytic	1:12,000
Fatal hemolytic	1:100,000
Anaphylactic	1:150,000
Infections[a]	
Hepatitis B	1:220,000
Hepatitis C	1:1,800,000
HIV-1, HIV-2	1:2,300,000
HTLV-I, HTLV-II	1:2,993,000
Malaria	1:4,000,000
Other complications	
RBC allosensitization	1:100
HLA allosensitization	1:10
Graft-versus-host disease	Rare

[a]Infectious agents rarely associated with transfusion, theoretically possible, or of unknown risk include West Nile virus, hepatitis A virus, parvovirus B-19, *Babesia microti* (babesiosis), *Borrelia burgdorferi* (Lyme disease), *Anaplasma phagocytophilum* (human granulocytic ehrlichiosis), *Trypanosoma cruzi* (Chagas' disease), *Treponema pallidum*, and human herpesvirus 8.

Abbreviations: FNHTR, febrile nonhemolytic transfusion reaction; HLA, human leukocyte antigen; HTLV, human T lymphotropic virus; TRALI, transfusion-related acute lung injury.

PLATELET TRANSFUSION

Prophylactic transfusions usually reserved for platelet count <10,000/μL (<20,000/μL in acute leukemia). One unit elevates the count by about 10,000/μL if no platelet antibodies are present as a result of prior transfusions. Efficacy assessed by 1- and 24-h posttransfusion platelet counts. HLA-matched single-donor platelets may be required in pts with platelet alloantibodies.

TRANSFUSION OF PLASMA COMPONENTS

Fresh frozen plasma (FFP) is a source of coagulation factors, fibrinogen, antithrombin, and proteins C and S. It is used to correct coagulation factor deficiencies, rapidly reverse warfarin effects, and treat thrombotic thrombocytopenic purpura (TTP). Cryoprecipitate is a source of fibrinogen, factor VIII, and von Willebrand factor; it may be used when recombinant factor VIII or factor VIII concentrates are not available.

THERAPEUTIC HEMAPHERESIS

Hemapheresis is removal of a cellular or plasma constituent of blood; the specific procedure is referred to by the blood fraction removed.

LEUKAPHERESIS

Removal of WBCs; most often used in acute leukemia, esp. acute myeloid leukemia (AML) in cases complicated by marked elevation (>100,000/μL) of the peripheral blast count, to lower risk of leukostasis (blast-mediated vasoocclusive events resulting in central nervous system or pulmonary infarction, hemorrhage). Leukapheresis is replacing bone marrow aspiration to obtain hematopoietic stem cells. After treatment with a chemotherapeutic agent and granulocyte-macrophage colony-stimulating factor, hematopoietic stem cells are mobilized from marrow to the peripheral blood; such cells are leukapheresed and then used for hematopoietic reconstitution after high-dose myeloablative therapy. A third emerging medical use of leukapheresis is to harvest lymphocytes to use as adoptive immunotherapy.

PLATELETPHERESIS

Used in some pts with thrombocytosis associated with myeloproliferative disorders with bleeding and/or thrombotic complications. Other treatments are generally used first. Plateletpheresis also enhances platelet yield from blood donors.

PLASMAPHERESIS

Indications

(1) *Hyperviscosity states*—e.g., Waldenström's macroglobulinemia; (2) *TTP*; (3) *immune-complex* and *autoantibody disorders*—e.g., Goodpasture's syndrome, rapidly progressive glomerulonephritis, myasthenia gravis; possibly Guillain-Barré, systemic lupus erythematosus, idiopathic thrombocytopenic purpura; (4) cold agglutinin disease, cryoglobulinemia. In plasma exchange, abnormal proteins are removed and normal plasma or plasma components are replaced; useful in TTP to remove anti-ADAMTS13 antibody and provide normal ADAMTS13 levels.

For a more detailed discussion, see Dzieczkowski JS, Anderson KC: Transfusion Biology and Therapy, Chap. 138e, in HPIM-19.

9 Palliative and End-of-Life Care

In 2014, 2,596,993 people died in the United States; death rates are declining. Nearly three-fourth of all deaths occur in people >65 years old. Heart disease and cancer are the two leading causes of death and together account for nearly half of all deaths. About 70% of deaths occur in people who have a condition that is known to be leading to their death; thus, planning for terminal care is relevant and important. An increasing fraction of deaths are occurring in hospices or at home rather than in the hospital.

Optimal care depends on a comprehensive assessment of pt needs in all four domains affected by illness: physical, psychological, social, and spiritual. A variety of assessment tools are available to assist in the process.

Communication and continuous assessment of management goals are key components to addressing end-of-life care. Physicians must be clear about the likely

outcome of the illness(es) and provide an anticipated schedule with goals and landmarks in the care process. When the goals of care have changed from cure to palliation, that transition must be clearly explained and defended. Seven steps are involved in establishing goals:

1. Ensure that the medical information is as complete as possible and understood by all relevant parties.
2. Explore the pt's goals while making sure the goals are achievable.
3. Explain the options.
4. Show empathy as the pt and the family adjust to changing expectations.
5. Make a plan with realistic goals.
6. Follow-through with the plan.
7. Review and revise the plan periodically as the pt's situation changes.

ADVANCE DIRECTIVES

About 70% of pts lack decision-making capacity in their final days. Advance directives define ahead of time the level of intervention the pt is willing to accept. Two types of legal documents can be used: the advance directive, in which specific instructions from the pt may be made known; and the durable attorney for health care, in which a person is designated as having the pt's authority to make health decisions on pt's behalf. Forms are available free of charge from the National Hospice and Palliative Care Organization (www.nhpco.org). Physicians also should complete these forms for themselves.

PHYSICAL SYMPTOMS AND THEIR MANAGEMENT

The most common physical and psychological symptoms among terminally ill pts are shown in Table 9-1. Studies of pts with advanced cancer have shown that pts experience an average of 11.5 symptoms.

TABLE 9-1 COMMON PHYSICAL AND PSYCHOLOGICAL SYMPTOMS OF TERMINALLY ILL PATIENTS

Physical Symptoms	Psychological Symptoms
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	Loss of libido
Swelling of arms or legs	
Itching	
Diarrhea	
Dysphagia	
Dizziness	
Fecal and urinary incontinence	
Numbness/tingling in hands/feet	

Pain

Pain is noted in 36–90% of terminally ill pts. The various types of pain and their management are discussed in Chap. 5.

Constipation

Constipation is noted in up to 87% of terminally ill pts. Medications that commonly contribute to constipation include opioids used to manage pain and dyspnea and tricyclic antidepressants with their anticholinergic effects. Inactivity, poor diet, and hypercalcemia may contribute. GI tract obstruction also may play a role in some settings.

Interventions Improved physical activity (if possible), adequate hydration; opioid effects can be antagonized by the μ-opioid receptor blocker methylnaltrexone (8–12 mg SC daily); rule out surgically correctable obstruction; laxatives and stool softeners (Table 9-2).

Nausea

Up to 70% of pts with advanced cancer have nausea. Nausea may result from uremia, liver failure, hypercalcemia, bowel obstruction, severe constipation, infection, gastroesophageal reflux disease, vestibular disease, brain metastases, medications (cancer chemotherapy, antibiotics, nonsteroidal anti-inflammatory drugs, opioids, proton pump inhibitors), and radiation therapy.

Interventions Treatment should be tailored to the cause. Offending medications should be stopped. Underlying conditions should be alleviated, if possible. If

TABLE 9-2 MEDICATIONS FOR THE MANAGEMENT OF CONSTIPATION

Intervention	Dose	Comment
Stimulant laxatives		These agents directly stimulate peristalsis and may reduce colonic absorption of water. Work in 6–12 h.
Prune juice	120–240 mL/d	
Senna (Senokot)	2–8 tablets PO bid	
Bisacodyl	5–15 mg/d PO, PR	
Osmotic laxatives		These agents are not absorbed. They attract and retain water in the gastrointestinal tract.
Lactulose	15–30 mL PO q4–8h	Lactulose may cause flatulence and bloating.
Magnesium hydroxide (Milk of Magnesia)	15–30 mL/d PO	Lactulose works in 1 day, magnesium products in 6 h.
Magnesium citrate	125–250 mL/d PO	
Stool softeners		These agents work by increasing water secretion and as detergents, increasing water penetration into the stool. Work in 1–3 days.
Sodium docusate (Colace)	300–600 mg/d PO	
Calcium docusate	300–600 mg/d PO	
Suppositories and enemas		
Bisacodyl	10–15 PR qd	
Sodium phosphate enema	PR qd	Fixed dose, 4.5 oz, Fleet's.

decreased bowel motility is suspected, metoclopramide may help. Nausea from cancer chemotherapy agents can generally be prevented with glucocorticoids and serotonin receptor blockers like ondansetron or dolasetron. Aprepitant is useful in controlling nausea from highly emetogenic agents like cisplatin. Vestibular nausea may respond to antihistamines (meclizine) or anticholinergics (scopolamine). Anticipatory nausea may be prevented with a benzodiazepine such as lorazepam. Haloperidol is sometimes useful when the nausea does not have a single specific cause.

Dyspnea

Up to 75% of dying pts experience dyspnea. Dyspnea exerts perhaps the greatest adverse effect on the pt, often even more distressing than pain. It may be caused by parenchymal lung disease, infection, effusions, pulmonary emboli, pulmonary edema, asthma, or compressed airway. While many of the causes may be treated, often the underlying cause cannot be reversed.

Interventions Underlying causes should be reversed, where possible, as long as the intervention is not more unpleasant (e.g., repeated thoracenteses) than the dyspnea. Most often the treatment is symptomatic (Table 9-3).

Fatigue

Fatigue is nearly a universal symptom in terminally ill pts. It is often a direct consequence of the disease process (and the cytokines produced in response to that process) and may be complicated by inanition, dehydration, anemia, infection, hypothyroidism, and drug effects. Depression may also contribute to fatigue. Functional assessments include the Karnofsky performance status or the Eastern Cooperative Oncology Group system based on how much time the pt spends in bed each day: 0, normal activity; 1, symptomatic without being bedridden; 2, in bed <50% of the day; 3, in bed >50% of the day; 4, bedbound.

TABLE 9-3 MEDICATIONS FOR THE MANAGEMENT OF DYSPNEA

Intervention	Dose	Comments
Weak opioids		For pts with mild dyspnea
Codeine (or codeine with 325-mg acetaminophen)	30 mg PO q4h	For opioid-naïve pts
Hydrocodone	5 mg PO q4h	
Strong opioids		For opioid-naïve pts with moderate to severe dyspnea
Morphine	5–10 mg PO q4h 30–50% of baseline opioid dose q4h	For pts already taking opioids for pain or other symptoms
Oxycodone	5–10 mg PO q4h	
Hydromorphone	1–2 mg PO q4h	
Anxiolytics		Give a dose every hour until the pt is relaxed, then provide a dose for maintenance
Lorazepam	0.5–2.0 mg PO/SL/IV qh then q4–6h	
Clonazepam	0.25–2.0 mg PO q12h	
Midazolam	0.5 mg IV q15min	

Interventions Modest exercise and physical therapy may reduce muscle wasting and depression and improve mood; discontinue medications that worsen fatigue, if possible; glucocorticoids may increase energy and enhance mood; dextroamphetamine (5–10 mg/d) or methylphenidate (2.5–5 mg/d) in the morning may enhance energy levels but should be avoided at night because they may produce insomnia; modafinil and L-carnitine have shown some promise.

Depression

Up to 75% of terminally ill pts experience depression. The inexperienced physician may feel that depression is an appropriate response to terminal illness; however, in a substantial fraction of pts the depression is more intense and disabling than usual. Pts with a previous history of depression are at greater risk. A number of treatable conditions can cause depression-like symptoms including hypothyroidism, Cushing's syndrome, electrolyte abnormalities (e.g., hypercalcemia), and drugs including dopamine blockers, interferon, tamoxifen, interleukin 2, vincristine, and glucocorticoids.

Interventions Dextroamphetamine or methylphenidate (see above); serotonin reuptake inhibitors such as fluoxetine, paroxetine, and citalopram; modafinil 100 mg/d; pemoline 18.75 mg in the A.M. and at noon.

Delirium

Delirium is a global cerebral dysfunction associated with altered cognition and consciousness; it is frequently preceded by anxiety. Unlike dementia, it is of sudden onset, is characterized by fluctuating consciousness and inattention, and may be reversible. It is generally manifested in the hours before death. It may be caused by metabolic encephalopathy in renal or liver failure, hypoxemia, infection, hypercalcemia, paraneoplastic syndromes, dehydration, constipation, urinary retention, and central nervous system spread of cancer. It is also a common medication side effect; offending agents include those commonly used in dying pts including opioids, glucocorticoids, anticholinergics, antihistamines, antiemetics, and benzodiazepines. Early recognition is key because the pt should be encouraged to use the periods of lucidity for final communication with loved ones. Day-night reversal with changes in mentation may be an early sign.

Interventions Stop any and all unnecessary medications that may have this side effect; provide a calendar, clock, newspaper, or other orienting signals; gently correct hallucinations or cognitive mistakes; pharmacologic interventions are shown in Table 9-4.

TABLE 9-4 MEDICATIONS FOR THE MANAGEMENT OF DELIRIUM

Interventions	Dose
Neuroleptics	
Haloperidol	0.5–5 mg q2–12h, PO/IV/SC/IM
Thioridazine	10–75 mg q4–8h, PO
Chlorpromazine	12.5–50 mg q4–12h, PO/IV/IM
Atypical neuroleptics	
Olanzapine	2.5–5 mg qd or bid, PO
Risperidone	1–3 mg q12h, PO
Quetiapine	50 mg qd, PO
Anxiolytics	
Lorazepam	0.5–2 mg q1–4h, PO/IV/IM
Midazolam	1–5 mg/h continuous infusion, IV/SC
Anesthetics	
Propofol	0.3–2.0 mg/h continuous infusion, IV

CARE DURING THE LAST HOURS

The clinical course of a dying pt may largely be predictable. Figure 9-1 shows common and uncommon changes during the last days of life. Informing families that these changes might occur can help minimize the distress that they cause. In particular, the physician needs to be sensitive to the sense of guilt and helplessness that family members feel. They should be reassured that the illness is taking its course and their care of the pt is not at fault in any way. The pt stops eating because they are dying; they are not dying because they have stopped eating. Families and caregivers should be encouraged to communicate directly with the dying pt whether or not the pt is unconscious. Holding the pt's hand may be a source of comfort to both the pt and the family member/caregiver. Table 9-5 provides a listing of some changes in the pt's condition in the final hours and advice on how to manage the changes.

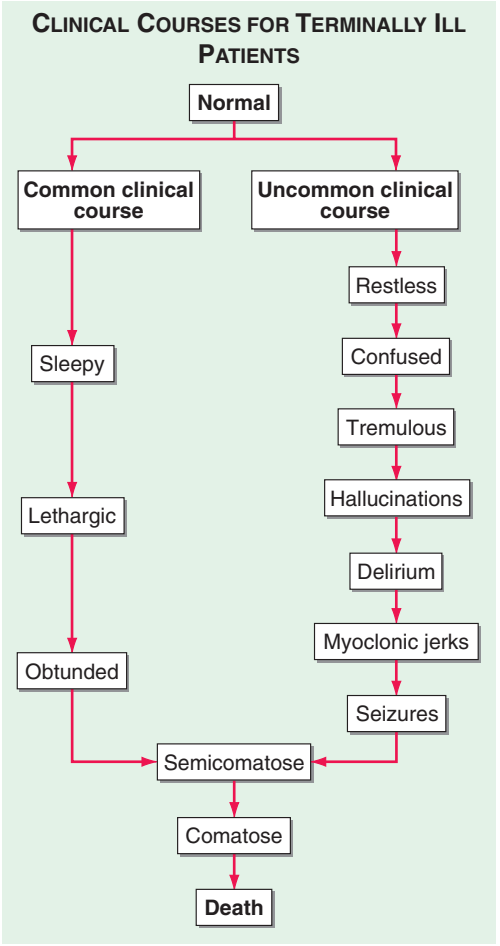


FIGURE 9-1 Common and uncommon clinical courses in the last days of terminally ill pts. *(Adapted from FD Ferris et al: Module 4: Palliative care, in Comprehensive Guide for the Care of Persons with HIV Disease. Toronto: Mt. Sinai Hospital and Casey Hospice, 1995.)*

TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS

Changes in the Patient's Condition	Potential Complication	Family's Possible Reaction and Concern	Advice and Intervention
Profound fatigue	Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain	Pt is lazy and giving up.	Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted. Use an air mattress if necessary.
Anorexia	None	Pt is giving up; pt will suffer from hunger and will starve to death.	Reassure family and caregivers that the pt is not eating because he or she is dying; not eating at the end of life does not cause suffering or death. Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life.
Dehydration	Dry mucosal membranes (see below)	Pt will suffer from thirst and die of dehydration.	Reassure family and caregivers that dehydration at the end of life does not cause suffering because pts lose consciousness before any symptom distress. IV hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong dying process.
Dysphagia	Inability to swallow oral medications needed for palliative care		Do not force oral intake. Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives. If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration.

(*Continued*)

TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS (*CONTINUED*)

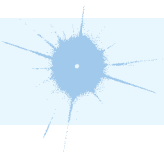
Changes in the Patient's Condition	Potential Complication	Family's Possible Reaction and Concern	Advice and Intervention
"Death rattle"—noisy breathing		Pt is choking and suffocating.	Reassure the family and caregivers that this is caused by secretions in the oropharynx and the pt is not choking. Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d). Reposition pt to permit drainage of secretions. Do not suction. Suction can cause pt and family discomfort and is usually ineffective.
Apnea, Cheyne-Stokes respirations, dyspnea		Pt is suffocating.	Reassure family and caregivers that unconscious pts do not experience suffocation or air hunger. Apneic episodes are frequently a premorbid change. Opioids or anxiolytics may be used for dyspnea. Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process.
Urinary or fecal incontinence	Skin breakdown if days until death Potential transmission of infectious agents to caregivers	Pt is dirty, malodorous, and physically repellent.	Remind family and caregivers to use universal precautions. Frequent changes of bedclothes and bedding. Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output.

(*Continued*)

TABLE 9-5 MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS (*CONTINUED*)

Changes in the Patient's Condition	Potential Complication	Family's Possible Reaction and Concern	Advice and Intervention
Agitation or delirium	Day/night reversal	Pt is in horrible pain and going to have a horrible death.	Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain.
	Hurt self or caregivers		Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modify medications.
			Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam.
Dry mucosal membranes	Cracked lips, mouth sores, and candidiasis can also cause pain.	Pt may be malodorous, physically repellent.	Use baking soda mouthwash or saliva preparation q15–30min.
	Odor		Use topical nystatin for candidiasis.
			Coat lips and nasal mucosa with petroleum jelly q60–90min.
			Use ophthalmic lubricants q4h or artificial tears q30min.

Additional resources for managing terminally ill pts may be found at the following websites: www.epec.net, www.eperc.mcw.edu, www.capc.org, and www.nhpco.org.



For a more detailed discussion, see Emanuel EJ: Palliative and End-of-Life Care, Chap. 10, p. 55, in HPIM-19.

10 Cardiovascular Collapse and Sudden Death

Unexpected cardiovascular collapse and death most often result from ventricular fibrillation in pts with acute or chronic atherosclerotic coronary artery disease. Other common etiologies are listed in Table 10-1. Arrhythmic causes may be provoked by electrolyte disorders (primarily hypokalemia), hypoxemia, acidosis, or massive sympathetic discharge, as may occur in CNS injury. Immediate institution of cardiopulmonary resuscitation (CPR) followed by advanced life support measures (see below) is mandatory. Ventricular fibrillation, or asystole, without institution of CPR within 4–6 min is usually fatal.

MANAGEMENT OF CARDIAC ARREST

Basic life support (BLS) must commence immediately (Fig. 10-1):

1. Phone emergency line (e.g., 911); retrieve automated external defibrillator (AED) if quickly available.
2. If respiratory stridor is present, assess for aspiration of a foreign body and perform Heimlich maneuver.

TABLE 10-1 CARDIAC ARREST AND SUDDEN CARDIAC DEATH

Structural Associations and Causes

1. Coronary heart disease (chronic, or acute coronary syndromes)
2. Myocardial hypertrophy (e.g., hypertrophic cardiomyopathy)
3. Dilated cardiomyopathy
4. Inflammatory (e.g., myocarditis) and infiltrative disorders
5. Valvular heart diseases
6. Electrophysiologic abnormalities (e.g., Wolff-Parkinson-White syndrome)
7. Inherited disorders associated with electrophysiological abnormalities (e.g., congenital long QT syndromes, right ventricular dysplasia, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia)

Functional Contributing Factors

1. Transient ischemia
2. Low cardiac output states (heart failure, shock)
3. Systemic metabolic abnormalities
   a. Electrolyte imbalance (e.g., hypokalemia)
   b. Hypoxemia, acidosis
4. Neurologic disturbances (e.g., CNS injury)
5. Toxic responses
   a. Proarrhythmic drug effects
   b. Cardiac toxins (e.g., cocaine, digitalis intoxication)

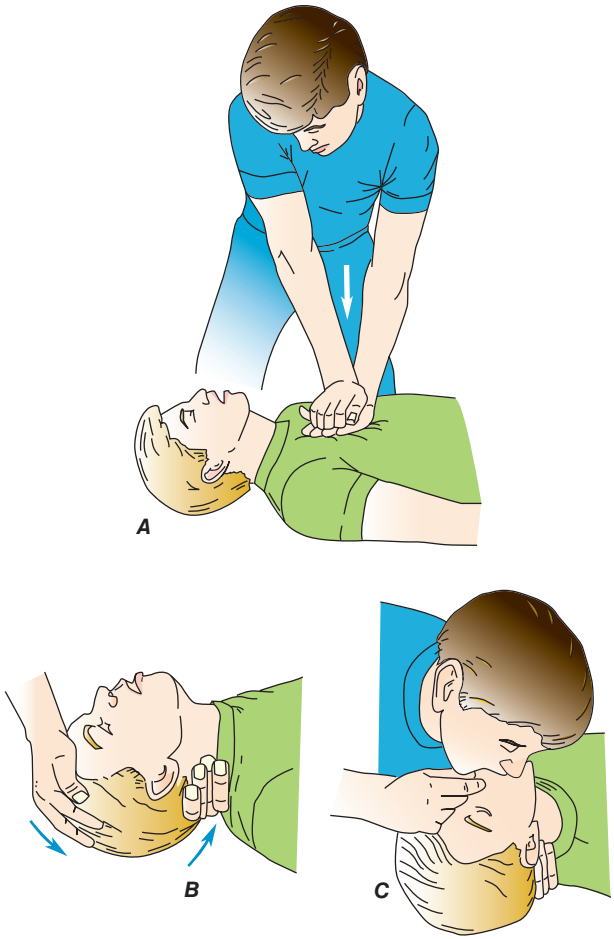


FIGURE 10-1 Major steps in cardiopulmonary resuscitation. **A.** Begin cardiac compressions at 100 compressions/min. **B.** Confirm that victim has an open airway. **C.** Trained rescuers begin ventilation if advanced life support equipment is not available (pocket mask preferred if available). *(Modified from J Henderson, Emergency Medical Guide, 4th ed, New York, McGraw-Hill, 1978.)*

3. Perform chest compressions (depressing sternum 4–5 cm) at rate of 100 per min without interruption. A second rescuer should attach and utilize AED if available.
4. If second *trained* rescuer available, tilt pt's head backward, lift chin, and begin rescue breathing (pocket mask is preferable to mouth-to-mouth respiration to prevent transmission of infection), while chest compressions continue. The lungs should be inflated twice in rapid succession for every 30 chest compressions. For *untrained* lay rescuers, chest compression only, without ventilation, is recommended until advanced life support capability arrives.
5. As soon as resuscitation equipment is available, begin **advanced life support** with continued chest compressions and ventilation. Although performed as

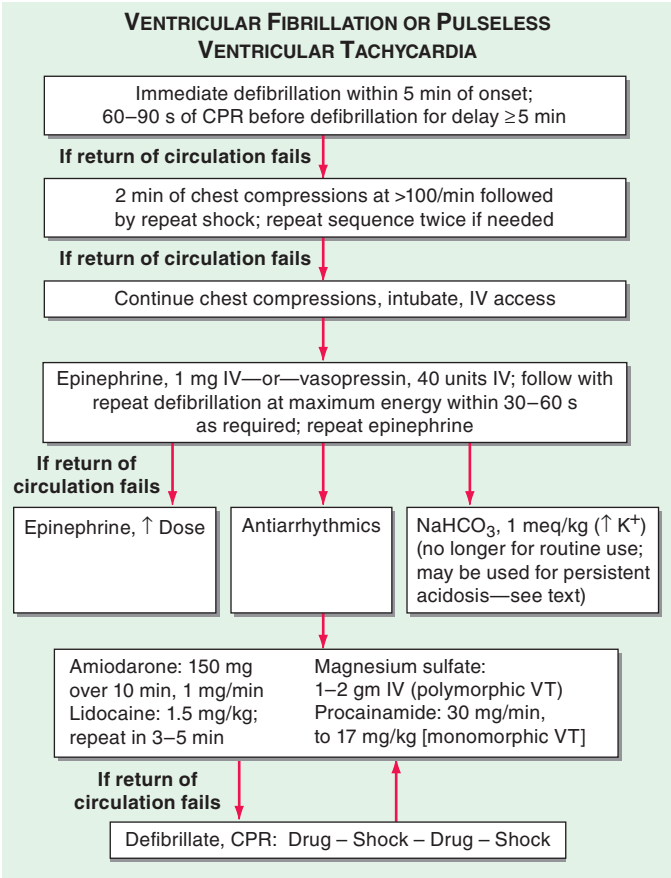


FIGURE 10-2 Management of cardiac arrest. The algorithm of ventricular fibrillation or hypotensive ventricular tachycardia begins with defibrillation attempts, separated by 2 min of chest compressions. If that fails, it is followed by epinephrine or vasopressin (intravenous or intraosseous) and then antiarrhythmic drugs. CPR, cardiopulmonary resuscitation; VT, ventricular tachycardia. *(Modified from Myerburg RJ, Castellanos A. Chap. 327, HPIM-19.)*

simultaneously as possible, defibrillation (150–200 J biphasic, or 360 J monophasic) takes highest priority (Fig. 10-2), followed by placement of IV access and intubation (if pt is less than fully conscious). One hundred percent O_2 should be administered by endotracheal tube or, if rapid intubation cannot be accomplished, by bag-valve-mask device. Once an advanced airway is placed, ventilate at rate of 1 breath every 6–8 s without interrupting chest compressions. Use quantitative capnography to confirm and monitor appropriate endotracheal tube placement.

6. Initial IV access should be through the antecubital vein, but if drug administration is ineffective, an intraosseous or central line (internal jugular or subclavian) should be placed. IV $NaHCO_3$ should be administered only if there is persistent

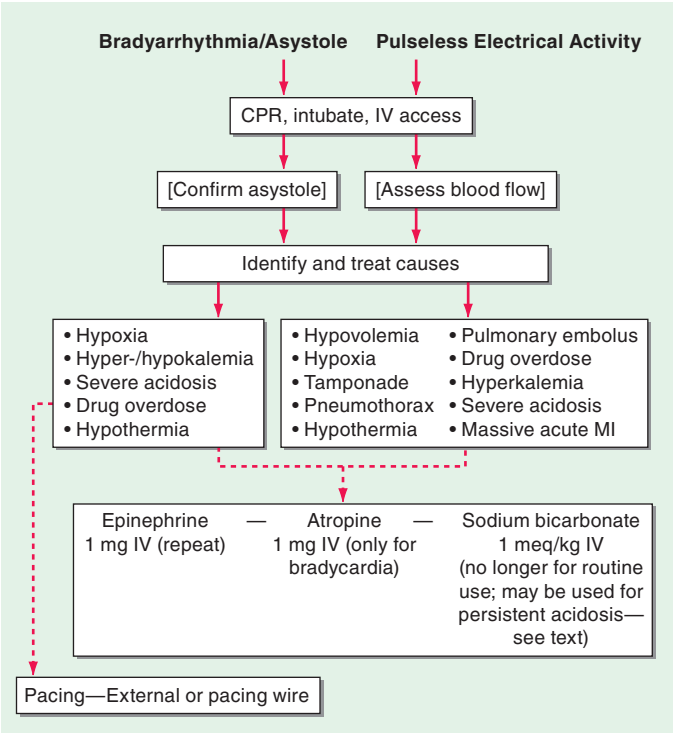


FIGURE 10-3 The algorithms for bradyarrhythmia/asystole (left) or pulseless electrical activity (right) are dominated first by continued life support and a search for reversible causes. CPR, cardiopulmonary resuscitation; MI, myocardial infarction. *(Modified from Myerburg RJ, Castellanos A. Chap. 327, HPIM-19.)*

severe acidosis (pH <7.15) despite adequate ventilation. Calcium is not routinely administered but should be given to pts with known hypocalcemia, those who have received toxic doses of calcium channel antagonists, or if acute hyperkalemia is thought to be the triggering event for resistant ventricular fibrillation.

7. The approach to cardiovascular collapse caused by bradyarrhythmias, asystole, or pulseless electrical activity is shown in Fig. 10-3.
8. Therapeutic hypothermia (cooling to 32–34°C [89.6–93.2°F] for 12–24 h) should be considered for unconscious survivors of cardiac arrest.

FOLLOW-UP

If cardiac arrest resulted from ventricular fibrillation in initial hours of an acute MI, follow-up is standard post-MI care (Chap. 119). For other survivors of a ventricular fibrillation arrest, further assessment, including evaluation of coronary anatomy, and left ventricular function, is typically recommended. In absence of a transient or reversible cause, placement of an implantable cardioverter defibrillator is usually indicated.

For a more detailed discussion, see Myerburg RJ, Castellanos A: Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death, Chap. 327, p. 1764, in HPIM-19.

11 Shock

DEFINITION

Condition of severe impairment of tissue perfusion leading to cellular injury and dysfunction. Rapid recognition and treatment are essential to prevent irreversible organ damage and death. Common causes are listed in Table 11-1.

CLINICAL MANIFESTATIONS

- Hypotension (mean arterial bp <60 mmHg), tachycardia, tachypnea, pallor, restlessness, and altered sensorium.
- Signs of intense peripheral vasoconstriction, with weak pulses and cold clammy extremities. In distributive (e.g., septic) shock, vasodilation predominates and extremities are warm.
- Oliguria (<20 mL/h) and metabolic acidosis common.

TABLE 11-1 CATEGORIES OF SHOCK

Hypovolemic shock
Hemorrhage
Intravascular volume depletion (e.g., vomiting, diarrhea, ketoacidosis)
Internal sequestration (ascites, pancreatitis, intestinal obstruction)
Cardiogenic shock
Myopathic (acute MI, fulminant myocarditis)
Mechanical (e.g., acute mitral regurgitation, ventricular septal defect, severe aortic stenosis, aortic dissection with aortic insufficiency)
Arrhythmic
Extracardiac obstructive shock
Pericardial tamponade
Massive pulmonary embolism
Tension pneumothorax
Distributive shock (profound decrease in systemic vascular tone)
Sepsis
Toxic overdoses
Anaphylaxis
Neurogenic (e.g., spinal cord injury)
Endocrinologic (Addison's disease, myxedema)

- Acute lung injury and acute respiratory distress syndrome (ARDS; see Chap. 14) with noncardiogenic pulmonary edema, hypoxemia, and diffuse pulmonary infiltrates.

APPROACH TO THE PATIENT: Shock

Obtain history for underlying causes, including cardiac disease (coronary disease, heart failure, pericardial disease), recent fever or infection leading to sepsis, drug effects (e.g., excess diuretics or antihypertensives), conditions leading to pulmonary embolism (Chap. 133), and potential sources of bleeding.

PHYSICAL EXAMINATION

Jugular veins are flat in oligemic or distributive (septic) shock; jugular venous distention (JVD) suggests cardiogenic shock; JVD in presence of paradoxical pulse (Chap. 110) may reflect cardiac tamponade (Chap. 116). Check for asymmetry of pulses (aortic dissection—Chap. 125). Assess for evidence of heart failure (Chap. 124), murmurs of aortic stenosis, acute mitral or aortic regurgitation, and ventricular septal defect. Tenderness or rebound in abdomen may indicate peritonitis or pancreatitis; high-pitched bowel sounds suggest intestinal obstruction. Perform stool guaiac to rule out GI bleeding.

Fever and chills typically accompany septic shock. Sepsis may not cause fever in elderly, uremic, or alcoholic pts. Skin lesions may suggest specific pathogens in septic shock: petechiae or purpura (*Neisseria meningitidis* or *Haemophilus influenzae*), ecthyma gangrenosum (*Pseudomonas aeruginosa*), generalized erythroderma (toxic shock due to *Staphylococcus aureus* or *Streptococcus pyogenes*).

LABORATORY

Obtain hematocrit, WBC, electrolytes, platelet count, PT, PTT, DIC screen, electrolytes. Arterial blood gas usually shows metabolic acidosis (in septic shock, respiratory alkalosis precedes metabolic acidosis). If sepsis suspected, draw blood cultures, perform urinalysis, and obtain Gram stain and cultures of sputum, urine, and other suspected sites.

Obtain ECG (myocardial ischemia or acute arrhythmia) and chest x-ray (heart failure, tension pneumothorax, pneumonia). Echocardiogram is often helpful (cardiac tamponade, left/right ventricular dysfunction, aortic dissection).

CVP or pulmonary capillary wedge (PCW) pressure measurements may be necessary to distinguish between different categories of shock (Table 11-2): Mean PCW <6 mmHg suggests oligemic or distributive shock; PCW >20 mmHg suggests left

TABLE 11-2 PHYSIOLOGIC CHARACTERISTICS OF FORMS OF SHOCK

Type of Shock	CVP and PCWP	Cardiac Output	Systemic Vascular Resistance	Venous O_2 Saturation
Hypovolemic	↓	↓	↑	↓
Cardiogenic	↑	↓	↑	↓
Septic				
Hyperdynamic	↓↑	↑	↓	↑
Hypodynamic	↓↑	↓	↑	↑↓
Traumatic	↓	↓↑	↑↓	↓
Neurogenic	↓	↓	↓	↓
Hypoadrenal	↓	↓	=↓	↓

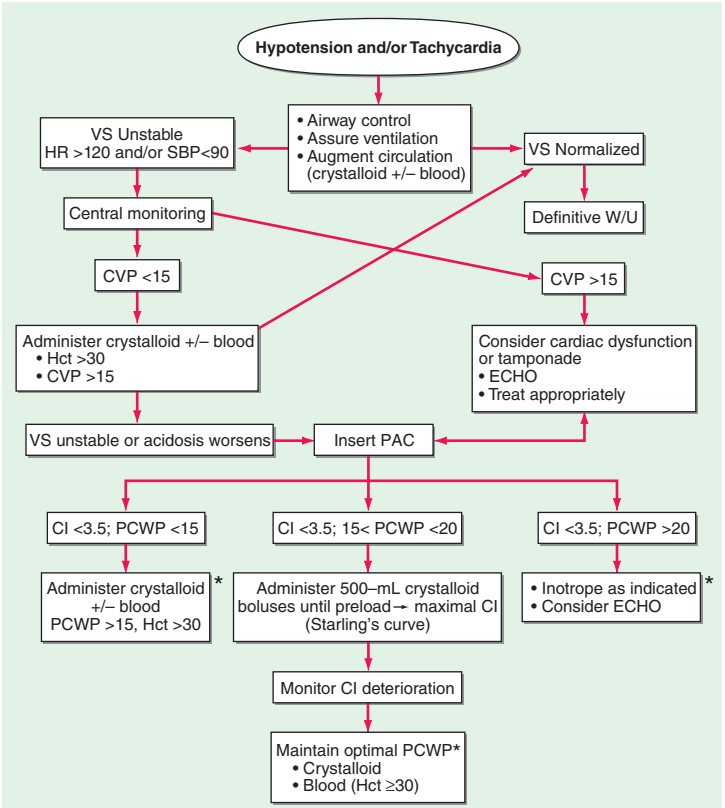
Abbreviations: PCWP, pulmonary capillary wedge pressure.

ventricular failure. Cardiac output (thermodilution) is decreased in cardiogenic and oligemic shock, and usually increased initially in septic shock.

TREATMENT SHOCK (FIG. 11-1)

Aimed at rapid improvement of tissue hypoperfusion and respiratory impairment:

- Serial measurements of bp (intraarterial line preferred), heart rate, continuous ECG monitor, urine output, pulse oximetry, blood studies: Hct, electrolytes, creatinine, BUN, ABGs, pH, calcium, phosphate, lactate, urine Na concentration (<20 mmol/L suggests volume depletion). Consider monitoring of CVP and/or pulmonary artery pressure/PCW pressures in pts with ongoing blood loss,



*Monitor Svo_2, SVRI, and RVEDVI as additional markers of correction for perfusion and hypovolemia. Consider age-adjusted CI.

FIGURE 11-1 An algorithm for the resuscitation of the pt in shock. Svo_2, saturation of hemoglobin with O_2 in venous blood; SVRI, systemic vascular resistance index; RVEDVI, right-ventricular end-diastolic volume index. CI, cardiac index in (L/min) per m^2; ECHO, echocardiogram; Hct, hematocrit; HR, heart rate; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure in mmHg; SBP, systolic blood pressure; VS, vital signs; W/U, work up.

marked fluid shifts, or suspected cardiac dysfunction (the majority of pts do *not* require pulmonary artery catheter monitoring).

- Insert Foley catheter to monitor urine flow.
- Assess mental status frequently.
- Augment systolic bp to >100 mmHg: (1) Place in reverse Trendelenburg position; (2) IV volume infusion (500- to 1000-mL bolus), unless cardiogenic shock suspected (begin with normal saline or Ringer's lactate, then whole blood, or packed RBCs, if anemic); continue volume replacement as needed to restore vascular volume.
- Add vasoactive drugs after intravascular volume is optimized; administer vasopressors (**Table 11-3**) if systemic vascular resistance (SVR) is decreased (begin with norepinephrine [preferred] or dopamine; for persistent hypotension add phenylephrine or vasopressin).
- If heart failure is present, add inotropic agents (usually dobutamine) (Table 11-3); aim to maintain cardiac index >2.2(L/m^2)/min [>4.0(L/m^2)/min in septic shock].
- Administer 100% O_2; intubate with mechanical ventilation if PO_2 <70 mmHg.
- If severe metabolic acidosis present (pH <7.15), administer $NaHCO_3$.

TABLE 11-3 VASOPRESSORS USED IN SHOCK STATES[a]

Drug	Dose	Notes
Dopamine	1–2 μg/kg per min	Facilitates diuresis
	2–10 μg/kg per min	Positive inotropic and chronotropic effects; may increase O_2 consumption as well as O_2 delivery; use may be limited by tachycardia
	10–20 μg/kg per min	Generalized vasoconstriction (decrease renal perfusion)
Norepinephrine	0.5–30 μg/min	Potent vasoconstrictor; moderate inotropic effect; in septic shock is thought to increase tissue O_2 consumption as well as O_2 delivery; may be chosen over dopamine in sepsis due to less chronotropic and adverse effects; may be useful in cardiogenic shock with reduced SVR but should generally be reserved for refractory hypotension
Dobutamine	2–20 μg/kg per min	Primarily for cardiogenic shock (**Chap. 119**): positive inotrope; lacks vasoconstrictor activity; most useful when only mild hypotension present and avoidance of tachycardia desired
Phenylephrine	40–180 μg/min	Potent vasoconstrictor without inotropic effect; may be useful in distributive (septic) shock
Vasopressin	0.01–0.04 U/min	Occasionally used in refractory septic (distributive) shock; restores vascular tone in vasopressin-deficient states (e.g., sepsis)

[a]Isoproterenol not recommended in shock states because of potential hypotension and arrhythmogenic effects.

Abbreviation: SVR, systemic vascular resistance.

- Identify and treat underlying cause of shock. Cardiogenic shock in acute MI is discussed in Chap. 119. Emergent coronary revascularization may be lifesaving if persistent ischemia is present.

SEPTIC SHOCK (SEE CHAP. 11)



For a more detailed discussion, see Maier RV: Approach to the Patient with Shock, Chap. 324, p.1744, and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

12 Sepsis and Septic Shock

DEFINITIONS

- *Possibly harmful systemic response:* Two or more of the following:
  - Fever (oral temperature >38°C [100.4°F]) or hypothermia (oral temperature <36°C [96.8°F])
  - Tachypnea (>24 breaths/min)
  - Tachycardia (>90 beats/min)
  - Leukocytosis (>12,000/μL), leukopenia (<4000/μL), or >10% bands; may have a noninfectious etiology
- *Sepsis (or severe sepsis):* Harmful systemic response (including some degree of organ hypofunction) with a proven or suspected microbial etiology
- *Septic shock:* Sepsis with hypotension (arterial bp <90 mmHg or 40 mmHg below pt's normal bp for at least 1 h despite fluid resuscitation) or need for vasopressors to maintain systolic bp ≥90 mmHg or mean arterial bp ≥70 mmHg

ETIOLOGY

- Blood cultures are positive in 20–40% of sepsis cases and in 40–70% of septic shock cases.
- For infected pts in ICUs, respiratory infections have been most common (64%). Microbiologic results have revealed that 62% of isolates are gram-negative bacteria (most commonly *Pseudomonas* spp. and *Escherichia coli*), 47% are gram-positive bacteria (most commonly *Staphylococcus aureus*), and 19% are fungi (most commonly *Candida* spp.), with some cultures being polymicrobial.

EPIDEMIOLOGY

- The incidence of severe sepsis and septic shock in the United States continues to increase, with >750,000 cases each year contributing to >200,000 deaths.
- Invasive bacterial infections are a prominent cause of death around the world, especially among young children.

- Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity, with two-thirds of cases occurring in pts with significant underlying disease.
- The increasing incidence of sepsis has been attributable to the aging of the population, longer survival of pts with chronic diseases, a relatively high frequency of sepsis among AIDS pts, and medical treatments that circumvent host defenses (e.g., immunosuppressive agents, indwelling catheters, and mechanical devices).

PATHOPHYSIOLOGY

Local and Systemic Host Responses

- Hosts have numerous receptors that recognize highly conserved microbial molecules (e.g., lipopolysaccharide, lipoproteins, double-stranded RNA), triggering the release of cytokines and other host molecules that increase blood flow and neutrophil migration to the infected site, enhance local vascular permeability, and elicit pain.
- Many local and systemic control mechanisms diminish cellular responses to microbial molecules, including intravascular thrombosis (which prevents spread of infection and inflammation) and an increase in anti-inflammatory cytokines (e.g., IL-4 and IL-10).

Organ Dysfunction and Shock

- Widespread vascular endothelial injury is believed to be the major mechanism for multiorgan dysfunction.
- Septic shock is characterized by compromised oxygen delivery to tissues followed by a vasodilatory phase (a decrease in peripheral vascular resistance despite increased levels of vasopressor catecholamines).

CLINICAL FEATURES

- Hyperventilation that produces respiratory alkalosis
- Encephalopathy (disorientation, confusion)
- Acrocyanosis and ischemic necrosis of peripheral tissues (e.g., digits) due to hypotension and DIC
- Skin: hemorrhagic lesions, bullae, cellulitis, pustules. Skin lesions may suggest specific pathogens; e.g., petechiae and purpura suggest *Neisseria meningitidis*, and ecthyma gangrenosum suggests *Pseudomonas aeruginosa*.
- GI: nausea, vomiting, diarrhea, ileus, cholestatic jaundice

Major Complications

- *Cardiopulmonary manifestations*
  - Ventilation-perfusion mismatch, increased alveolar capillary permeability, increased pulmonary water content, and decreased pulmonary compliance impede oxygen exchange and lead to ARDS (progressive diffuse pulmonary infiltrates and arterial hypoxemia) in ~50% of pts.
  - Hypotension: Normal or increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic and hypovolemic shock.
  - The ejection fraction is decreased, but ventricular dilation allows maintenance of a normal stroke volume.
- *Adrenal insufficiency:* may be difficult to diagnose in critically ill pts
- *Renal manifestations*: oliguria or polyuria, azotemia, proteinuria, and renal failure due to acute tubular necrosis
- *Neurologic manifestations*: delirium in the acute phase, polyneuropathy with distal motor weakness in prolonged sepsis. Survivors may have long-term cognitive impairment.
- *Immunosuppression*: Pts may have reactivation of HSV, CMV, or VZV.

Laboratory Findings

- *CBC:* leukocytosis with a left shift, thrombocytopenia
- *Coagulation:* prolonged thrombin time, decreased fibrinogen, presence of D-dimers suggestive of DIC. With DIC, platelet counts usually fall below 50,000/μL.
- *Chemistries:* metabolic acidosis, elevated anion gap, elevated lactate levels
- *LFTs:* transaminitis, hyperbilirubinemia, azotemia, hypoalbuminemia

DIAGNOSIS

Definitive diagnosis requires isolation of the microorganism from blood or a local site of infection. Culture of infected cutaneous lesions may help establish the diagnosis.

TREATMENT SEPSIS AND SEPTIC SHOCK

Pts in whom sepsis is suspected must be managed expeditiously, if possible within 1 h of presentation.

1. Antibiotic treatment: See Table 12-1.
2. Removal or drainage of a focal source of infection
   a. Remove indwelling intravascular catheters; replace Foley and other drainage catheters; drain local sources of infection.
   b. Rule out sinusitis in pts with nasal intubation.
   c. Image the chest, abdomen, and/or pelvis to evaluate for abscess.
3. Hemodynamic, respiratory, and metabolic support
   a. Initiate treatment with 1–2 L of normal saline administered over 1–2 h, keeping the CVP at 8–12 cmH_2O, urine output at >0.5 mL/kg per hour, and mean arterial bp at >65 mmHg. Add vasopressor therapy if needed.
   b. If hypotension does not respond to fluid replacement therapy, hydrocortisone (50 mg IV q6h) should be given. If clinical improvement results within 24–48 h, most experts would continue hydrocortisone treatment for 5–7 days.
   c. Maintain oxygenation with ventilator support as indicated. Recent studies favor the use of low tidal volumes—typically 6 mL/kg of ideal body weight—provided the plateau pressure is ≤30 cmH_2O.
   d. Erythrocyte transfusion is recommended when the blood Hb level decreases to ≤7 g/dL, with a target level of 9 g/dL.
4. General support: Nutritional supplementation should be given to pts with prolonged sepsis (i.e., that lasting >2–3 days), with available evidence suggesting an enteral delivery route. Prophylactic heparin should be administered to prevent deep-venous thrombosis if no active bleeding or coagulopathy is present. Insulin should be used only if it is needed to maintain the blood glucose concentration below ~180 mg/dL.

PROGNOSIS

In all, 20–35% of pts with severe sepsis and 40–60% of pts with septic shock die within 30 days, and further deaths occur within 6 months. Prognostic stratification systems (e.g., APACHE II) can estimate the risk of dying of severe sepsis.

TABLE 12-1 INITIAL ANTIMICROBIAL THERAPY FOR SEVERE SEPSIS WITH NO OBVIOUS SOURCE IN ADULTS WITH NORMAL RENAL FUNCTION

Clinical Condition	Antimicrobial Regimens (Intravenous Therapy)
Immunocompetent adult	The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h), ertapenem (1 g q24h), or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the pt is allergic to β-lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h) or (2) piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the pt has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily), voriconazole (6 mg/kg q12h for 2 doses, then 3 mg/kg q12h), or a lipid formulation of amphotericin B should be added if the pt is hypotensive, has been receiving broad-spectrum antibacterial drugs, or remains febrile 5 days after initiation of empirical antibacterial therapy.
Splenectomy	Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the pt is allergic to β-lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) should be used.
IV drug user	Vancomycin (15 mg/kg q12h) is essential.
AIDS	Cefepime alone (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the pt is allergic to β-lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.
Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy,* 43rd ed, 2013, Antimicrobial Therapy, Inc., Sperryville, VA.

PREVENTION

Nosocomial infections cause most episodes of severe sepsis and septic shock in the United States. Measures to reduce those infections could reduce the incidence of sepsis.

For a more detailed discussion, see Munford RS: Severe Sepsis and Septic Shock, Chap. 325, p. 1751, in HPIM-19.

13 Acute Pulmonary Edema

Life-threatening, acute development of alveolar lung edema due to one or more of the following:

1. Elevation of hydrostatic pressure in the pulmonary capillaries (left heart failure, mitral stenosis).
2. Specific precipitants (Table 13-1), resulting in cardiogenic pulmonary edema in pts with previously compensated heart failure or without previous cardiac history.
3. Increased permeability of pulmonary alveolar-capillary membrane (noncardiogenic pulmonary edema). For common causes, see Table 13-2.

PHYSICAL FINDINGS

Pt appears severely ill, often diaphoretic, sitting bolt upright, tachypneic, and cyanosis may be present. Bilateral pulmonary rales; third heart sound may be present. Frothy, blood-tinged sputum may occur.

LABORATORY

Early arterial blood gases show reductions of both PaO_2 and $PaCO_2$. With progressive respiratory failure, hypercapnia develops with acidemia. CXR shows pulmonary vascular redistribution, diffuse haziness in lung fields with perihilar "butterfly" appearance.

TREATMENT ACUTE PULMONARY EDEMA

Immediate, aggressive therapy is mandatory for survival. The following measures should be instituted as simultaneously as possible for cardiogenic pulmonary edema:

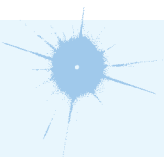
TABLE 13-1 PRECIPITANTS OF ACUTE PULMONARY EDEMA

Acute tachy- or bradyarrhythmia
Infection, fever
Acute MI
Severe hypertension
Acute mitral or aortic regurgitation
Increased circulating volume (Na^+ ingestion, blood transfusion, pregnancy)
Increased metabolic demands (exercise, hyperthyroidism)
Pulmonary embolism
Noncompliance (sudden discontinuation) of chronic CHF medications

TABLE 13-2 COMMON CAUSES OF NONCARDIOGENIC PULMONARY EDEMA

Direct Injury to Lung	
Chest trauma, pulmonary contusion	Pneumonia
Aspiration	Oxygen toxicity
Smoke inhalation	Pulmonary embolism, reperfusion
Hematogenous Injury to Lung	
Sepsis	Multiple transfusions
Pancreatitis	IV drug use, e.g., heroin
Nonthoracic trauma	Cardiopulmonary bypass
Possible Lung Injury Plus Elevated Hydrostatic Pressures	
High-altitude pulmonary edema	Reexpansion pulmonary edema
Neurogenic pulmonary edema	

1. Administer 100% O_2 by mask to achieve PaO_2 >60 mmHg; if inadequate, use positive-pressure ventilation by face or nasal mask, and if necessary, proceed to endotracheal intubation.
2. Reduce preload:
   a. Seat pt upright to reduce venous return, if not hypotensive.
   b. Intravenous loop diuretic (e.g., furosemide, initially 0.5–1.0 mg/kg); use lower dose if pt does not take diuretics chronically.
   c. Nitroglycerin (sublingual 0.4 mg × 3 q5min) followed by 5–20 μg/ min IV if needed.
   d. Morphine 2–4 mg IV; assess frequently for hypotension or respiratory depression; naloxone should be available to reverse effects of morphine if necessary.
   e. Consider ACE inhibitor if pt is hypertensive, or in setting of acute MI with heart failure.
   f. Consider nesiritide (2-μg/kg bolus IV followed by 0.01 μg/kg per min) for refractory symptoms—do not use in acute MI or cardiogenic shock.
3. Inotropic agents are indicated in cardiogenic pulmonary edema and severe LV dysfunction: dopamine, dobutamine, milrinone (Chap. 11).
4. The precipitating cause of cardiogenic pulmonary edema (Table 13-1) should be sought and treated, particularly acute arrhythmias or infection. For refractory pulmonary edema associated with persistent cardiac ischemia, early coronary revascularization may be life-saving. For noncardiac pulmonary edema, identify and treat/remove cause (Table 13-2).



For a more detailed discussion, see Schwartzstein RM: Dyspnea, Chap. 47e; and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

14 Acute Respiratory Distress Syndrome

DEFINITION AND ETIOLOGY

Acute respiratory distress syndrome (ARDS) develops rapidly and includes severe dyspnea, diffuse pulmonary infiltrates, and hypoxemia; it typically causes respiratory failure. Key diagnostic criteria for ARDS include (1) diffuse bilateral pulmonary infiltrates on CXR; (2) PaO_2 (arterial partial pressure of oxygen in mmHg)/FIO_2 (inspired O_2 fraction) ≤200 mmHg; and (3) absence of elevated left atrial pressure (pulmonary capillary wedge pressure ≤18 mmHg). Acute lung injury is a related but milder syndrome, with less profound hypoxemia (PaO_2/FIO_2 ≤300 mmHg), that can develop into ARDS. Although many medical and surgical conditions can cause ARDS, most cases (>80%) result from sepsis, bacterial pneumonia, trauma, multiple blood transfusions, gastric acid aspiration, and drug overdose. Individuals with more than one predisposing factor have a greater risk of developing ARDS. Other risk factors include older age, chronic alcohol abuse, metabolic acidosis, and overall severity of critical illness.

CLINICAL COURSE AND PATHOPHYSIOLOGY

There are three phases in the natural history of ARDS:

1. *Exudative phase:* Characterized by alveolar edema and neutrophil inflammation, with subsequent development of hyaline membranes from diffuse alveolar damage. The alveolar edema, which is most prominent in the dependent portions of the lung, causes atelectasis and reduced lung compliance. Hypoxemia, tachypnea, and progressive dyspnea develop, and increased pulmonary dead space can also lead to hypercarbia. Respiratory failure frequently develops during this phase. CXR reveals bilateral, diffuse alveolar, and interstitial opacities. The differential diagnosis is broad, but common alternative etiologies to consider are cardiogenic pulmonary edema, pneumonia, and alveolar hemorrhage. Unlike cardiogenic pulmonary edema, the CXR in ARDS rarely shows cardiomegaly, pleural effusions, or pulmonary vascular redistribution. The exudative phase duration is typically up to 7 days in length and usually begins within 12–36 h after the inciting insult.
2. *Proliferative phase:* This phase typically lasts from approximately days 7 to 21 after the inciting insult. Although most pts recover, some will develop progressive lung injury and evidence of pulmonary fibrosis. Even among pts who show rapid improvement allowing removal of mechanical ventilatory support, dyspnea and hypoxemia often persist during this phase.
3. *Fibrotic phase:* Although the majority of pts recover within 3–4 weeks of the initial pulmonary injury, some experience progressive fibrosis, necessitating prolonged ventilatory support and/or supplemental O_2. Increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space are observed during this phase.

TREATMENT ARDS

Progress in recent therapy has emphasized the importance of general critical care of pts with ARDS in addition to lung protective ventilatory strategies. General care requires treatment of the underlying medical or surgical problem that caused lung injury, minimizing iatrogenic complications, prophylaxis to prevent venous thromboembolism and GI hemorrhage, prompt treatment of nosocomial

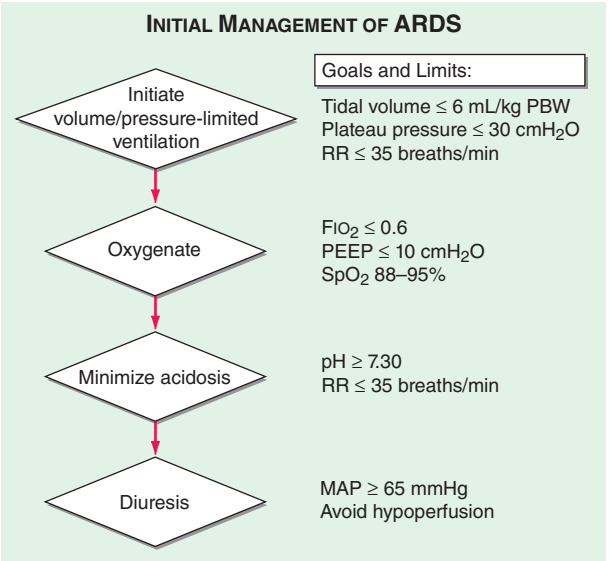


FIGURE 14-1 Algorithm for the initial management of acute respiratory distress syndrome (ARDS). Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill pts with ARDS. FIO_2, inspired O_2 percentage; MAP, mean arterial pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate; SpO_2, arterial oxyhemoglobin saturation measured by pulse oximetry.

infections, and adequate nutritional support. An algorithm for the initial management of ARDS is presented in Fig. 14-1.

MECHANICAL VENTILATORY SUPPORT Pts with ARDS typically require mechanical ventilatory support due to hypoxemia and increased work of breathing. A substantial improvement in outcomes from ARDS occurred with the recognition that mechanical ventilator–related overdistention of normal lung units with positive pressure can produce or exacerbate lung injury, causing or worsening ARDS. Currently recommended ventilator strategies limit alveolar distention but maintain adequate tissue oxygenation.

It has been clearly shown that low tidal volumes (≤6-mL/kg predicted body weight) provide reduced mortality compared with higher tidal volumes (12-mL/kg predicted body weight). In ARDS, alveolar collapse can occur due to alveolar/interstitial fluid accumulation and loss of surfactant, thus worsening hypoxemia. Therefore, low tidal volumes are combined with the use of positive end-expiratory pressure (PEEP) at levels that strive to minimize alveolar collapse and achieve adequate oxygenation with the lowest required FIO_2. Use of PEEP levels higher than necessary to optimize oxygenation has not been proven to reduce ARDS mortality. Measurement of esophageal pressures to estimate transpulmonary pressure may help to identify an optimal level of PEEP. Other techniques that may improve oxygenation while limiting alveolar distention include extending the time of inspiration on the ventilator (inverse ratio ventilation) and placing the pt in the prone position. However, these approaches are not of proven benefit in reducing mortality from ARDS.

ANCILLARY THERAPIES Pts with ARDS have increased pulmonary vascular permeability leading to interstitial and alveolar edema. Therefore, they should receive IV fluids only as needed to achieve adequate cardiac output and tissue O_2 delivery as assessed by urine output, acid-base status, and arterial pressure. A recent study suggested that neuromuscular blockage with cisatracurium for 48 h could potentially reduce mortality in severe ARDS. There is not convincing evidence currently to support the use of glucocorticoids or nitric oxide in ARDS.

OUTCOMES

Mortality from ARDS has declined with improvements in general critical care treatment and with the introduction of low tidal volume ventilation. Current mortality from ARDS is 26–44%, with most deaths due to sepsis and nonpulmonary organ failure. Increased risk of mortality from ARDS is associated with advanced age, preexisting organ dysfunction (e.g., chronic conditions of liver disease, alcohol abuse, immunosuppression, or renal disease). Increased mortality has also been associated with ARDS related to direct lung injury (e.g., pneumonia, pulmonary contusion, and aspiration) compared with indirect lung injury (e.g., sepsis, trauma, and pancreatitis). Most surviving ARDS pts do not have significant long-term pulmonary disability.

For a more detailed discussion, see Levy BD, Choi AMK: Acute Respiratory Distress Syndrome, Chap. 322, p. 1736, in HPIM-19.

15 Respiratory Failure

DEFINITION AND CLASSIFICATION OF RESPIRATORY FAILURE

Respiratory failure is defined as inadequate gas exchange due to malfunction of one or more components of the respiratory system. There are two main types of acute respiratory failure: hypoxemic and hypercarbic. Hypoxemic respiratory failure is defined by arterial O_2 saturation <90% while receiving an increased inspired O_2 fraction. Acute hypoxemic respiratory failure can result from pneumonia, pulmonary edema (cardiogenic or noncardiogenic), and alveolar hemorrhage. Hypoxemia results from ventilation-perfusion mismatch and intrapulmonary shunting.

Hypercarbic respiratory failure is characterized by alveolar hypoventilation and respiratory acidosis. Hypercarbic respiratory failure results from decreased minute ventilation and/or increased physiologic dead space. Conditions associated with hypercarbic respiratory failure include neuromuscular diseases (e.g., myasthenia gravis), disease processes causing diminished respiratory drive (e.g., drug overdose, brainstem injury), and respiratory diseases associated with respiratory muscle fatigue (e.g., exacerbations of asthma and chronic obstructive pulmonary disease [COPD]). In acute hypercarbic respiratory failure, $PaCO_2$ is typically >50 mmHg. With acute-on-chronic respiratory failure, as is often seen with COPD exacerbations, considerably higher $PaCO_2$ values may be observed. The degree of respiratory acidosis, the

pt's mental status, and the pt's degree of respiratory distress are better indicators of the need for mechanical ventilation than a specific $PaCO_2$ level in acute-on-chronic respiratory failure. Two other types of respiratory failure are commonly considered: (1) perioperative respiratory failure related to atelectasis, and (2) hypoperfusion of respiratory muscles related to shock.

MODES OF MECHANICAL VENTILATION

Respiratory failure often requires treatment with mechanical ventilation to decrease the work of breathing and reverse severe hypoxemia and respiratory acidosis. There are two general classes of mechanical ventilation: noninvasive ventilation (NIV) and conventional mechanical ventilation. NIV, administered through a tightly fitting nasal or facial mask, is widely used in acute-on-chronic respiratory failure related to COPD exacerbations. NIV typically involves a preset positive pressure applied during inspiration and a lower pressure applied during expiration; it is associated with fewer complications such as nosocomial pneumonia than conventional mechanical ventilation through an endotracheal tube. However, NIV is contraindicated in cardiopulmonary arrest, severe encephalopathy, severe GI hemorrhage, hemodynamic instability, unstable coronary artery disease, facial surgery or trauma, upper airway obstruction, inability to protect the airway, and inability to clear secretions.

Most pts with acute respiratory failure require conventional mechanical ventilation via a cuffed endotracheal tube. The goal of mechanical ventilation is to optimize oxygenation while avoiding ventilator-induced lung injury. Various modes of conventional mechanical ventilation are commonly used; different modes are characterized by a trigger (what the ventilator senses to initiate a machine-delivered breath), a cycle (what determines the end of inspiration), and limiting factors (operator-specified values for key parameters that are monitored by the ventilator and not allowed to be exceeded). Three of the common modes of mechanical ventilation are described below; additional information is provided in Table 15-1.

- Assist-control ventilation: The trigger for a machine-delivered breath is the pt's inspiratory effort, which causes a synchronized breath to be delivered. If no effort is detected over a prespecified time interval, a timer-triggered machine breath is delivered. Assist-control is volume-cycled with an operator-determined tidal volume. Limiting factors include the minimum respiratory rate, which is specified by the operator; pt efforts can lead to higher respiratory rates. Other limiting factors include the airway pressure limit, which is also set by the operator. Because the pt will receive a full tidal breath with each inspiratory effort, tachypnea due to nonrespiratory factors, such as pain, can lead to respiratory alkalosis. In pts with airflow obstruction (e.g., asthma or COPD), auto-PEEP (positive end-expiratory pressure) can develop.
- Synchronized intermittent mandatory ventilation (SIMV): As with assist-control, SIMV is volume-cycled, with similar limiting factors. As with assist-control, the trigger for a machine-delivered breath can be either pt effort or a specified time interval. However, if the pt's next inspiratory effort occurs before the time interval for another mandatory breath has elapsed, only their spontaneous respiratory effort (without machine support) is delivered. Thus, the number of machine-delivered breaths is limited in SIMV, allowing pts to exercise their inspiratory muscles between assisted breaths.
- Pressure-support ventilation (PSV): PSV is triggered by the pt's inspiratory effort. The cycle of PSV is determined by the inspiratory flow rate. Because a specific respiratory rate is not provided, this mode of ventilation may be combined with SIMV to ensure that an adequate respiratory rate is achieved in pts with respiratory depression.

TABLE 15-1 CLINICAL CHARACTERISTICS OF COMMONLY USED MODES OF MECHANICAL VENTILATION

Ventilator Mode	Independent Variables (Set by User)	Dependent Variables (Monitored by User)	Trigger/Cycle Limit	Advantages	Disadvantages
ACMV	FIO_2 Tidal volume Ventilator rate Level of PEEP Inspiratory flow pattern Peak inspiratory flow Pressure limit	Peak airway pressure Minute ventilation Plateau pressure Mean airway pressure I/E ratio	Pt effort Timer Pressure limit	Timer backup Pt-vent synchrony Pt controls minute ventilation	Not useful for weaning Potential for dangerous respiratory alkalosis due to hyperventilation Barotrauma risk
SIMV	Same as for ACMV	Same as for ACMV	Same as for ACMV	Timer backup is useful for weaning Comfort from spontaneous breaths	Potential dyssynchrony
PSV	FIO_2 Inspiratory pressure level PEEP pressure limit	Tidal volume Respiratory rate Minute ventilation ABG	Inspiratory flow Pressure limit	Assures synchrony Good for weaning	No timer backup; may result in hypoventilation
NIV	Inspiratory and expiratory pressure levels FIO_2	Tidal volume Respiratory rate I/E ratio Minute ventilation ABG	Pressure limit Inspiratory flow	Pt control	Discomfort and bruising from mask Leaks are common Hypoventilation risk

Abbreviations: ACMV, assist-control mandatory ventilation; I/E, inspiration/expiration; FIO_2, inspired O_2; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PSV, pressure-support ventilation; SIMV, synchronized intermittent mandatory ventilation.

Other modes of ventilation may be appropriate in specific clinical situations; for example, pressure-control ventilation is helpful to regulate airway pressures in pts with barotrauma or in the postoperative period from thoracic surgery.

MANAGEMENT OF MECHANICALLY VENTILATED PATIENTS

General care of mechanically ventilated pts is reviewed in Chap. 4, along with weaning from mechanical ventilation. A cuffed endotracheal tube is often used to provide positive pressure ventilation with conditioned gas. A protective ventilation approach is generally recommended, including the following elements: (1) target tidal volume of ~6 mL/kg of ideal body weight; (2) avoid plateau pressures >30 cm H_2O; (3) use the lowest fraction of inspired oxygen (FIO_2) to maintain arterial oxygen saturation ≥90%; and (4) apply PEEP to maintain alveolar patency while avoiding overdistention. This approach may result in a permissible degree of hypercapnia. After an endotracheal tube has been in place for an extended period of time, tracheostomy should be considered, primarily to improve pt comfort, reduce needs for sedative medications, and provide a more secure airway. No absolute time frame for tracheostomy placement exists, but pts who are likely to require mechanical ventilatory support for >2 weeks should be considered for a tracheostomy.

A variety of complications can result from mechanical ventilation. Barotrauma—overdistention and damage of lung tissue—can cause pneumomediastinum, subcutaneous emphysema, and pneumothorax. Ventilator-related pneumothorax typically requires treatment with tube thoracostomy. Ventilator-associated pneumonia is a major complication in intubated pts; common pathogens include *Pseudomonas aeruginosa* and other gram-negative bacilli, as well as *Staphylococcus aureus*.

For a more detailed discussion, see Celli BR: Mechanical Ventilatory Support, Chap. 323, p. 1740; and Kress JP, Hall JB: Approach to the Patient with Critical Illness, Chap. 321, p. 1729, in HPIM-19.

16 Confusion, Stupor, and Coma

APPROACH TO THE PATIENT: Disorders of Consciousness

Disorders of consciousness are common; these always signify a disorder of the nervous system. Assessment should determine the level of consciousness (drowsy, stuporous, comatose) and/or content of consciousness (confusion, perseveration, hallucinations). *Confusion* is a lack of clarity in thinking with inattentiveness; *delirium* is used to describe an acute confusional state; *stupor*, a state in which vigorous stimuli are needed to elicit a response; *coma*, a condition of unresponsiveness. Pts in such states are usually seriously ill, and etiologic factors must be assessed (Tables 16-1 and 16-2).

TABLE 16-1 COMMON ETIOLOGIES OF DELIRIUM

Toxins
Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines
Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, "bath salts," marijuana and its synthetic forms
Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic conditions
Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia
Hypothermia and hyperthermia
Pulmonary failure: hypoxemia and hypercarbia
Liver failure/hepatic encephalopathy
Renal failure/uremia
Cardiac failure
Vitamin deficiencies: B_{12}, thiamine, folate, niacin
Dehydration and malnutrition
Anemia
Infections
Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis
CNS infections: meningitis, encephalitis, brain abscess
Endocrine conditions
Hyperthyroidism, hypothyroidism
Hyperparathyroidism
Adrenal insufficiency
Cerebrovascular disorders
Global hypoperfusion states
Hypertensive encephalopathy
Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune disorders
CNS vasculitis
Cerebral lupus
Neurologic paraneoplastic syndromes
Seizure-related disorders
Nonconvulsive status epilepticus
Intermittent seizures with prolonged postictal states
Neoplastic disorders
Diffuse metastases to the brain
Gliomatosis cerebri
Carcinomatous meningitis
CNS lymphoma
Hospitalization
Terminal end-of-life delirium

Abbreviations: GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.

TABLE 16-2 STEPWISE EVALUATION OF A PATIENT WITH DELIRIUM

Initial evaluation
History with special attention to medications (including over-the-counter and herbals)
General physical examination and neurologic examination
Complete blood count
Electrolyte panel including calcium, magnesium, phosphorus
Liver function tests, including albumin
Renal function tests
First-tier further evaluation guided by initial evaluation
Systemic infection screen
Urinalysis and culture
Chest radiograph
Blood cultures
Electrocardiogram
Arterial blood gas
Serum and/or urine toxicology screen (perform earlier in young persons)
Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
Suspected CNS infection: lumbar puncture after brain imaging
Suspected seizure-related etiology: EEG (if high suspicion, should be performed immediately)
Second-tier further evaluation
Vitamin levels: B_{12}, folate, thiamine
Endocrinologic laboratories: TSH and free T_4; cortisol
Serum ammonia
Sedimentation rate
Autoimmune serologies: ANA, complement levels; p-ANCA, c-ANCA. consider paraneoplastic serologies
Infectious serologies: RPR; fungal and viral serologies if high suspicion; HIV antibody
Lumbar puncture (if not already performed)
Brain MRI with and without gadolinium (if not already performed)

Abbreviations: c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CNS, central nervous system; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; RPR, rapid plasmin reagin; TSH, thyroid-stimulating hormone.

DELIRIUM

Delirium is a clinical diagnosis made at the bedside; a careful history and physical examination are necessary, focusing on common etiologies of delirium, especially toxins and metabolic conditions. Observation will usually reveal an altered level of consciousness or a deficit of attention. Attention can be assessed through a simple bedside test of digits forward—pts are asked to repeat successively longer random strings of digits beginning with two digits in a row; a digit span of four digits or less usually indicates an attentional deficit unless hearing or language barriers are present. Delirium is vastly underrecognized, especially in pts presenting with a quiet, hypoactive state and those in the ICU.

A cost-effective approach to the evaluation of delirium allows the history and physical examination to guide tests. No single algorithm will fit all pts due to the large number of potential etiologies, but one step-wise approach is shown in Table 16-2.

http://internalmedicinebook.com

Management begins with treatment of the underlying inciting factor (e.g., pts with systemic infections should be given appropriate antibiotics, and electrolyte disturbances judiciously corrected). Relatively simple methods of supportive care can be quite effective, such as frequent reorientation by staff, preservation of sleep-wake cycles, and attempting to mimic the home environment as much as possible. Chemical restraints exacerbate delirium and should be used only when necessary to protect pt or staff from possible injury; antipsychotics at low dose are usually the treatment of choice.

COMA (TABLE 16-3)

Because coma demands immediate attention, the physician must employ an organized approach. Almost all instances of coma can be traced to either widespread abnormalities of the bilateral cerebral hemispheres or to reduced activity of the reticular activating system in the brainstem.

History

History should be obtained from witnesses or family members regarding use of insulin, narcotics, anticoagulants, other prescription drugs, suicidal intent, recent trauma, headache, epilepsy, significant medical problems, and preceding symptoms. History of sudden headache followed by loss of consciousness suggests intracranial hemorrhage; preceding vertigo, nausea, diplopia, ataxia, hemisensory disorder suggest basilar artery involvement; chest pain, palpitations, and faintness suggest a cardiovascular cause.

Immediate Assessment

Acute respiratory and cardiovascular problems should be attended to prior to the neurologic assessment. Vital signs should be evaluated, and appropriate support initiated. Thiamine, glucose, and naloxone should be administered if the etiology of coma is not immediately apparent. Blood should be drawn for glucose, electrolytes, calcium, and renal (BUN, creatinine) and hepatic (ammonia, transaminases) function; also screen for presence of alcohol and other toxins, and obtain blood cultures if infection is suspected. Arterial blood-gas analysis is helpful in pts with lung disease and acid-base disorders. Fever, especially with petechial rash, suggests meningitis. Examination of CSF is essential in diagnosis of meningitis and encephalitis; lumbar puncture should not be deferred if meningitis is a possibility, but CT scan should be obtained first if a mass lesion is suspected. Empirical antibiotic and glucocorticoid coverage for meningitis should be instituted until CSF results are available. Fever with dry skin suggests heat shock or intoxication with anticholinergics. Hypothermia suggests myxedema, intoxication, sepsis, exposure, or hypoglycemia. Marked hypertension occurs with increased intracranial pressure (ICP) and hypertensive encephalopathy.

Neurologic Examination

Focus on establishing pt's best level of function and uncovering signs that enable a specific diagnosis. Comatose pt's best motor and sensory function should be assessed by testing responses to noxious stimuli; carefully note any asymmetric responses, which suggest a focal lesion. Multifocal myoclonus indicates that a metabolic disorder is likely; intermittent twitching or subtle eye movements may be the only sign of a seizure.

Responsiveness

Stimuli of increasing intensity are applied to gauge the degree of unresponsiveness and any asymmetry in sensory or motor function. Motor responses may be purposeful or reflexive. Spontaneous flexion of elbows with leg extension, termed *decorticate posturing*, accompanies severe damage to contralateral hemisphere above midbrain. Internal rotation of the arms with extension of elbows, wrists, and legs, termed

http://internalmedicinebook.com

TABLE 16-3 DIFFERENTIAL DIAGNOSIS OF COMA

1. Diseases that cause no focal or lateralizing neurologic signs, usually with normal brainstem functions; CT scan and cellular content of the CSF are normal.
   a. Intoxications: alcohol, sedative drugs, opiates, etc.
   b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
   c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
   d. Shock from any cause
   e. Postseizure states, status epilepticus, nonconvulsive status epilepticus
   f. Hypertensive encephalopathy, eclampsia
   g. Severe hyperthermia, hypothermia
   h. Concussion
   i. Acute hydrocephalus
2. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF, usually without focal or lateralizing cerebral or brainstem signs; CT or MRI shows no mass lesion.
   a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
   b. Acute bacterial meningitis
   c. Viral encephalitis
   d. Miscellaneous: fat embolism, cholesterol embolism, carcinomatous and lymphomatous meningitis, etc.
3. Diseases that cause focal brainstem or lateralizing cerebral signs, with or without changes in the CSF; CT and MRI are abnormal
   a. Hemispheral hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
   b. Brainstem infarction due to basilar artery thrombosis or embolism
   c. Brain abscess, subdural empyema
   d. Epidural and subdural hemorrhage, brain contusion
   e. Brain tumor with surrounding edema
   f. Cerebellar and pontine hemorrhage and infarction
   g. Widespread traumatic brain injury
   h. Metabolic coma (see above) with preexisting focal damage
   i. Miscellaneous: Cortical vein thrombosis, herpes simplex encephalitis, multiple cerebral emboli due to bacterial endocarditis, acute hemorrhagic leukoencephalitis, acute disseminated (postinfectious) encephalomyelitis, thrombotic thrombocytopenic purpura, cerebral vasculitis, neurologic paraneoplastic syndromes, gliomatosis cerebri, pituitary apoplexy, intravascular lymphoma, etc.

http://internalmedicinebook.com

decerebrate posturing, suggests damage to midbrain or caudal diencephalon. These postural reflexes occur in profound encephalopathic states.

Pupillary Signs

In comatose pts, equal, round, reactive pupils exclude midbrain damage as cause and suggest a metabolic abnormality. Pinpoint pupils occur in narcotic overdose, pontine damage, hydrocephalus, or thalamic hemorrhage; the response to naloxone and presence of reflex eye movements (usually intact with drug overdose) can distinguish these. A unilateral, enlarged, often oval, poorly reactive pupil is caused by midbrain lesions or compression of third cranial nerve, as occurs in transtentorial herniation. Bilaterally dilated, unreactive pupils indicate severe bilateral midbrain damage, anticholinergic overdose, or ocular trauma.

Ocular Movements

Examine spontaneous and reflex eye movements. Intermittent horizontal divergence is common in drowsiness. Slow, to-and-fro horizontal movements suggest bihemispheric dysfunction. Conjugate eye deviation to one side indicates damage to the pons on the opposite side or a lesion in the frontal lobe on the same side ("*The eyes look toward a hemispheral lesion and away from a brainstem lesion*"). An adducted eye at rest with impaired ability to turn eye laterally indicates an abducens (VI) nerve palsy, common in raised ICP or pontine damage. The eye with a dilated, unreactive pupil is often abducted at rest and cannot adduct fully due to third nerve dysfunction, as occurs with transtentorial herniation. Vertical separation of ocular axes (skew deviation) occurs in pontine or cerebellar lesions. Doll's head maneuver (oculocephalic reflex) and cold caloric–induced eye movements allow diagnosis of gaze or cranial nerve palsies in pts who do not move their eyes purposefully. Doll's head maneuver is tested by observing eye movements in response to lateral rotation of head (this should not be performed in pts with possible neck injury); full conjugate movement of eyes occurs in bihemispheric dysfunction. In comatose pts with intact brainstem function, raising head to 60° above the horizontal and irrigating external auditory canal with cool water causes tonic deviation of gaze to side of irrigated ear ("cold calorics"). In conscious pts, it causes nystagmus, vertigo, and emesis.

Respiratory Patterns

Cheyne-Stokes (periodic) breathing occurs in bihemispheric dysfunction and is common in metabolic encephalopathies. Respiratory patterns composed of gasps or other irregular breathing patterns are indicative of lower brainstem damage; such pts usually require intubation and ventilatory assistance.

Radiologic Examination

Lesions causing raised ICP commonly cause impaired consciousness. CT or MRI scan of the brain is often abnormal in coma but may not be diagnostic; appropriate therapy should not be postponed while awaiting a CT or MRI scan. Pts with disordered consciousness due to high ICP can deteriorate rapidly; emergent CT study is necessary to confirm the presence of mass effect and guide surgical decompression. CT scan is normal in some pts with subarachnoid hemorrhage; the diagnosis then rests on clinical history combined with RBCs or xanthochromia in spinal fluid. CT, MR, or conventional angiography may be necessary to establish basilar artery thrombosis as cause of coma in pts with brainstem signs. The EEG is useful in metabolic or drug-induced states but is rarely diagnostic except in coma due to seizures or herpes simplex encephalitis.

BRAIN DEATH

This results from total cessation of cerebral function while somatic function is maintained by artificial means and the heart continues to pump. It is legally and ethically equivalent to cardiorespiratory death. The pt is unresponsive to all forms of

http://internalmedicinebook.com

stimulation (widespread cortical destruction), brainstem reflexes are absent (global brainstem damage), and there is complete apnea (destruction of the medulla). Demonstration of apnea requires that the PCO_2 be high enough to stimulate respiration, while PO_2 and bp are maintained. EEG is isoelectric at high gain. The absence of deep tendon reflexes is not required because the spinal cord may remain functional. Special care must be taken to exclude drug toxicity and hypothermia prior to making a diagnosis of brain death. Diagnosis should be made only if the state persists for some agreed-upon period, usually 6–24 h.

For a more detailed discussion, see Josephson SA, Miller BL: Confusion and Delirium, Chap. 34, p. 166, and Ropper AH: Coma, Chap. 328, p. 1771, in HPIM-19.

17 Stroke

Sudden onset of a neurologic deficit from a vascular mechanism: ~85% are ischemic; ~15% are primary hemorrhages (subarachnoid [Chap. 18] and intraparenchymal). An ischemic deficit that resolves rapidly without radiologic evidence of an infarction is termed a *transient ischemic attack* (TIA); 24 h is a commonly used boundary between TIA and stroke, although most TIAs last between 5 and 15 min. Stroke is a leading cause of neurologic disability in adults; 200,000 deaths annually in the United States. Much can be done to limit morbidity and mortality through prevention and acute intervention.

PATHOPHYSIOLOGY

Ischemic stroke can be due to embolic occlusion of large cerebral vessels; source of emboli may be heart, aortic arch, or other arteries such as the internal carotids. Small, deep ischemic lesions are most often related to intrinsic small-vessel disease (lacunar strokes). Low-flow strokes are occasionally seen with severe proximal stenosis and inadequate collaterals challenged by systemic hypotensive episodes. Hemorrhages most frequently result from rupture of aneurysms or small vessels within brain tissue. Variability in stroke recovery is influenced by collateral vessels, blood pressure, and the specific site and mechanism of vessel occlusion; if blood flow is restored prior to significant cell death, the pt may experience only transient symptoms, i.e., a TIA.

CLINICAL FEATURES

Ischemic Stroke

Abrupt and dramatic onset of focal neurologic symptoms is typical. Pts may not seek assistance on their own because they are rarely in pain and may lose appreciation that something is wrong (*anosognosia*). Symptoms reflect the vascular territory involved (Table 17-1). Transient monocular blindness (amaurosis fugax) is a particular form of TIA due to retinal ischemia; pts describe a shade descending over the visual field.

http://internalmedicinebook.com

TABLE 17-1 ANATOMIC LOCALIZATION IN STROKE

Signs and Symptoms
Cerebral Hemisphere, Lateral Aspect (Middle Cerebral A.)
Hemiparesis
Hemisensory deficit
Motor aphasia (Broca's)—hesitant speech with word-finding difficulty and preserved comprehension
Sensory aphasia (Wernicke's)—anomia, poor comprehension, jargon speech
Unilateral neglect, apraxias
Homonymous hemianopia or quadrantanopia
Gaze preference with eyes deviated toward side of lesion
Cerebral Hemisphere, Medial Aspect (Anterior Cerebral A.)
Paralysis of foot and leg with or without paresis of arm
Cortical sensory loss over leg
Grasp and sucking reflexes
Urinary incontinence
Gait apraxia
Cerebral Hemisphere, Posterior Aspect (Posterior Cerebral A.)
Homonymous hemianopia
Cortical blindness
Memory deficit
Dense sensory loss, spontaneous pain, dysesthesias, choreoathetosis
Brainstem, Midbrain (Posterior Cerebral A.)
Third nerve palsy and contralateral hemiplegia
Paralysis/paresis of vertical eye movement
Convergence nystagmus, disorientation
Brainstem, Pontomedullary Junction (Basilar A.)
Facial paralysis
Paresis of abduction of eye
Paresis of conjugate gaze
Hemifacial sensory deficit
Horner's syndrome
Diminished pain and thermal sense over half body (with or without face)
Ataxia
Brainstem, Lateral Medulla (Vertebral A.)
Vertigo, nystagmus
Horner's syndrome (miosis, ptosis, decreased sweating)
Ataxia, falling toward side of lesion
Impaired pain and thermal sense over half body with or without face

Lacunar Syndromes (Small-Vessel Strokes)

Most common are:

- Pure motor hemiparesis of face, arm, and leg (internal capsule or pons)
- Pure sensory stroke (ventral thalamus)
- Ataxic hemiparesis (pons or internal capsule)
- Dysarthria—clumsy hand (pons or genu of internal capsule)

Intracranial Hemorrhage

Vomiting and drowsiness occur in some cases with increased intracranial pressure (ICP), and headache is common. Signs and symptoms are often not confined to a

http://internalmedicinebook.com

TABLE 17-2 CAUSES OF INTRACRANIAL HEMORRHAGE

Cause	Location	Comments
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural)	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~30–100 μm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion
Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–3% per year for bleeding if previously unruptured
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; associated with dementia, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in *KRIT1*, *CCM2*, and *PDCD10* genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

single vascular territory. Etiologies are diverse but hypertension related is the most common (Table 17-2). Hypertensive hemorrhages typically occur in the following locations:

- Putamen: contralateral hemiparesis often with homonymous hemianopia
- Thalamus: hemiparesis with prominent sensory deficit
- Pons: quadriplegia, "pinpoint" pupils, impaired horizontal eye movements
- Cerebellum: headache, vomiting, gait ataxia

A neurologic deficit that evolves gradually over 30–90 min strongly suggests intracerebral bleeding.

TREATMENT STROKE

Principles of management are outlined in Fig. 17-1. Stroke needs to be distinguished from potential mimics, including seizure, migraine, tumor, and metabolic derangements.

http://internalmedicinebook.com

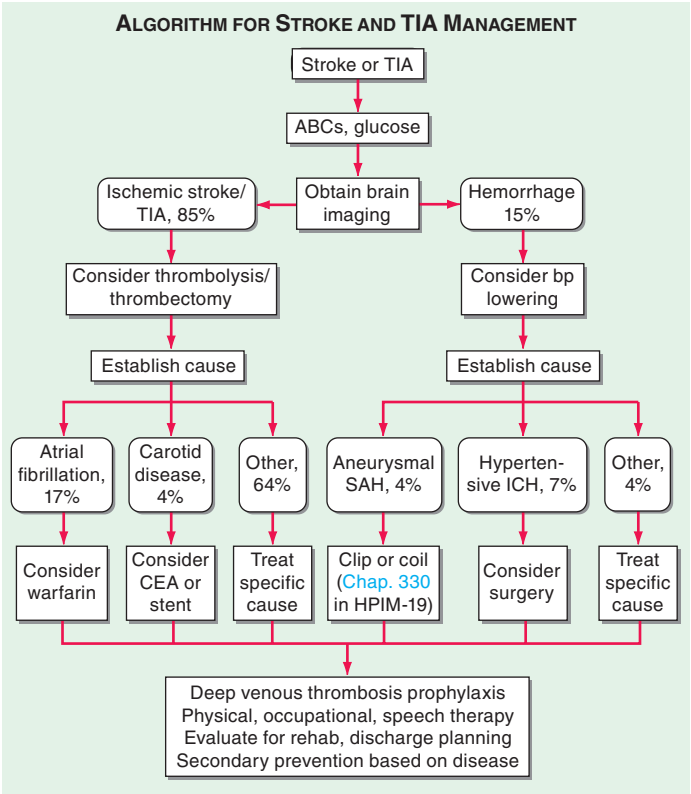


FIGURE 17-1 Medical management of stroke and TIA. *Rounded boxes* are diagnoses; *rectangles* are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; bp, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

- Imaging. After initial stabilization, an emergency noncontrast head CT scan is necessary to differentiate ischemic from hemorrhagic stroke. With large ischemic strokes, CT abnormalities are usually evident within the first few hours, but small infarcts can be difficult to visualize by CT. CT or MR angiography (CTA/MRA) may help reveal vascular occlusions. Diffusion-weighted MRI has a high sensitivity for identifying ischemic stroke even minutes after onset.

ACUTE ISCHEMIC STROKE Treatments designed to reverse or lessen tissue infarction include: (1) medical support, (2) intravenous thrombolysis, (3) endovascular revascularization, (4) antiplatelet agents, (5) anticoagulation, and (6) neuroprotection.

MEDICAL SUPPORT Optimize perfusion in ischemic penumbra surrounding the infarct.

- Blood pressure should never be lowered precipitously (exacerbates the underlying ischemia), and only in the most extreme situations should gradual lowering

http://internalmedicinebook.com

be undertaken (e.g., malignant hypertension with bp > 220/120 mmHg or, if thrombolysis planned, bp > 185/110 mmHg).

- Intravascular volume should be maintained with isotonic fluids because volume restriction is rarely helpful. Osmotic therapy with mannitol may be necessary to control edema in large infarcts, but isotonic volume must be replaced to avoid hypovolemia.
- In cerebellar infarction (or hemorrhage), rapid deterioration can occur from brainstem compression and hydrocephalus, requiring neurosurgical intervention.

INTRAVENOUS THROMBOLYSIS

- Ischemic deficits of <3 h duration, with no hemorrhage by CT criteria, may benefit from thrombolytic therapy with IV recombinant tissue plasminogen activator (Table 17-3).
- Based on trial data, IV rtPA is used in many centers for deficits of 3–4.5 h duration, but is not yet approved for this window in the United States.

TABLE 17-3 ADMINISTRATION OF INTRAVENOUS RTPA FOR AIS[a]

Indication	Contraindication
Clinical diagnosis of stroke	Sustained bp >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤4.5 h[b]	Platelets <100,000; Hct <25%; glucose <50 or >400 mg/dL
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Use of heparin within 48 h and prolonged PTT, or elevated INR
Age 18 ≥ years	Rapidly improving symptoms
Consent by patient or surrogate	Prior stroke or head injury within 3 months; prior intracranial hemorrhage
	Major surgery in preceding 14 days
	Minor stroke symptoms
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction
	Coma or stupor

Administration of rtPA

IV access with two peripheral IV lines (avoid arterial or central line placement).
Review eligibility for rtPA.
Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h.
Frequent cuff blood pressure monitoring.
No other antithrombotic treatment for 24 h.
For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently.
Avoid urethral catheterization for ≥2 h.

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.
[b]Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.
Abbreviations: AIS, acute ischemic stroke; INR, international normalized ratio; MCA, middle cerebral artery; rtPA, recombinant tissue plasminogen activator; PTT, partial thromboplastin time.

http://internalmedicinebook.com

ENDOVASCULAR REVASCULARIZATION

- Ischemic stroke from large-vessel intracranial occlusion results in high rates of morbidity and mortality; pts with such occlusions likely benefit from embolectomy (<6 h duration) administered at the time of an urgent cerebral angiogram at specialized centers. CT angiography is becoming more commonly used as part of initial imaging protocols to identify these patients rapidly.

ANTIPLATELET AGENTS

- Aspirin (up to 325 mg/d) is safe and has a small but definite benefit in acute ischemic stroke.

ANTICOAGULATION

- Trials do not support the use of heparin or other anticoagulants acutely for pts with acute stroke.

NEUROPROTECTION

- Hypothermia is effective in coma following cardiac arrest but has not been shown to benefit stroke patients. Other neuroprotective agents have shown no efficacy in human trials despite promising animal data.

STROKE CENTERS AND REHABILITATION

- Pt care in comprehensive stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality.

ACUTE INTRACEREBRAL HEMORRHAGE

- Noncontrast head CT will confirm diagnosis.
- Rapidly identify and correct any coagulopathy.
- 35–45% of pts die in the first month; prognosis is determined by volume and location of hematoma.
- Stuporous or comatose pts generally are treated presumptively for elevated ICP. Treatment for edema and mass effect with osmotic agents may be necessary; glucocorticoids not helpful.
- Neurosurgical consultation should be sought for possible urgent evacuation of cerebellar hematoma; in other locations, data do not support surgical intervention.

EVALUATION: DETERMINING THE CAUSE OF STROKE

Although initial management of acute ischemic stroke or TIA does not depend on the etiology, establishing a cause is essential to reduce risk of recurrence (Table 17-4); particular attention should be on atrial fibrillation and carotid atherosclerosis because these etiologies have proven secondary prevention strategies. Nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should be focused on the peripheral and cervical vascular system. Routine studies include CXR and ECG, urinalysis, CBC/platelets, electrolytes, glucose, ESR, lipid profile, PT, and PTT. If a hypercoagulable state is suspected, further studies of coagulation are indicated.

Imaging evaluation may include brain MRI (compared with CT, increased sensitivity for small infarcts of cortex and brainstem); MR or CT angiography (evaluate patency of intracranial vessels and extracranial carotid and vertebral vessels); noninvasive carotid ultrasound; or cerebral angiography ("gold standard" for evaluation of intracranial and extracranial vascular disease). For suspected cardiogenic source, cardiac echocardiogram with attention to right-to-left shunts, and inpatient cardiac telemetry and long-term cardiac event monitoring indicated.

http://internalmedicinebook.com

TABLE 17-4 CAUSES OF ISCHEMIC STROKE

Common Causes	Uncommon Causes
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency[a]
Large-vessel thrombosis	Protein S deficiency[a]
Dehydration	Antithrombin III deficiency[a]
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation[a]
Carotid bifurcation	Prothrombin G20210 mutation[a]
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias[a]
Mechanical valve	Nephrotic syndrome[a]
Bacterial endocarditis	Inflammatory bowel disease[a]
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosis[b]
Patent foramen ovale	Fibromuscular dysplasia
Atrial septal aneurysm	Vasculitis
Spontaneous echo contrast	Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis)
Stimulant drugs: cocaine, amphetamine	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Noninflammatory vasculopathy
	Reversible vasoconstriction syndrome
	Fabry's disease
	Angiocentric lymphoma
	Cardiogenic
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Moyamoya disease
	Eclampsia

[a]Chiefly cause venous sinus thrombosis.
[b]May be associated with any hypercoagulable disorder.
Abbreviations: PAN, polyarteritis nodosa.

http://internalmedicinebook.com

PRIMARY AND SECONDARY PREVENTION OF STROKE

Risk Factors

Atherosclerosis is a systemic disease affecting arteries throughout the body. Multiple factors including hypertension, diabetes, hyperlipidemia, and family history influence stroke and TIA risk (Table 17-5). Cardioembolic risk factors include atrial fibrillation/flutter, MI, valvular heart disease, and cardiomyopathy. Hypertension and diabetes are also specific risk factors for lacunar stroke and intraparenchymal hemorrhage. Smoking is a potent risk factor for all vascular mechanisms of stroke. *Identification of modifiable risk factors and prophylactic interventions to lower risk is probably the best approach to stroke overall.*

Antiplatelet Agents

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting formation of intraarterial platelet aggregates. Aspirin (50–325 mg/d) inhibits thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. Aspirin, clopidogrel (blocks the platelet adenosine diphosphate [ADP] receptor), and the combination of aspirin plus extended-release dipyridamole (inhibits platelet uptake of adenosine) are the antiplatelet agents most commonly used. In general, antiplatelet agents reduce new stroke events by 25–30%. Every pt who has experienced an atherothrombotic stroke or TIA and has no contraindication

TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS

Condition	Recommendation
Nonvalvular atrial fibrillation	Calculate CHADS2[a] score
• CHADS2 score 0	Aspirin or no antithrombotic
• CHADS2 score 1	Aspirin or OAC
• CHADS2 score >1	OAC
Rheumatic mitral valve disease	
• With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm	OAC
• Embolization or appendage clot despite OAC	OAC plus aspirin
Mitral valve prolapse	
• Asymptomatic	No therapy
• With otherwise cryptogenic stroke or TIA	Aspirin
• Atrial fibrillation	OAC
Mitral annular calcification	
• Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA	Aspirin
• Recurrent embolization despite aspirin	OAC
• With atrial fibrillation	OAC
Aortic valve calcification	
• Asymptomatic	No therapy
• Otherwise cryptogenic stroke or TIA	Aspirin
Aortic arch mobile atheroma	
• Otherwise cryptogenic stroke or TIA	Aspirin or OAC
Patent foramen ovale	
• Otherwise cryptogenic ischemic stroke or TIA	Aspirin
• Indication for OAC (deep venous thrombosis or hypercoagulable state)	OAC

(*Continued*)

http://internalmedicinebook.com

TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS (*CONTINUED*)

Condition	Recommendation
Mechanical heart value	
• Aortic position, bileaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm	VKA INR 2.5, range 2–3
• Mitral position tilting disk or bileaflet valve	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, anterior-apical myocardial infarct, or left atrial enlargement	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease	Aspirin plus VKA INR 3.0, range 2.5–3.5
• Systemic embolization despite target INR	Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4
Bioprosthetic valve	
• No other indication for VKA therapy	Aspirin
Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis	
• With systemic embolization	Full-dose unfractionated heparin or SC LMWH

[a]CHADS2 score calculated as follows: 1 point for age >75 years, 1 point for hypertension, 1 point for congestive heart failure, 1 point for diabetes, and 2 points for stroke or TIA; sum of points is the total CHADS2 score.
Note: Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.
Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.
Sources: Modified from DE Singer et al: *Chest* 133:546S, 2008; DN Salem et al: *Chest* 133:593S, 2008.

should take an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%. The choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are marginally more effective than aspirin but the cost is higher.

Embolic Stroke

In pts with atrial fibrillation and stroke, anticoagulants are generally the treatment of choice.

Anticoagulation Therapy for Noncardiogenic Stroke

Data do not support the use of long-term warfarin for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease.

Carotid Revascularization

Carotid endarterectomy benefits many pts with *symptomatic* severe (>70%) *carotid stenosis*; the relative risk reduction is ~65%. However, if the perioperative stroke

http://internalmedicinebook.com

rate is >6% for any surgeon, the benefit is questionable. Endovascular stenting is an emerging option; there remains controversy as to who should receive a stent or undergo endarterectomy. Surgical results in pts with *asymptomatic carotid stenosis* are less robust, and medical therapy for reduction of atherosclerosis risk factors plus antiplatelet medications is generally recommended in this group.

For a more detailed discussion, see Smith WS, Johnston SC, Hemphill JC III: Cerebrovascular Diseases, Chap. 446, p. 2559, in HPIM-19.

18 Subarachnoid Hemorrhage

Excluding head trauma, the most common cause of subarachnoid hemorrhage (SAH) is rupture of an intracranial (saccular) aneurysm; other etiologies include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Approximately 2% of the population harbor aneurysms, and 25,000–30,000 cases of aneurysmal rupture producing SAH occur each year in the United States; rupture risk for aneurysms <10 mm in size is 0.1% per year; for unruptured aneurysms, the surgical morbidity rate far exceeds the percentage.

CLINICAL PRESENTATION

Sudden, severe headache, often with transient loss of consciousness at onset; vomiting is common. Bleeding may injure adjacent brain tissue and produce focal neurologic deficits. A progressive third nerve palsy, usually involving the pupil, along with headache, suggests posterior communicating artery aneurysm. In addition to dramatic presentations, aneurysms can undergo small ruptures with leaks of blood into the subarachnoid space (sentinel bleeds). The initial clinical manifestations of SAH can be graded using established scales (Table 18-1); prognosis for good outcome falls as the grade increases.

INITIAL EVALUATION

- Noncontrast CT is initial study of choice and usually demonstrates hemorrhage if obtained within 72 h. LP is required for diagnosis of suspected SAH if CT is nondiagnostic; xanthochromia of the spinal fluid is seen within 6–12 h after rupture and lasts for 1–4 weeks.
- Cerebral angiography is necessary to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist; angiography should be performed as soon as possible after diagnosis of SAH.
- ECG may reveal ST-segment and T-wave changes similar to cardiac ischemia; caused by circulating catecholamines and excessive discharge of sympathetic neurons. A reversible cardiomyopathy producing shock or congestive heart failure may result.
- Studies of coagulation and platelet count should be obtained, with rapid correction indicated if SAH is documented.

http://internalmedicinebook.com

TABLE 18-1 GRADING SCALES FOR SUBARACHNOID HEMORRHAGE

Grade	Hunt-Hess Scale	WFNS Scale
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS[a] score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3–6, with or without motor deficits

[a]Glasgow Coma Scale; see Table 19-2.

Abbreviation: WFNS, World Federation of Neurosurgical Societies.

TREATMENT SUBARACHNOID HEMORRHAGE

ANEURYSM REPAIR

- Early aneurysm repair prevents rerupture.
- The International Subarachnoid Aneurysm Trial (ISAT) demonstrated improved outcomes with endovascular therapy compared to surgery; however, some aneurysms have morphology not amenable to endovascular treatment, and therefore surgery is still an important treatment option for some pts.

MEDICAL MANAGEMENT

- Closely follow serum electrolytes and osmolality; hyponatremia ("cerebral salt wasting") frequently develops several days after SAH, and supplemental oral salt plus IV normal saline or hypertonic saline may be needed to overcome renal losses.
- Anticonvulsants are sometimes begun until the aneurysm is treated, although most experts reserve this therapy only for pts in whom a seizure has occurred.
- Blood pressure should be carefully controlled, while preserving cerebral blood flow, in order to decrease the risk of rerupture until the aneurysm is repaired.
- All pts should have pneumatic compression stockings applied to prevent pulmonary embolism; unfractionated heparin administered subcutaneously for deep-vein thrombosis prophylaxis can be initiated immediately following endovascular treatment and within days following craniotomy and surgical clipping.

HYDROCEPHALUS

- Severe hydrocephalus may require urgent placement of a ventricular catheter for external CSF drainage; some pts will require permanent shunt placement.
- Deterioration of a SAH pt in the first hours to days should prompt repeat CT scanning to evaluate ventricular size.

VASOSPASM

- The leading cause of mortality and morbidity following initial rupture; may appear 4–14 days after the initial hemorrhage, leading to focal ischemia and stroke.

http://internalmedicinebook.com

- Treatment with the calcium channel antagonist nimodipine (60 mg PO q4h) improves outcomes, perhaps by preventing ischemic injury rather than reducing risk of vasospasm.
- Cerebral perfusion can be improved in symptomatic vasospasm by increasing mean arterial pressure with vasopressor agents such as phenylephrine or norepinephrine, and intravascular volume can be expanded with crystalloid, augmenting cardiac output and reducing blood viscosity by reducing the hematocrit; this so-called "triple-H" (hypertension, hemodilution, and hypervolemic) therapy is widely used.
- If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and angioplasty of the cerebral vessels can be effective.



For a more detailed discussion, see Hemphill JC III, Smith WS, and Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage. Chap. 330, p. 1777, in HPIM-19.

19 Increased Intracranial Pressure and Head Trauma

INCREASED INTRACRANIAL PRESSURE

A limited volume of extra tissue, blood, CSF, or edema can be added to the intracranial contents without raising the intracranial pressure (ICP). Clinical deterioration or death may follow increases in ICP that shift intracranial contents, distort vital brainstem centers, or compromise cerebral perfusion. Cerebral perfusion pressure (CPP), defined as the mean arterial pressure (MAP) minus the ICP, is the driving force for circulation across capillary beds of the brain; decreased CPP is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg.

CLINICAL FEATURES

Elevated ICP may occur in a wide range of disorders including head trauma, intracerebral hemorrhage, subarachnoid hemorrhage (SAH) with hydrocephalus, and fulminant hepatic failure.

Symptoms of high ICP include drowsiness, headache (especially a constant ache that is worse upon awakening), nausea, emesis, diplopia, and blurred vision. Papilledema and sixth nerve palsies are common. If not controlled, cerebral hypoperfusion, pupillary dilation, coma, focal neurologic deficits, posturing, abnormal respirations, systemic hypertension, and bradycardia may result.

http://internalmedicinebook.com

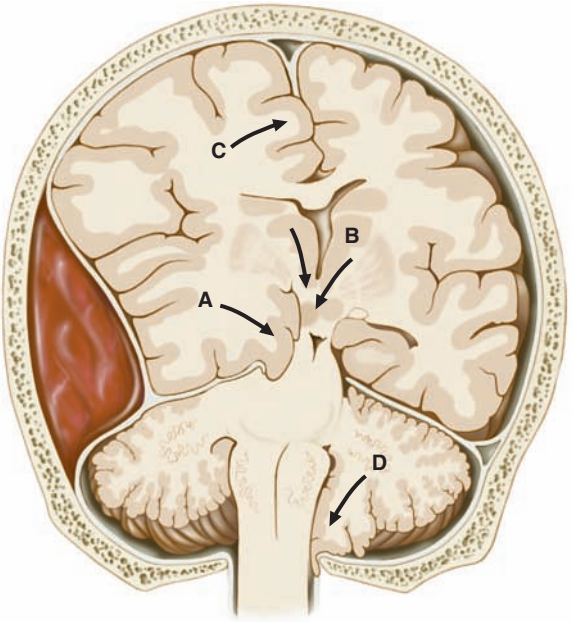


FIGURE 19-1 Types of cerebral herniation. **A.** uncal; **B.** central; **C.** transfalcial; **D.** foraminal.

Masses that cause raised ICP also distort midbrain and diencephalic anatomy, leading to stupor and coma. Brain tissue is pushed away from the mass against fixed intracranial structures and into spaces not normally occupied. Posterior fossa masses, which may initially cause ataxia, stiff neck, and nausea, are especially dangerous because they can both compress vital brainstem structures and cause obstructive hydrocephalus.

Herniation syndromes (Fig. 19-1) include:

- *Uncal:* Medial temporal lobe displaced through the tentorium, compressing the third cranial nerve and pushing the cerebral peduncle of the midbrain against the tentorium, leading to ipsilateral pupillary dilation, contralateral hemiparesis, and posterior cerebral artery compression.
- *Central:* Downward displacement of the thalamus through the tentorium; miotic pupils and drowsiness are early signs.
- *Transfalcial:* Cingulate gyrus displaced under the midline falx, leading to anterior cerebral artery compression.
- *Foraminal:* Cerebellar tonsils displaced into the foramen magnum, causing medullary compression and respiratory arrest.

TREATMENT INCREASED INTRACRANIAL PRESSURE

- A number of different interventions may lower ICP, and ideally the selection of treatment will be based on the underlying mechanism responsible for the elevated ICP (Table 19-1).
- With hydrocephalus, the principal cause of elevated ICP is impaired CSF drainage; in this setting, ventricular drainage of CSF may be sufficient.

http://internalmedicinebook.com

TABLE 19-1 STEPWISE APPROACH TO TREATMENT OF ELEVATED ICP[a]

Insert ICP monitor—ventriculostomy versus parenchymal device

General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP >20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to $PaCO_2$ 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP
   a. Decompressive craniectomy
   b. High-dose barbiturate therapy ("pentobarb coma")
   c. Hypothermia to 33°C (91.4°F)

[a]Throughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP.

Abbreviations: CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide.

- If cytotoxic edema is responsible, as in head trauma or stroke, use of osmotic diuretics such as mannitol or hypertonic saline is an appropriate early step.
- Elevated ICP may cause tissue ischemia; resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase MAP may actually lower ICP by increasing perfusion; therefore, hypertension should be treated carefully, if at all.
- Free water should be restricted.
- Fever should be treated aggressively.
- Hyperventilation is best used for only short periods of time until a more definitive treatment can be instituted.
- ICP monitoring may help guide medical and surgical decisions in selected pts with cerebral edema (Fig. 19-2).

After stabilization and initiation of the above therapies, a CT scan (or MRI, if feasible) is performed to delineate the cause of the elevated ICP. Emergency surgery is sometimes necessary to decompress the intracranial contents in cerebellar stroke with edema, surgically accessible tumor, and subdural or epidural hemorrhage.

http://internalmedicinebook.com

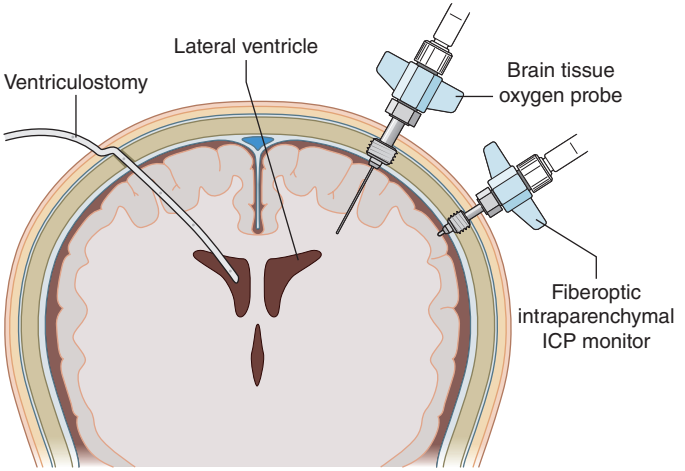


FIGURE 19-2 Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

HEAD TRAUMA

Almost 10 million head injuries occur annually in the United States, about 20% of which are serious enough to cause brain damage.

CLINICAL FEATURES

Head trauma can cause immediate loss of consciousness. Prolonged alterations in consciousness may be due to parenchymal, subdural, or epidural hematoma or to diffuse shearing of axons in the white matter. The term "*concussion*" is now applied to all cognitive and perceptual changes experienced after a blow to the head, whether or not consciousness is lost. Skull fracture should be suspected in pts with CSF rhinorrhea, hemotympanum, and periorbital or mastoid ecchymoses. Glasgow Coma Scale (Table 19-2) is useful for grading severity of brain injury.

APPROACH TO THE PATIENT: Head Injury

Medical personnel caring for head injury pts should be aware that:

- Spinal injury often accompanies head injury and care must be taken to prevent compression of the spinal cord due to instability of the spinal column.
- Intoxication is a frequent accompaniment of traumatic brain injury; when appropriate, testing should be carried out for drugs and alcohol.
- Accompanying systemic injuries, including ruptures of abdominal organs, may produce vascular collapse or respiratory compromise requiring immediate attention.

Minor Head Injury The pt with minor head injury who is alert and attentive after a short period of unconsciousness (<1 min) may have headache, dizziness,

http://internalmedicinebook.com

TABLE 19-2 GLASGOW COMA SCALE FOR HEAD INJURY

Eye Opening (E)		Verbal Response (V)	
Spontaneous	4	Oriented	5
To loud voice	3	Confused, disoriented	4
To pain	2	Inappropriate words	3
Nil	1	Incomprehensible sounds	2
		Nil	1
Best Motor Response (M)			
Obeys	6		
Localizes	5		
Withdraws (flexion)	4		
Abnormal flexion posturing	3		
Extension posturing	2		
Nil	1		

Note: Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative, whereas scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

faintness, nausea, a single episode of emesis, difficulty with concentration, or slight blurring of vision. Such pts have usually sustained a concussion and are expected to have a brief amnestic period.

Two studies have indicated that older age, two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It may be appropriate to be more liberal in obtaining CT scans in children, although the risks of radiation must be considered.

In the current absence of adequate data, a common sense approach to athletic concussion has been to remove the individual from play immediately and avoid contact sports for at least several days after a mild injury and for a longer period if there are more severe injuries or if there are protracted neurologic symptoms such as headache and difficulty concentrating.

Injury Of Intermediate Severity Pts who are not comatose but who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be hospitalized and have a CT scan. A cerebral contusion or subdural hematoma is often found. Pts with intermediate head injury require medical observation to detect increasing drowsiness, respiratory dysfunction, pupillary enlargement, or other changes in the neurologic examination. Abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, although some cognitive deficits may be persistent.

Severe Injury Pts who are comatose from onset require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and plantar responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the pt should be transported to

http://internalmedicinebook.com

a critical care unit. CT scan may be normal in comatose pts with axonal shearing lesions in cerebral white matter.

The finding of an epidural or subdural hematoma or large intracerebral hemorrhage requires prompt decompressive surgery in otherwise salvageable pts. Measurement of ICP with a ventricular catheter or fiberoptic device in order to guide treatment has been favored by many units but has not improved outcome. Use of prophylactic anticonvulsants has been recommended but there is little supportive data.



For a more detailed discussion, see Hemphill JC III, Smith WS, Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage, Chap. 330, p. 1777; Ropper AH: Concussion and Other Traumatic Head Injuries, Chap. 457e; and Ropper AH: Coma, Chap. 328, p. 1771; in HPIM-19.

20 Spinal Cord Compression

APPROACH TO THE PATIENT: Spinal Cord Compression

Initial symptoms of focal neck or back pain may evolve over days to weeks; followed by combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving over hours to several days. Partial lesions may selectively involve one or more tracts and may be limited to one side of the cord. In severe or abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days to weeks. With thoracic lesions, a sensory level to pain may be present on the trunk, indicating localization to the cord at that dermatomal level.

In pts with spinal cord symptoms, the first priority is to exclude treatable compression by a mass. Compression is more likely to be preceded by warning signs of neck or back pain, bladder disturbances, and sensory symptoms prior to development of weakness; noncompressive etiologies such as infarction and hemorrhage are more likely to produce myelopathy without antecedent symptoms.

MRI with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure. CT myelography can be helpful in pts who have contraindications to MRI. It is important to image the entire spine to search for additional clinically silent lesions. Infectious etiologies, unlike tumor, often cross the disc space to involve adjacent vertebral bodies.

NEOPLASTIC SPINAL CORD COMPRESSION

Occurs in 5–10% of pts with cancer; epidural tumor may be the initial manifestation of malignancy. Most neoplasms are epidural in origin and result from metastases to

http://internalmedicinebook.com

the adjacent spinal bones. Almost any malignant tumor can metastasize to the spinal column with lung, breast, prostate, kidney, lymphoma, and plasma cell dyscrasia being particularly frequent. The thoracic cord is most commonly involved; exceptions include prostate and ovarian tumors, which preferentially involve the lumbar and sacral segments from spread through veins in the anterior epidural space. Urgent MRI is indicated when the diagnosis is suspected; up to 40% of pts with neoplastic cord compression at one level are found to have asymptomatic epidural disease elsewhere. Plain radiographs will miss 15–20% of metastatic vertebral lesions.

TREATMENT NEOPLASTIC SPINAL CORD COMPRESSION

- Glucocorticoids to reduce edema (dexamethasone, up to 40 mg daily) can be administered before the imaging study if the clinical suspicion is high, and continued at a lower dose until radiotherapy (generally 3000 cGy administered in 15 daily fractions) and/or surgical decompression is completed.
- Early surgery, either decompression by laminectomy or vertebral body resection, followed by radiotherapy is more effective than radiotherapy alone for pts with a single area of spinal cord compression by extradural tumor.
- Time is of the essence; fixed motor deficits (paraplegia or quadriplegia) once established for >12 h do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor.
- Biopsy is needed if there is no history of underlying malignancy; a simple systemic workup including chest imaging, mammography, measurement of prostate-specific antigen (PSA), and abdominal CT usually reveals the diagnosis.

SPINAL EPIDURAL ABSCESS

Presents as a triad of pain, fever, and progressive limb weakness. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally <2 weeks but may be several months or longer. Fever is usually present along with elevated white blood cell count, sedimentation rate, and C-reactive protein. Risk factors include an impaired immune status (diabetes mellitus, HIV, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of skin or other soft tissues. Most cases are due to *Staphylococcus aureus*; other causes include gram-negative bacilli, *Streptococcus*, anaerobes, fungi, and tuberculosis.

MRI localizes the abscess. Lumbar puncture (LP) is required only if encephalopathy or other clinical signs raise question of associated meningitis, a feature found in <25% of cases. The level of the LP should be planned to minimize risk of meningitis due to passage of the needle through infected tissue.

TREATMENT SPINAL EPIDURAL ABSCESS

- Decompressive laminectomy with debridement combined with long-term antibiotic treatment.
- Surgical evacuation is unlikely to improve deficits of more than several days duration.
- Broad-spectrum antibiotics should be started empirically before surgery, modified on the basis of culture results, and continued for at least 6 weeks.
- With prompt diagnosis and treatment, up to two-thirds of pts experience significant recovery.

http://internalmedicinebook.com

SPINAL EPIDURAL HEMATOMA

Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasia is a predisposing condition; rarely, hematomas complicate LP or epidural anesthesia. Treatment consists of prompt reversal of any underlying bleeding disorder and surgical decompression.



For a more detailed discussion, see Gucalp R, Dutcher J: Oncologic Emergencies, Chap. 331, p. 1787; and Hauser SL, Ropper AH: Diseases of the Spinal Cord, Chap. 456, p. 2650, in HPIM-19.

21 Hypoxic-Ischemic Encephalopathy

Results from lack of delivery of oxygen to the brain because of extreme hypotension or respiratory failure. Most common causes are MI, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxemia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxemia* because they cause a direct impairment of the respiratory chain.

CLINICAL MANIFESTATIONS

Mild degrees of pure hypoxemia (e.g., at high altitude) cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but with longer periods permanent cerebral damage usually results. It may be difficult to judge the precise degree of hypoxia-ischemia, and some pts make a relatively full recovery even after 8–10 min of global ischemia. The distinction between pure hypoxemia and hypoxia-ischemia is important, because a PaO_2 as low as 2.7 kPa (20 mmHg) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after an insult (especially cardiac arrest) helps to assess prognosis. The prognosis is better for pts with intact brainstem function, as indicated by normal pupillary light responses, intact oculocephalic (doll's eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A low likelihood of a favorable outcome is suggested by the absence of a pupillary light reflex or an extensor or absent motor response to pain on day 3 following the injury. Bilateral absence of the cortical somatosensory evoked potentials (SSEP) in the first several days also conveys a poor prognosis, as does a very elevated serum level (>33 μg/L) of the biochemical marker neuron-specific enolase (NSE). Usefulness of SSEP and NSE is often limited: difficult to obtain in a timely fashion, need for expert interpretation (SSEP), and lack of standardization

http://internalmedicinebook.com

(NSE measurements). Administration of mild hypothermia after cardiac arrest may change the time points when these clinical and electrophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery.

Long-term consequences include persistent coma or vegetative state, dementia, visual agnosia, parkinsonism, choreoathetosis, ataxia, myoclonus, seizures, and an amnestic state. Delayed postanoxic encephalopathy is an uncommon phenomenon in which pts appear to make an initial recovery following an insult and then have a relapse with a progressive course often characterized by widespread demyelination on imaging studies.

TREATMENT HYPOXIC-ISCHEMIC ENCEPHALOPATHY

- Initial treatment is directed at restoring normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluids, pressors, or cardiac pacing.
- Mild hypothermia (33°C [91°F]), initiated as early as possible and continued for 12–24 h, may improve outcome in pts who remain comatose after cardiac arrest, based on trials in pts whose initial rhythm was primarily ventricular fibrillation or pulseless ventricular tachycardia. Potential complications include coagulopathy and an increased risk of infection.
- Anticonvulsants are not usually given prophylactically but may be used to control seizures.
- Posthypoxic myoclonus can be controlled with clonazepam (1.5–10 mg/d) or valproate (300–1200 mg/d) in divided doses.
- Myoclonic status epilepticus within 24 h after a hypoxic-ischemic insult portends a very poor prognosis, even if seizures are controlled.

For a more detailed discussion, see Hemphill JC III, Smith WS, Gress DR: Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy and Subarachnoid Hemorrhage, Chap. 330, p. 1777, in HPIM-19.

22 Status Epilepticus

Defined as continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. The duration of seizure activity to meet the definition has traditionally been 15–30 min. A more practical definition is any situation requiring the acute use of anticonvulsants; in generalized convulsive status epilepticus (GCSE), this is typically when seizures last >5 min.

http://internalmedicinebook.com

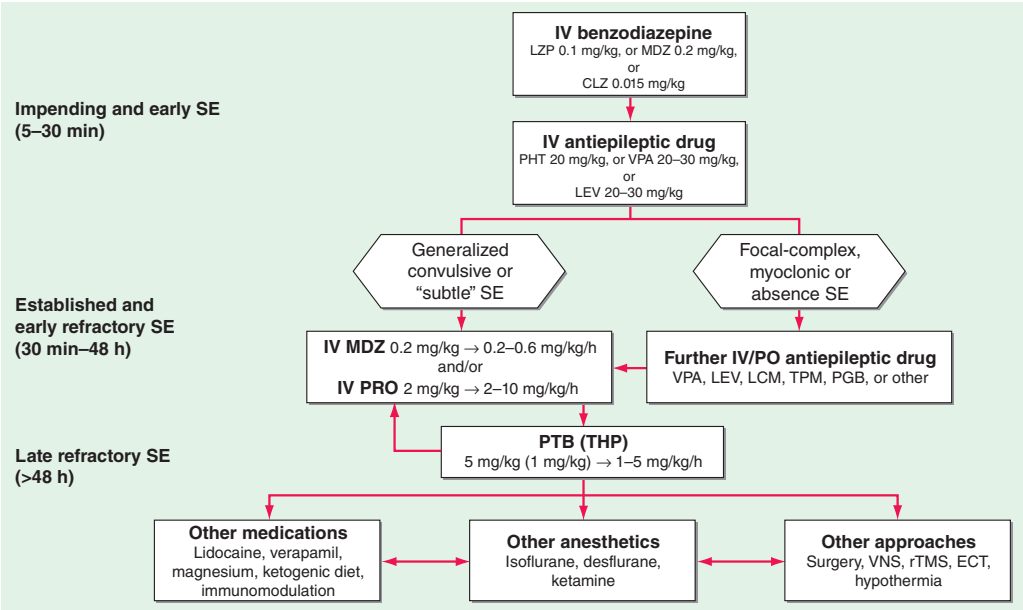


FIGURE 22-1 Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fos-phenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. *(From AO Rossetti, DH Lowenstein: Lancet Neurol 10:922, 2011.)*

http://internalmedicinebook.com

CLINICAL FEATURES

Has numerous subtypes: GCSE (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements), and nonconvulsive status epilepticus (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities). GCSE is obvious when overt convulsions are present, but after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle (mild clonic movements of the fingers; fine, rapid movements of the eyes; or paroxysmal episodes of tachycardia, pupillary dilatation, and hypertension). EEG may be the only method of diagnosis with these subtle signs; therefore, if a pt remains comatose after a seizure, EEG should be performed to exclude ongoing status epilepticus. GCSE is life threatening when accompanied by cardiorespiratory dysfunction, hyperthermia, and metabolic derangements such as acidosis (from prolonged muscle activity). Irreversible neuronal injury may occur from persistent seizures, even when a pt is paralyzed from neuromuscular blockade.

ETIOLOGY

Principal causes of GCSE are antiepileptic drug withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infections, CNS tumors, refractory epilepsy, and head trauma.

TREATMENT STATUS EPILEPTICUS

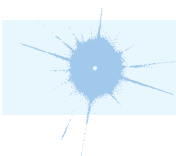
GCSE is a medical emergency and must be treated immediately.

- First attend to any acute cardiorespiratory problems or hyperthermia.
- Perform a brief medical and neurologic examination, establish venous access, and send laboratory tests results to screen for metabolic abnormalities including anticonvulsant levels if pt has a history of epilepsy.
- Anticonvulsant therapy should then begin without delay (Fig. 22-1)
- In parallel, it is essential to determine the cause of the seizures to prevent recurrence and treat any underlying abnormalities.

The treatment of nonconvulsive status epilepticus is somewhat less urgent because the ongoing seizures are not accompanied by the severe metabolic disturbances of GCSE; however, evidence suggests cellular injury in the region of the seizure focus, so the condition should be treated as promptly as possible using the general approach for GCSE.

PROGNOSIS

The mortality rate is 20% in GCSE, and the incidence of permanent neurologic sequelae is 10–50%.



For a more detailed discussion, see Lowenstein DH: Seizures and Epilepsy, Chap. 445, p. 2542, in HPIM-19.

http://internalmedicinebook.com

23 Diabetic Ketoacidosis and Hyperosmolar Coma

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes mellitus (DM). DKA is seen primarily in individuals with type 1 DM and HHS in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental status. The metabolic similarities and differences in DKA and HHS are summarized in Table 23-1.

DIABETIC KETOACIDOSIS

ETIOLOGY

DKA results from insulin deficiency with a relative or absolute increase in glucagon and may be caused by inadequate insulin administration, infection (pneumonia, urinary tract infection, gastroenteritis, sepsis), infarction (cerebral, coronary, mesenteric, peripheral), surgery, trauma, drugs (cocaine), or pregnancy. A common precipitating scenario is the pt with type 1 DM who erroneously stops administering insulin because of anorexia/lack of food intake caused by a minor illness, followed by lipolysis and progressive ketosis leading to DKA.

CLINICAL FEATURES

The initial symptoms of DKA include anorexia, nausea, vomiting, polyuria, and thirst. Abdominal pain, altered mental function, or frank coma may ensue. Classic signs of DKA include Kussmaul respirations and an acetone odor on the pt's breath. Volume depletion can lead to dry mucous membranes, tachycardia, and hypotension. Fever and abdominal tenderness may also be present. Laboratory evaluation reveals hyperglycemia, ketosis (β-hydroxybutyrate > acetoacetate), and metabolic acidosis (arterial pH 6.8–7.3) with an increased anion gap (Table 23-1). The fluid deficit is often 3–5 L and can be greater. Despite a total-body potassium deficit, the serum potassium at presentation may be normal or mildly high as a result of acidosis. Similarly, phosphate may be normal at presentation despite total-body phosphate depletion. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are common. Hyperamylasemia is usually of salivary origin but may suggest a diagnosis of pancreatitis. The measured serum sodium is reduced as a consequence of osmotic fluid shifts due to hyperglycemia (1.6-meq reduction for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose).

TREATMENT DIABETIC KETOACIDOSIS

The management of DKA is outlined in Table 23-2.

HYPERGLYCEMIC HYPEROSMOLAR STATE

ETIOLOGY

Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Hyperglycemia induces an osmotic diuresis that leads to profound intravascular volume depletion. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or sepsis and compounded by conditions that impede access to water.

http://internalmedicinebook.com

TABLE 23-1 LABORATORY VALUES IN DKA AND HHS (REPRESENTATIVE RANGES AT PRESENTATION)

	DKA	HHS
Glucose,[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)[c]
Sodium, meq/L	125–135	135–145
Potassium,[a] meq/L	Normal to ↑[b]	Normal
Magnesium[a]	Normal[b]	Normal
Chloride[a]	Normal	Normal
Phosphate[a]	Normal to ↓[b]	Normal
Creatinine, μmol/L (mg/dL)	Slightly ↑	Moderately ↑
Osmolality (mosmol/mL)	300–320	330–380
Plasma ketones[a]	++++	±
Serum bicarbonate,[a] meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial PCO_2,[a] mmHg	20–30	Normal
Anion gap[a] [Na – (Cl + HCO_3)], meq/L	↑	Normal to slightly ↑

[a]Large changes occur during treatment of DKA.
[b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.
[c]Large changes occur during treatment
Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state.

CLINICAL FEATURES

Presenting symptoms include polyuria, thirst, and altered mental state, ranging from lethargy to coma. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA. The prototypical pt is an elderly individual with a several week history of polyuria, weight loss, and diminished oral intake. The laboratory features are summarized in Table 23-1. In contrast to DKA, acidosis and ketonemia are usually not found; however, a small anion gap may be due to lactic acidosis, and moderate ketonuria may occur from starvation. Prerenal azotemia is typically present. Although the measured serum sodium may be normal or slightly low, the corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). HHS, even when adequately treated, has a significant mortality rate (up to 15%), which is in part explained by comorbidities and pt age.

TREATMENT HYPERGLYCEMIC HYPEROSMOLAR STATE

The precipitating problem should be sought and treated. Sufficient IV fluids (1–3 L of 0.9% normal saline over the first 2–3 h) should be given to stabilize the hemodynamic status. The calculated free water deficit (usually 9–10 L) should be reversed over the next 1–2 days, using 0.45% saline initially then 5% dextrose in water. Overly rapid fluid replacement should be avoided to prevent worsening of neurologic status. Potassium repletion is usually necessary. The plasma glucose may drop precipitously with hydration alone, though insulin therapy with an IV bolus of 0.1 units/kg followed by a constant infusion rate (0.1 units/kg per hour) is usually required. If the serum glucose does not fall, the insulin infusion rate should be doubled. Glucose should be added to IV fluid, and the insulin infusion

http://internalmedicinebook.com

TABLE 23-2 MANAGEMENT OF DIABETIC KETOACIDOSIS

1. Confirm diagnosis (plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.
3. Assess: Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate) Acid-base status—pH, HCO_3^-, PCO_2, β-hydroxybutyrate renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (10–15 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 14 mmol/L (250 mg/dL).
5. Administer short-acting insulin: IV (0.1 units/kg) or IM (0.3 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. If initial serum potassium is <3.3 meq/L, do not administer insulin until the potassium is corrected to >3.3 meq/L. If the initial serum potassium is >5.2 meq/L, do not supplement K^+ until the potassium is corrected.
6. Assess pt: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, chest x-ray, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace K^+: 10 meq/h when plasma K^+ <5.0–5.2 meq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ <3.5 meq/L or if bicarbonate is given. If initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement K^+ until the potassium is corrected.
10. Continue above until pt is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as pt is eating. Allow for overlap in insulin infusion and SC insulin injection.

Source: Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 1998; and AE Kitabchi et al: *Diabetes Care* 29:2739, 2006.

rate decreased when the plasma glucose falls to 13.9 mmol/L (250 mg/dL). The insulin infusion should be continued until the pt has resumed eating and can be transitioned to a subcutaneous insulin regimen.

For a more detailed discussion, see Powers AC: Diabetes Mellitus: Management and Therapies, Chap. 418, p. 2407 in HPIM-19.

http://internalmedicinebook.com

24 Hypoglycemia

Glucose is an obligate metabolic fuel for the brain. Hypoglycemia should be considered in any pt with confusion, altered level of consciousness, or seizures. Counterregulatory responses to hypoglycemia include insulin suppression and the release of catecholamines, glucagon, growth hormone, and cortisol.

The laboratory diagnosis of hypoglycemia is usually defined as a plasma glucose level <2.5–2.8 mmol/L (<45–50 mg/dL), although the absolute glucose level at which symptoms occur varies among individuals. For this reason, *Whipple's triad* should be present: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration measured by a method capable of accurately measuring low glucose levels (not a glucose monitor), and (3) relief of symptoms after the plasma glucose level is raised.

ETIOLOGY

Hypoglycemia occurs most commonly as a result of treating pts with diabetes mellitus. Additional factors to be considered in any pt with hypoglycemia are listed below.

1. Drugs: insulin, insulin secretagogues (especially chlorpropamide, repaglinide, nateglinide), alcohol, high doses of salicylates, sulfonamides, pentamidine, quinine, quinolones
2. Critical illness: hepatic, renal, or cardiac failure; sepsis; prolonged starvation
3. Hormone deficiencies: adrenal insufficiency, hypopituitarism (particularly in young children)
4. Insulinoma (pancreatic β cell tumor), β cell hyperplasia (nesidioblastosis; congenital or after gastric or bariatric surgery)
5. Other rare etiologies: non–β cell tumors (large mesenchymal or epithelial tumors producing an incompletely processed IGF-II, other nonpancreatic tumors), antibodies to insulin or the insulin receptor, inherited enzymatic defects such as hereditary fructose intolerance and galactosemia

CLINICAL FEATURES

Symptoms of hypoglycemia can be divided into autonomic (adrenergic: palpitations, tremor, and anxiety; cholinergic: sweating, hunger, and paresthesia) and neuroglycopenic (behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death). Signs of autonomic discharge, such as tachycardia, elevated systolic blood pressure, pallor, and diaphoresis, are typically present in a pt with hypoglycemia awareness but may be absent in a pt with pure neuroglycopenia.

Recurrent hypoglycemia shifts thresholds for the autonomic symptoms and counterregulatory responses to lower glucose levels, leading to hypoglycemic unawareness. Under these circumstances, the first manifestation of hypoglycemia is neuroglycopenia, placing pts at risk of being unable to treat themselves.

DIAGNOSIS

Diagnosis of the hypoglycemic mechanism is critical for choosing a treatment that prevents recurrent hypoglycemia (Fig. 24-1). Urgent treatment is often necessary in pts with suspected hypoglycemia. Nevertheless, blood should be drawn at the time of symptoms, whenever possible before the administration of glucose, to allow documentation of hypoglycemia as the cause of symptoms. If the glucose level is low and the cause of hypoglycemia is unknown, additional assays should be performed

http://internalmedicinebook.com

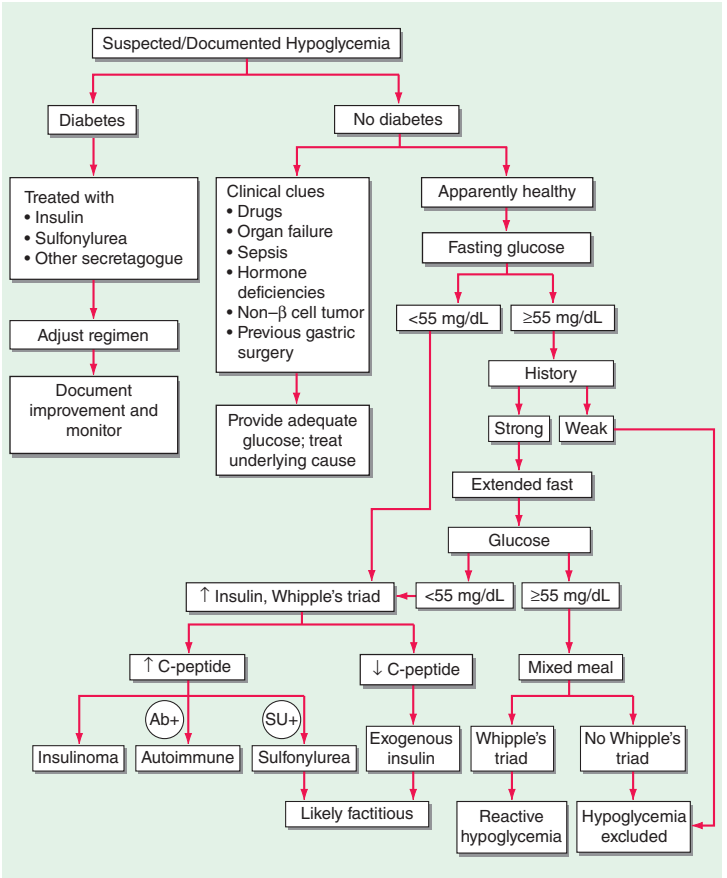


FIGURE 24-1 Diagnostic approach to a pt with suspected hypoglycemia based on a history of symptoms, a low plasma glucose concentration, or both. AB+, positive for antibodies against insulin or the insulin receptor; SU+, positive for sulfonylurea.

on blood obtained at the time of a low plasma glucose. These should include insulin, proinsulin, C-peptide, sulfonylurea levels, cortisol, and ethanol. In the absence of documented spontaneous hypoglycemia, overnight fasting or food deprivation during observation in the outpatient setting will sometimes elicit hypoglycemia and allow diagnostic evaluation. An extended (up to 72 h) fast under careful supervision in the hospital may be required—the test should be terminated if plasma glucose drops below 2.5 mmol/L (45 mg/dL) and the pt has symptoms.

Interpretation of fasting test results is shown in Table 24-1.

TREATMENT HYPOGLYCEMIA

The syndrome of hypoglycemic unawareness in pts with diabetes mellitus is reversible after as little as 2 weeks of scrupulous avoidance of hypoglycemia. This involves a shift of glycemic thresholds for sympathetic autonomic symptoms back to higher glucose concentrations.

http://internalmedicinebook.com

TABLE 24-1 DIAGNOSTIC INTERPRETATION OF HYPOGLYCEMIA

Diagnosis	Glucose, mmol/L (mg/dL)	Insulin, μU/mL	C-Peptide, pmol/L	Proinsulin, pmol/L	Urine or Plasma Sulfonylurea
Nonhypoglycemic	≥2.2 (≥40)	<3	<200	<5	No
Insulinoma	≤2.5 (≤45)	≥3	≥200	≥5	No
Exogenous insulin	≤2.5 (≤45)	≥3[a]	<200	<5	No
Sulfonylurea	≤2.5 (≤45)	≥3	≥200	≥5	Yes
Non-insulin mediated	≤2.5 (≤45)	<3	<200	<5	No

[a]Often very high.

Acute therapy of hypoglycemia requires administration of oral glucose or, if unavailable, rapidly absorbable sugar (e.g., fruit juice), or 25 g of a 50% solution IV followed by a constant infusion of 5% or 10% dextrose if parenteral therapy is necessary. Hypoglycemia from sulfonylureas is often prolonged, requiring treatment and monitoring for 24 h or more. SC or IM glucagon can be used in diabetics. Prevention of recurrent hypoglycemia requires treatment of the underlying cause of hypoglycemia, including discontinuation or dose reduction of offending drugs, treatment of critical illnesses, replacement of hormonal deficiencies, and surgery of insulinomas or other tumors. Diazoxide or octreotide therapy can be used to control hypoglycemia in inoperable metastatic insulinoma or nesidioblastosis. Treatment of other forms of hypoglycemia is dietary, with avoidance of fasting and ingestion of frequent small meals.

For a more detailed discussion, see Cryer PE, Davis SN: Hypoglycemia, Chap. 420, p. 2430, in HPIM-19.

25 Oncologic Emergencies

Emergencies in the cancer pt may be classified into three categories: effects from tumor expansion, metabolic or hormonal effects mediated by tumor products, and treatment complications.

http://internalmedicinebook.com

STRUCTURAL/OBSTRUCTIVE ONCOLOGIC EMERGENCIES

The most common problems are superior vena cava syndrome; pericardial effusion/tamponade; spinal cord compression; seizures (Chap. 181) and/or increased intracranial pressure; and intestinal, urinary, or biliary obstruction. The last three conditions are discussed in Chap. 331 in HPIM-19.

SUPERIOR VENA CAVA SYNDROME

Obstruction of the superior vena cava reduces venous return from the head, neck, and upper extremities. About 85% of cases are due to lung cancer; lymphoma and thrombosis of central venous catheters are also causes. Pts often present with facial swelling, dyspnea, and cough. In severe cases, the mediastinal mass lesion may cause tracheal obstruction. Dilated neck veins and increased collateral veins on anterior chest wall are noted on physical examination. Chest x-ray (CXR) documents widening of the superior mediastinum; 25% of pts have a right-sided pleural effusion.

TREATMENT SUPERIOR VENA CAVA SYNDROME

Radiation therapy is the treatment of choice for non-small-cell lung cancer; addition of chemotherapy to radiation therapy is effective in small-cell lung cancer and lymphoma. Symptoms recur in 10–30% and can be palliated by venous stenting. Clotted central catheters producing this syndrome should be removed and anticoagulation therapy initiated.

PERICARDIAL EFFUSION/TAMPONADE

Accumulation of fluid in the pericardium impairs filling of the heart and decreases cardiac output. Most commonly seen in pts with lung or breast cancers, leukemias, or lymphomas, pericardial tamponade may also develop as a late complication of mediastinal radiation therapy (constrictive pericarditis). Common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, and cyanosis are frequent physical findings. Paradoxical pulse, decreased heart sounds, pulsus alternans, and friction rub are less common with malignant than nonmalignant pericardial disease. Echocardiography is diagnostic; pericardiocentesis may show serous or bloody exudate, and cytology usually shows malignant cells.

TREATMENT PERICARDIAL EFFUSION/TAMPONADE

Drainage of fluid from the pericardial sac may be lifesaving until a definitive surgical procedure (pericardial stripping or window) can be performed.

SPINAL CORD COMPRESSION

Primary spinal cord tumors occur rarely, and cord compression is most commonly due to epidural metastases from vertebral bodies involved with tumor, especially from prostate, lung, breast, lymphoma, and myeloma primaries. Pts present with back pain, worse when recumbent, with local tenderness. Loss of bowel and bladder control may occur. On physical examination, pts have a loss of sensation below a horizontal line on the trunk, called a *sensory level*, which usually corresponds to one or two vertebrae below the site of compression. Weakness and spasticity of the legs and hyperactive reflexes with upgoing toes on Babinski testing are often noted. Spine radiographs may reveal erosion of the pedicles (winking owl sign), lytic or sclerotic vertebral body lesions, and vertebral collapse. Collapse alone is not a reliable indicator of tumor; it is a common manifestation of a more common disease, osteoporosis. MRI can visualize the cord throughout its length and define the extent of tumor involvement.

http://internalmedicinebook.com

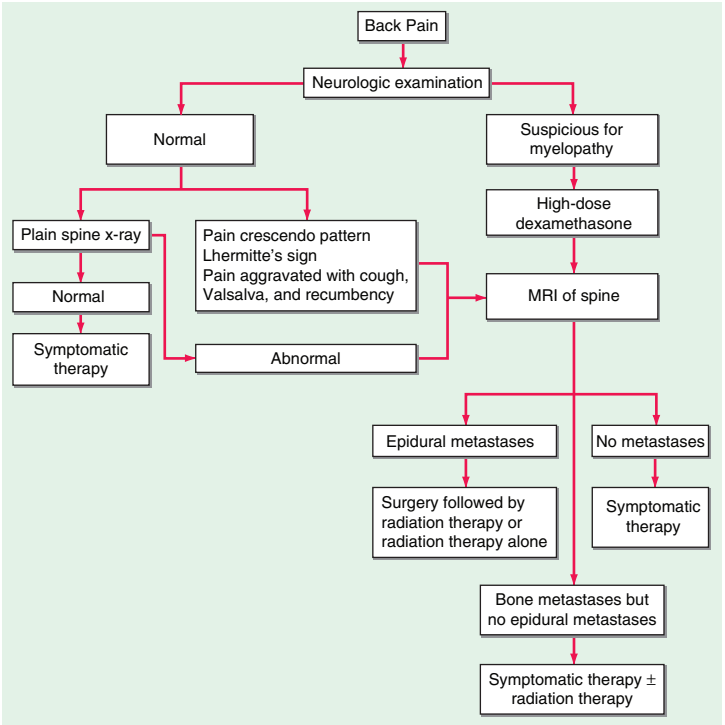


FIGURE 25-1 Management of cancer pts with back pain.

TREATMENT **SPINAL CORD COMPRESSION (FIG. 25-1)**

Radiation therapy plus dexamethasone, 4 mg IV or PO q4h, is successful in arresting and reversing symptoms in about 75% of pts who are diagnosed while still ambulatory. Surgery results in better recovery rates but may be extensive (vertebral body resection with spine stabilization). Only 10% of pts made paraplegic by the tumor recover the ability to ambulate.

EMERGENT PARANEOPLASTIC SYNDROMES

Most paraneoplastic syndromes have an insidious onset (Chap. 76). Hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and adrenal insufficiency may present as emergencies.

HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia occurs in about 10% of cancer pts, particularly those with lung, breast, head and neck, and kidney cancer and myeloma. Bone resorption mediated by parathyroid hormone–related protein is the most common mechanism; interleukin 1 (IL-1), IL-6, tumor necrosis factor, and transforming growth factor β may act locally in tumor-involved bone. Pts usually present with nonspecific symptoms: fatigue, anorexia, constipation, weakness. Hypoalbuminemia associated with malignancy may make symptoms worse for any

http://internalmedicinebook.com

given serum calcium level because more calcium will be free rather than protein bound.

TREATMENT HYPERCALCEMIA

Saline hydration, antiresorptive agents (e.g., pamidronate, 60–90 mg IV over 4 h, or zoledronate, 4–8 mg IV), and glucocorticoids usually lower calcium levels significantly within 1–3 days. Treatment effects usually last several weeks. Treatment of the underlying malignancy is also important.

SIADH

Induced by the action of arginine vasopressin produced by certain tumors (especially small cell cancer of the lung), SIADH is characterized by hyponatremia, inappropriately concentrated urine, and high urine sodium excretion in the absence of volume depletion. Most pts with SIADH are asymptomatic. When serum sodium falls to <115 meq/L, pts may experience anorexia, depression, lethargy, irritability, confusion, weakness, and personality changes.

TREATMENT SIADH

Water restriction controls mild forms. Demeclocycline (150–300 mg PO tid or qid) inhibits the effects of vasopressin on the renal tubule but has a slow onset of action (1 week). Conivaptan can be given PO (20–120 mg bid) or IV (10–40 mg); tolvaptan (15 mg PO daily) is a vasopressin agonist that can be used. Treatment of the underlying malignancy is also important. If the pt has mental status changes with sodium levels <115 meq/L, normal saline infusion plus furosemide to increase free water clearance may provide more rapid improvement. Rate of correction should not exceed 0.5–1 meq/L per h. More rapid change can produce fluid shifts that lead to brain damage.

ADRENAL INSUFFICIENCY

The infiltration of the adrenals by tumor and their destruction by hemorrhage are the two most common causes. In addition, the immunologic checkpoint inhibiting antibodies, ipilimumab, nivolumab, and pembrolizumab can produce an autoimmune hypophysitis that leads to adrenal insufficiency. Symptoms such as nausea, vomiting, anorexia, and orthostatic hypotension may be attributed to progressive cancer or to treatment side effects. Certain treatments (e.g., ketoconazole, aminoglutethimide) may directly interfere with steroid synthesis in the adrenal.

TREATMENT ADRENAL INSUFFICIENCY

In emergencies, a bolus of 100-mg IV hydrocortisone is followed by a continuous infusion of 10 mg/h. In nonemergent but stressful circumstances, 100–200 mg/d oral hydrocortisone is the beginning dose, tapered to maintenance of 15–37.5 mg/d. Fludrocortisone (0.1 mg/d) may be required in the presence of hyperkalemia.

TREATMENT COMPLICATIONS

Complications from treatment may occur acutely or emerge only many years after treatment. Toxicity may be either related to the agents used to treat the cancer or from the response of the cancer to the treatment (e.g., leaving a perforation in a

http://internalmedicinebook.com

hollow viscus or causing metabolic complications such as tumor lysis syndrome). Several treatment complications present as emergencies. Fever and neutropenia and tumor lysis syndrome will be discussed here; others are discussed in Chap. 331 in HPIM-19.

FEVER AND NEUTROPENIA

Many cancer pts are treated with myelotoxic agents. When peripheral blood granulocyte counts are <1000/μL, the risk of infection is substantially increased (48 infections/100 pts). A neutropenic pt who develops a fever (>38°C [100.4°F]) should undergo physical examination with special attention to skin lesions, mucous membranes, IV catheter sites, and perirectal area. Two sets of blood cultures from different sites should be drawn and a CXR performed, and any additional tests should be guided by findings from the history and physical examination. Any fluid collections should be tapped, and urine and/or fluids should be examined under the microscope for evidence of infection.

TREATMENT FEVER AND NEUTROPENIA

After cultures are obtained, all pts should receive IV broad-spectrum antibiotics (e.g., ceftazidime, 1 g q8h). If an obvious infectious site is found, the antibiotic regimen is designed to cover organisms that may cause the infection. Usually therapy should be started with an agent or agents that cover both gram-positive and -negative organisms. If the fever resolves, treatment should continue until neutropenia resolves. Persistence of febrile neutropenia after 7 days should lead to addition of amphotericin B (or another broad-spectrum antifungal agent like posaconazole) to the antibiotic regimen.

TUMOR LYSIS SYNDROME

When rapidly growing tumors are treated with effective chemotherapy regimens, the dying tumor cells can release large amounts of nucleic acid breakdown products (chiefly uric acid), potassium, phosphate, and lactic acid. The phosphate elevations can lead to hypocalcemia. The increased uric acid, especially in the setting of acidosis, can precipitate in the renal tubules and lead to renal failure. The renal failure can exacerbate the hyperkalemia.

TREATMENT TUMOR LYSIS SYNDROME

Prevention is the best approach. Maintain hydration with 3 L/d of saline, keep urine pH > 7.0 with bicarbonate administration, and start allopurinol, 300 mg/m^2 per day, 24 h before starting chemotherapy. Once chemotherapy is given, monitor serum electrolytes every 6 h. If after 24 h, uric acid (>8 mg/dL) and serum creatinine (>1.6 mg/dL) are elevated, rasburicase (recombinant urate oxidase), 0.2 mg/kg IV daily, may lower uric acid levels. If serum potassium is >6.0 meq/L and renal failure ensues, hemodialysis may be required. Maintain normal calcium levels.



For a more detailed discussion, see Finberg RW: Infections in Patients with Cancer, Chap. 104, p. 484; Jameson JL, Longo DL: Paraneoplastic Syndromes: Endocrinologic/Hematologic, Chap. 121, p. 608, and Gucalp R, Dutcher J: Oncologic Emergencies, Chap. 331, p. 1787, in HPIM-19.

http://internalmedicinebook.com

26 Anaphylaxis

DEFINITION

A life-threatening systemic hypersensitivity reaction to contact with an allergen; it may appear within minutes of exposure to the offending substance. Manifestations include respiratory distress, pruritus, urticaria, mucous membrane swelling, GI disturbances (including nausea, vomiting, abdominal pain, and diarrhea), and vascular collapse. Virtually any allergen may trigger an anaphylactic reaction, but among the more common agents are proteins such as antisera, hormones, pollen extracts, Hymenoptera venom, and foods; drugs (especially antibiotics); and diagnostic agents such as IV contrast material. Atopy does not seem to predispose to anaphylaxis from penicillin or venom exposures. Anaphylactic transfusion reactions are covered in Chap. 8.

CLINICAL PRESENTATION

Time to onset is variable, but symptoms usually occur within seconds to minutes of exposure to the offending antigen:

- Respiratory: mucous membrane swelling, hoarseness, stridor, wheezing
- Cardiovascular: tachycardia, hypotension
- Cutaneous: pruritus, urticaria, angioedema

DIAGNOSIS

Made by obtaining history of exposure to offending substance with subsequent development of characteristic complex of symptoms.

TREATMENT ANAPHYLAXIS

Mild symptoms such as pruritus and urticaria can be controlled by administration of 0.3–0.5 mL of 1:1000 (1.0 mg/mL) epinephrine SC or IM, with repeated doses as required at 5- to 20-min intervals for a severe reaction.

An IV infusion should be initiated for administration of 2.5 mL of 1:10,000 epinephrine solution at 5- to 10-min intervals, and volume expanders such as normal saline, and vasopressor agents, e.g., dopamine, if intractable hypotension occurs.

Epinephrine provides both α- and β-adrenergic effects, resulting in vasoconstriction and bronchial smooth-muscle relaxation. Beta blockers are relatively contraindicated in persons at risk for anaphylactic reactions.

The following should also be used as necessary:

- Antihistamines such as diphenhydramine 50–100 mg IM or IV.
- Nebulized albuterol or aminophylline 0.25–0.5 g IV for bronchospasm.
- Oxygen; endotracheal intubation or tracheostomy may be necessary for progressive hypoxemia.
- Glucocorticoids (methylprednisolone 0.5–1.0 mg/kg IV); not useful for acute manifestations but may help alleviate later recurrence of hypotension, bronchospasm, or urticaria.
- For antigenic material injected into an extremity consider: use of a tourniquet proximal to the site, 0.2 mL of 1:1000 epinephrine into the site, removal without compression of an insect stinger if present.

http://internalmedicinebook.com

PREVENTION

Avoidance of offending antigen, where possible; skin testing and desensitization to materials such as penicillin and Hymenoptera venom, if necessary. Individuals should wear an informational bracelet and have immediate access to an unexpired epinephrine kit.



For a more detailed discussion, see Boyce JA, Austen KF: Allergies, Anaphylaxis, and Systemic Mastocytosis, Chap. 376, p. 2113, in HPIM-19.

27 Bites, Venoms, Stings, and Marine Poisonings

MAMMALIAN BITES

- Each year, there are ~300 dog and cat bites per 100,000 population in the United States, with most bites inflicted by pet animals.
- The microbiology of bite wounds typically reflects the oral flora of the biting animal.
- Bites from many different animals can transmit rabies and tularemia.

DOG BITES

- **Epidemiology:** Dogs bite ≥4.7 million people per year, causing 80% of all animal bites; 15–20% of dog bites become infected.
- **Bacteriology (Table 27-1):** includes aerobic and anaerobic organisms, such as β-hemolytic streptococci; *Eikenella corrodens*; *Capnocytophaga canimorsus*; and *Pasteurella*, *Staphylococcus*, *Actinomyces*, and *Fusobacterium* species
- **Clinical features:** typically manifest within 8–24 h after the bite as local cellulitis with purulent, sometimes foul-smelling discharge. Systemic spread (e.g., bacteremia, endocarditis, brain abscess) can occur. *C. canimorsus* infection can present as sepsis syndrome, DIC, and renal failure, particularly in pts who are splenectomized, have hepatic dysfunction, or are otherwise immunosuppressed.

CAT BITES

- **Epidemiology:** Cat bites and scratches result in infection in >50% of cases.
- **Bacteriology** (Table 27-1)**:** includes organisms similar to those involved in dog bites. *Pasteurella multocida* and *Bartonella henselae* (the agent of cat-scratch disease) are important cat-associated pathogens.
- **Clinical features:** *P. multocida* infections can cause rapidly advancing inflammation and purulent discharge within a few hours after the bite. Because of deep tissue penetration by narrow, sharp feline incisors, cat bites are more likely than dog bites to cause septic arthritis or osteomyelitis.

http://internalmedicinebook.com

TABLE 27-1 MANAGEMENT OF WOUND INFECTIONS FOLLOWING ANIMAL AND HUMAN BITES

Biting Species	Commonly Isolated Pathogens	Preferred Antibiotic(s)[a]	Alternative in Penicillin-Allergic Pt	Prophylaxis Advised for Early Uninfected Wounds	Other Considerations
Dog	*Staphylococcus aureus*, *Pasteurella multocida*, anaerobes, *Capnocytophaga canimorsus*	Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h)	Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid)	Sometimes[b]	Consider rabies prophylaxis.
Cat	*P. multocida*, *S. aureus*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Usually	Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration.
Human, occlusional	Viridans streptococci, *S. aureus*, *Haemophilus influenzae*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Erythromycin (500 mg PO qid) or a fluoroquinolone	Always	
Human, clenched-fist	As for occlusional, plus *Eikenella corrodens*	Ampicillin/sulbactam as above or imipenem (500 mg q6h)	Cefoxitin[c]	Always	Examine for tendon, nerve, or joint involvement.

http://internalmedicinebook.com

Monkey	As for human bite	As for human bite	As for human bite	Always	For macaque monkeys, consider B virus prophylaxis with acyclovir.
Snake	*Pseudomonas aeruginosa*, *Proteus* spp., *Bacteroides fragilis*, *Clostridium* spp.	Ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Sometimes, especially with venomous snakes	Administer antivenin for venomous snakebite.
Rodent	*Streptobacillus moniliformis*, *Leptospira* spp., *P. multocida*	Penicillin VK (500 mg PO qid)	Doxycycline (100 mg PO bid)	Sometimes	—

[a]Antibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized pts. A single IV dose of antibiotics may be given to pts who will be discharged after initial management.

[b]Prophylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present (see text).

[c]May be hazardous in pts with immediate-type hypersensitivity to penicillin.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

http://internalmedicinebook.com

OTHER NONHUMAN MAMMALIAN BITES

- Old World monkeys (*Macaca* species): Bites may transmit herpes B virus (*Herpesvirus simiae*), which can cause CNS infections with high mortality rates.
- Seals, walruses, polar bears: Bites may cause a chronic suppurative infection known as *seal finger*, which is probably due to *Mycoplasma* species.
- Small rodents (and their predators): Bites may transmit *rat-bite fever*, caused by *Streptobacillus moniliformis* (in the United States) or *Spirillum minor* (in Asia).
  - Rat-bite fever occurs after the initial wound has healed, a feature distinguishing it from an acute bite-wound infection.
  - *S. moniliformis* infections manifest 3–10 days after the bite as fever, chills, myalgias, headache, and severe migratory arthralgias followed by a maculopapular rash involving the palms and soles. Disease can progress to metastatic abscesses, endocarditis, meningitis, and pneumonia.
    - Haverhill fever is an *S. moniliformis* infection acquired from contaminated milk or drinking water and has manifestations similar to those described above.
  - *S. minor* infections cause local pain, purple swelling at the bite site, and associated lymphangitis and regional lymphadenopathy 1–4 weeks after the bite, with evolution into a nonspecific systemic illness.

HUMAN BITES

- **Epidemiology:** Human bites become infected 10–15% of the time.
  - *Occlusional* injuries are inflicted by actual biting; *clenched-fist* injuries result when the fist of one individual strikes the teeth of another.
  - *Clenched-fist* injuries are more common and typically result in more serious infections (e.g., septic arthritis, tenosynovitis).
- **Bacteriology:** See Table 27-1.

TREATMENT MAMMALIAN BITES

- *Wound management:* Wound closure is controversial in bite injuries. After thorough cleansing, facial wounds are usually sutured for cosmetic reasons and because the abundant facial blood supply lessens the risk of infection. For wounds elsewhere on the body, many authorities do not attempt primary closure, preferring instead to irrigate the wound copiously, debride devitalized tissue, remove foreign bodies, and approximate the margins. Delayed primary closure may be undertaken after the risk of infection has passed. Puncture wounds due to cat bites should be left unsutured because of the high rate at which they become infected.
- *Antibiotic therapy:* See Table 27-1. Antibiotics are typically given for 3–5 days (as prophylaxis in pts presenting within 8 h of the bite) or for 10–14 days (as treatment for established infections).
- *Other prophylaxis:* Rabies prophylaxis (passive immunization with rabies immune globulin and active immunization with rabies vaccine) should be given in consultation with local and regional public health authorities. A tetanus booster for pts immunized previously but not boosted within 5 years should be considered, as should primary immunization and tetanus immune globulin administration for pts not previously immunized against tetanus.

VENOMOUS SNAKEBITES

- **Epidemiology:** Worldwide, 1.2–5.5 million snakebites are sustained each year, with 421,000–1,841,000 envenomations and 20,000–94,000 deaths.
  - Bite rates are highest in temperate and tropical climates where populations subsist by manual agriculture and fishing.

http://internalmedicinebook.com

  - Differentiation of venomous from nonvenomous snake species can be difficult; color pattern is notoriously misleading.
- **Clinical features:** Snake venoms are complex mixtures of enzymes and other substances that promote vascular leaking, cause tissue necrosis, affect the coagulation cascade, and impair organ function.
  - Specific presentations differ somewhat with the particular snake species.
  - Systemic symptoms may include hypotension, pulmonary edema, hemorrhage, altered mental status, or paralysis (including muscles of respiration).
- **Prognosis:** The overall mortality rate for venomous snakebite is <1% among U.S. victims who receive antivenom; the incidence of permanent functional loss in a bitten extremity is substantial.

TREATMENT VENOMOUS SNAKEBITES

FIELD MANAGEMENT

- Get the victim to definitive care as soon as possible.
- Splint a bitten extremity and keep it at heart level to lessen bleeding and discomfort.
- *Avoid* incisions into the bite wound, cooling, consultation with traditional healers, tourniquets, and electric shock because these measures are ineffective and may increase local tissue damage.
- If the offending snake is reliably identified and known to be primarily neurotoxic, pressure immobilization (wrapping of the entire limb in a bandage at a pressure of 40–70 mmHg for upper limbs or 55–70 mmHg for lower limbs) may be used. The victim must be carried to medical care, because walking will disperse venom from the bite site regardless of its anatomic location.

HOSPITAL MANAGEMENT

- Monitor vital signs, cardiac rhythm, urine output, and O_2 saturation closely, and watch for evidence of cranial nerve dysfunction (e.g., ptosis), which may precede difficulty swallowing or respiratory insufficiency.
- Note the level of swelling and the circumference of the affected limb every 15 min until swelling has stabilized.
- Treat shock initially with isotonic saline (20–40 mL/kg IV); if hypotension persists, try 5% albumin (10–20 mL/kg IV) and vasopressors.
- Begin the search for appropriate, specific antivenom early in all cases of known venomous snakebite. In the United States, round-the-clock assistance is available from regional poison control centers.
  1. Any evidence of systemic envenomation (systemic symptoms or signs, laboratory abnormalities) and significant, progressive local findings (e.g., swelling that crosses a joint or involves more than half of the bitten limb) are indications for antivenom administration.
  2. Treating physicians should seek advice from snakebite experts regarding indications for and dosing of antivenom. The duration of antivenom administration depends on the offending snake species, but multiple doses are not effective in reversing bite responses that have already been established (e.g., renal failure, established paralysis, necrosis).
  3. Worldwide, antivenom quality varies; rates of anaphylactoid reaction can exceed 50%, prompting some authorities to recommend pretreatment with IV antihistamines (diphenhydramine, 1 mg/kg to a maximum of 100 mg; and cimetidine, 5–10 mg/kg to a maximum of 300 mg) or even a prophylactic SC or IM dose of epinephrine (0.01 mg/kg, up to 0.3 mg). CroFab, an antivenom

http://internalmedicinebook.com

used in the United States against North American pit viper species, poses a low risk of allergy elicitation.

4. A trial of acetylcholinesterase inhibitors should be undertaken for pts with objective evidence of neurologic dysfunction because this treatment may cause neurologic improvement in pts bitten by snakes with postsynaptic neurotoxins.

- Elevate the bitten extremity above heart level once antivenom administration has been initiated.
- Update tetanus immunization.
- Observe pts for muscle-compartment syndrome.
- Observe pts with signs of envenomation in the hospital for at least 24 h. Pts with "dry" bites should be watched for at least 8 h because symptoms are commonly delayed.

MARINE ENVENOMATIONS

- Much of the management of envenomation by marine creatures is supportive in nature. Specific marine antivenom can be used when appropriate.

INVERTEBRATES

- **Etiology:** Injuries from cnidocysts (stinging cells) of hydroids, fire coral, jellyfish, Portuguese man-of-wars, and sea anemones cause similar clinical symptoms that differ in severity. Other invertebrates (e.g., sea sponges, annelid worms, sea urchins) have spines that can inflict painful stings.
- **Clinical features:** Pain (prickling, burning, and throbbing), pruritus, and paresthesia develop immediately at the site of the bite. Neurologic, GI, renal, cardiovascular, respiratory, rheumatologic, and ocular symptoms have been described.

TREATMENT MARINE INVERTEBRATE ENVENOMATIONS

- Decontaminate the skin immediately with lidocaine (up to 4%). Vinegar (5% acetic acid), rubbing alcohol (40–70% isopropanol), baking soda, papain (unseasoned meat tenderizer), lemon or lime juice, household ammonia, olive oil, or sugar may be effective, depending on the species of the stinging creature.
- Shaving the skin may help remove remaining nematocysts.
- After decontamination, topical anesthetics, antihistamines, or steroid lotions may be helpful.
- Narcotics may be necessary for persistent pain.
- Muscle spasms may respond to diazepam (2–5 mg titrated upward as needed) or IV 10% calcium gluconate (5–10 mL).

VERTEBRATES

- **Etiology:** Many marine vertebrates, including stingrays, scorpionfish (e.g., lionfish and stonefish), marine catfish, and horned venomous sharks are capable of envenomating humans.
- **Clinical features:** depend on the offending fish
  - Stingrays: represent both an envenomation and a traumatic wound. The venom causes immediate, intense pain that may last up to 48 h. The wound often becomes ischemic and heals poorly. Systemic effects can include weakness, dysrhythmias, hypotension, paralysis, and rare deaths.

http://internalmedicinebook.com

– Stonefish: Because of the neuromuscular toxicity of the venom, stings may be life-threatening, and death may occur within 6–8 h. Local pain is immediate and intense and may last for days. Systemic effects are similar to those of stingray envenomations.

TREATMENT MARINE VERTEBRATE ENVENOMATIONS

- Immerse the affected part immediately in nonscalding hot water (113°F/45°C) for 30–90 min or until there is significant pain relief. Repeated hot-water therapy may help with recurrent pain.
- Explore, debride, and vigorously irrigate the wound after local/regional anesthetics are given.
- Antivenom is available for stonefish and serious scorpionfish envenomations. In the United States, contact the nearest regional poison control center for assistance.
- Leave wounds to heal by secondary intention or to be treated by delayed primary closure.
- Update tetanus immunization.
- Consider empirical antibiotics to cover *Staphylococcus* and *Streptococcus* species for serious wounds or envenomations in immunocompromised hosts. Coverage should be broadened to include *Vibrio* species if the wound is primarily closed.

MARINE POISONINGS

CIGUATERA

- **Epidemiology:** the most common fish-associated nonbacterial food poisoning in the United States, with most cases occurring in Florida and Hawaii
  – In all, 20,000–50,000 people are affected annually.
  – Three-quarters of cases involve barracuda, snapper, jack, or grouper found in the Indian Ocean, the South Pacific, and the Caribbean Sea.
- **Pathogenesis:** Ciguatera toxin is created by microalgae, whose consumption by fish allows the toxin to accumulate in the food chain. Three major ciguatoxins—CTX-1, -2, and -3—are found in the flesh and viscera of ciguateric fish, are typically unaffected by external factors (e.g., heat, cold, freeze-drying, gastric acid), and do not generally affect the fish (e.g., odor, color, or taste).
- **Clinical features:** Virtually all pts are affected within 24 h; most experience symptoms within 2–6 h. The diagnosis is made on clinical grounds.
  – Symptoms can be numerous (>150 reported) and include diarrhea, vomiting, abdominal pain, neurologic signs (e.g., paresthesias, weakness, fasciculations, ataxia), maculopapular or vesicular rash, and hemodynamic instability.
  – A pathognomonic symptom—reversal of hot and cold tactile perception—develops within 3–5 days and can last for months.

TREATMENT CIGUATERA POISONING

- Therapy is supportive and based on symptoms.
- Cool showers, hydroxyzine (25 mg PO q6–8h), or amitriptyline (25 mg PO bid) may ameliorate pruritus and dysesthesias.
- For 6 months after disease onset, the pt should avoid ingestion of fish (fresh or preserved), shellfish, fish oils, fish or shellfish sauces, alcohol, nuts, and nut oils.

http://internalmedicinebook.com

PARALYTIC SHELLFISH POISONING

- **Etiology:** induced by ingestion of contaminated filter-feeding organisms (e.g., clams, oysters, scallops, mussels) that concentrate water-soluble, heat- and acid-stable chemical toxins
  - The best-characterized and most frequently identified paralytic shellfish toxin is saxitoxin.
  - Paralytic shellfish toxins cannot be destroyed by ordinary cooking.
- **Clinical features:** Oral paresthesias (initially tingling and burning, later numbness) develop within minutes to hours after ingestion of contaminated shellfish and progress to involve the neck and distal extremities. Flaccid paralysis and respiratory insufficiency may follow 2–12 h later; 12% of pts die, usually within 18 h.

TREATMENT PARALYTIC SHELLFISH POISONING

- If pts present within hours of ingestion, gastric lavage and stomach irrigation with 2 L of a 2% sodium bicarbonate solution may be of benefit, as may administration of activated charcoal (50–100 g) and non-magnesium-based cathartics (e.g., sorbitol, 20–50 g).
- The pt should be monitored for respiratory paralysis for at least 24 h.

SCOMBROID

- **Etiology:** histamine intoxication due to bacterial decomposition of inadequately preserved or refrigerated scombroid fish (e.g., tuna, mackerel, saury, needlefish, wahoo, skipjack, and bonito)
  - This syndrome can also occur with nonscombroid fish (e.g., sardines, herring, dolphinfish, amberjack, and bluefish).
  - Affected fish typically have a sharply metallic or peppery taste but may be normal in appearance and flavor.
  - Because of uneven distribution of decay within the fish, not all people who eat an affected fish will become ill.
- **Clinical features:** Within 15–90 min of ingestion, pts present with oral tingling, mild abdominal pain, and nausea. Pts with severe cases develop flushing (exacerbated by UV exposure), pruritus, urticaria, angioneurotic edema, bronchospasm, GI symptoms, and hypotension.
  - Symptoms generally resolve within 8–12 h.
  - May be worse in pts concurrently taking isoniazid because of inhibition of GI tract histaminases

TREATMENT SCOMBROID POISONING

- Treatment consists of antihistamine (H_1 or H_2) administration.
- If bronchospasm is severe, an inhaled bronchodilator or injected epinephrine may be used.

ARTHROPOD BITES AND STINGS

TICK BITES AND TICK PARALYSIS

- **Epidemiology:** Ticks are important carriers of vector-borne diseases (e.g., Lyme disease, babesiosis, anaplasmosis, ehrlichiosis) in the United States.
- **Etiology:** While ticks feed on blood from their hosts, their secretions may produce local reactions, transmit diverse pathogens, induce a febrile illness, or cause paralysis. Soft ticks attach for <1 h; hard ticks can feed for >1 week.
- **Clinical features:** Except for tick-borne diseases, most manifestations of tick bites are self-limited following tick removal.

http://internalmedicinebook.com

– Tick-induced fever, in the absence of pathogen transmission, is associated with headache, nausea, and malaise and usually resolves ≤36 h after the tick is removed.
– Tick paralysis is an ascending flaccid paralysis due to a toxin in tick saliva that causes neuromuscular block and decreased nerve conduction.
  - Weakness begins symmetrically in the lower extremities ≤6 days after the tick's attachment and ascends symmetrically, causing complete paralysis of the extremities and cranial nerves.
  - Deep tendon reflexes are decreased or absent, but sensory examination and LP yield normal findings.
  - Tick removal results in improvement within hours; failure to remove the tick may lead ultimately to respiratory paralysis and death.

TREATMENT TICK BITES AND TICK PARALYSIS

- Ticks should be removed with forceps applied close to the point of attachment, which should then be disinfected.
- Pts bitten by a deer tick in Lyme disease–endemic regions can receive a prophylactic oral dose of doxycycline (200 mg) within 72 h of tick removal.
- Tick removal within 36 h of attachment usually prevents transmission of the agents of Lyme disease, babesiosis, anaplasmosis, and ehrlichiosis.

SPIDER BITES

Recluse Spider Bites

Epidemiology: Brown recluse spiders occur mainly in the south-central United States, and their close relatives are found in the Americas, Africa, and the Middle East. These spiders only infrequently bite humans, typically if threatened or pressed against the skin.

Clinical Features

- Most bites by the brown recluse spider result in only minor injury with edema and erythema, although severe necrosis of the skin and SC tissue and systemic hemolysis may occur.
- Within hours, the site of the bite becomes painful and pruritic, with central induration surrounded by zones of ischemia and erythema.
- Fever and other nonspecific systemic symptoms may develop within 3 days of the bite.
- Lesions typically resolve within a few days, but severe cases can leave a large ulcer and a depressed scar that take months or years to heal.

TREATMENT RECLUSE SPIDER BITES

- Initial management includes RICE (rest, ice, compression, elevation); administration of analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be undertaken as indicated.
- Early debridement or surgical excision of the wound without closure delays healing.

Widow Spider Bites

Epidemiology: Black widow spiders, recognized by a red hourglass marking on a shiny black ventral abdomen, are most abundant in the southeastern United States. Other *Latrodectus* species are present in other temperate and subtropical parts of the world.

http://internalmedicinebook.com

Pathogenesis: Female widow spiders produce a potent neurotoxin that binds irreversibly to presynaptic nerve terminals and causes release and depletion of acetylcholine and other neurotransmitters.

Clinical features

- Within 60 min, painful cramps spread from the bite site to large muscles of the extremities and trunk.
- Extreme abdominal muscular rigidity and pain may mimic peritonitis, but the abdomen is nontender.
- Other features are similar to that of acetylcholine overdose (e.g., excessive salivation, lacrimation, urination, and defecation; GI upset; and emesis).
- Although pain may subside within the first 12 h, it can recur for weeks.
- Respiratory arrest, cerebral hemorrhage, or cardiac failure may occur.

TREATMENT WIDOW SPIDER BITES

- Treatment consists of RICE and tetanus prophylaxis.
- The use of antivenom is limited by questionable efficacy and concern about anaphylaxis and serum sickness.

SCORPION STINGS

Epidemiology: Only ~30 of the ~1000 species of scorpions produce potentially lethal venoms, causing >5000 deaths worldwide each year. Among scorpions in the United States, only the bark scorpion (*Centruroides sculpturatus* or *C. exilicauda*) in the Southwest produces a potentially lethal venom.

Clinical features: The severity of symptoms depends on the particular scorpion species. For the U.S. bark scorpion, symptoms progress to maximal severity in ~5 h and typically subside within 1–2 days, although pain and paresthesias can last for weeks.

- Bark scorpion: Swelling generally is not apparent; tapping on the affected area (the tap test) can accentuate pain, paresthesia, and hyperesthesia. Cranial nerve dysfunction and skeletal muscle hyperexcitability develop within hours. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, acidosis, and occasional fatal respiratory arrests.
- Outside the United States, scorpion envenomations can cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage.

TREATMENT SCORPION STINGS

- Stings of nonlethal species require at most ice packs, analgesics, or antihistamines.
- In severe envenomations, aggressive supportive care should include pressure dressings and cold packs to decrease the absorption of venom.
- A continuous IV infusion of midazolam helps control agitation and involuntary muscle movements.
- *C. sculpturatus* antivenom administered IV rapidly reverses cranial nerve dysfunction and muscular symptoms.

HYMENOPTERA STINGS

Epidemiology: The hymenoptera include bees, wasps, hornets, yellow jackets, and ants. About 100 deaths from hymenoptera stings occur annually in the United States,

http://internalmedicinebook.com

nearly all due to allergic reactions to venoms. An estimated 0.4–4.0% of the U.S. population exhibits immediate-type hypersensitivity to insect stings.

Clinical Features

- Uncomplicated stings cause pain, a wheal-and-flare reaction, and local edema that subside within hours.
- Multiple stings (e.g., from wasps, hornets, ants) can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, rhabdomyolysis, renal failure, and death.
- Large (>10-cm) local reactions (e.g., with erythema, edema, warmth, tenderness) progressing over 1–2 days are not uncommon; while they resemble cellulitis, they are in fact hypersensitivity reactions. Such reactions recur on subsequent exposure but are seldom accompanied by anaphylaxis.
- Serious reactions occur within 10 min (and rarely >5 h) after the sting and include upper airway edema, bronchospasm, hypotension, shock, and death.

TREATMENT HYMENOPTERA STINGS

- Stingers embedded in skin should be removed promptly by grasping with forceps or scraping with a blade or fingernail.
- The site should be disinfected and ice packs applied to slow the spread of venom.
- Elevation of the bite site and administration of analgesics, oral antihistamines, and topical calamine lotion may ease symptoms.
- Large local reactions may require a short course of glucocorticoids.
- Anaphylaxis is treated with epinephrine hydrochloride (0.3–0.5 mL of a 1:1000 solution, given SC q20–30min as needed). For profound shock, epinephrine (2–5 mL of a 1:10,000 solution by slow IV push) is indicated. Pts should be observed for 24 h for recurrent anaphylaxis.
- Pts with a history of allergy to insect stings should carry a sting kit and seek medical attention immediately after the kit is used.



For a more detailed discussion, see Madoff LC, Pereyra F: Infectious Complications of Bites, Chap. 167e; Lei C, Badowski NJ, Auerbach PS, Norris RL: Disorders Caused by Venomous Snakebites and Marine Animal Exposures, Chap. 474, p. 2733; and Pollack RJ, Norton SA: Ectoparasite Infestations and Arthropod Injuries, Chap. 475, p. 2744, in HPIM-19.

http://internalmedicinebook.com

This page intentionally left blank

http://internalmedicinebook.com

28 Fever, Hyperthermia, and Rash

DEFINITIONS

- *Temperature:* The hypothalamic thermoregulatory center balances excess heat production from metabolic activity in muscle and liver with heat dissipation from the skin and lungs to maintain a normal body temperature of 36.8° ± 0.4°C (98.2° ± 0.7°F), with diurnal variation (lower in A.M., higher in P.M.).
- *Fever*: an elevation of body temperature (>37.2°C/98.9°F in the morning and >37.7°C/99.9°F in the evening) in conjunction with an increase in the hypothalamic set point
- *Fever of unknown origin* (*FUO*): temperatures >38.3°C (>101°F) on two or more occasions and an illness duration of ≥3 weeks, with no known immunocompromised state and unrevealing laboratory and radiologic investigations into the cause
- *Hyperpyrexia*: temperatures >41.5°C (>106.7°F) that can occur with severe infections but more commonly occur with CNS hemorrhages
- *Hyperthermia*: an uncontrolled increase in body temperature that exceeds the body's ability to lose heat *without* a change in the hypothalamic set point. Hyperthermia does not involve pyrogenic molecules.
- *Pyrogen*: any fever-causing substance, including exogenous pyrogens (e.g., microbial toxins, lipopolysaccharide, superantigens) and pyrogenic cytokines (e.g., IL-1, IL-6, TNF)

FEVER

- **Pathogenesis:** The hypothalamic set point increases, causing peripheral vasoconstriction (i.e., heat conservation). The pt feels cold as a result of blood shunting to the internal organs. Mechanisms of heat production (e.g., shivering, increased hepatic thermogenesis) help to raise the body temperature to the new set point. Increases in peripheral prostaglandin E_2 account for the nonspecific myalgias and arthralgias that often accompany fever. When the set point is lowered again by resolution or treatment of fever, processes of heat loss (e.g., peripheral vasodilation and sweating) commence.
- **Etiology:** Most fevers are associated with self-limited infections (usually viral) and have causes that are easily identified.

APPROACH TO THE PATIENT: **Fever**

- *History:* A meticulous history is essential, with particular attention to the chronology of events (e.g., in the case of rash: the site of onset and the direction and rate of spread; see below) and the relation of symptoms to medications, pet exposure, sick contacts, sexual contacts, travel, trauma, and the presence of prosthetic materials.
- *Physical examination:* A thorough physical examination should be performed. A consistent site for taking temperatures should be used. Temperature–pulse dissociations (relative bradycardia) should be noted if present (sometimes present, for example, with typhoid fever, brucellosis, leptospirosis, factitious

http://internalmedicinebook.com

fever). Close attention should be paid to any rash, with precise definition of its salient features.

1. Lesion type (e.g., macule, papule, nodule, vesicle, pustule, purpura, ulcer; see Chap. 59 for details), configuration (e.g., annular or target), arrangement, distribution (e.g., central or peripheral)
2. Classification of rash
   a. Centrally distributed maculopapular eruptions (e.g., viral exanthems, exanthematous drug-induced eruptions)
   b. Peripheral eruptions (e.g., Rocky Mountain spotted fever, secondary syphilis, bacterial endocarditis)
   c. Confluent desquamative erythemas (e.g., toxic shock syndrome)
   d. Vesiculobullous eruptions (e.g., varicella, primary HSV infection, ecthyma gangrenosum)
   e. Urticaria-like eruptions: in the presence of fever, usually due to urticarial vasculitis caused by serum sickness, connective-tissue disease, infection (hepatitis B virus, enteroviral, or parasitic infection), or malignancy (particularly lymphoma)
   f. Nodular eruptions (e.g., disseminated fungal infection, erythema nodosum, Sweet's syndrome)
   g. Purpuric eruptions (e.g., meningococcemia, viral hemorrhagic fever, disseminated gonococcemia)
   h. Eruptions with ulcers or eschars (e.g., rickettsial diseases, tularemia, anthrax)

- *Laboratory tests:* CBC with differential, ESR, and C-reactive protein; other tests as indicated by history and physical examination

TREATMENT FEVER

- The use of antipyretics is not contraindicated in common viral or bacterial infections and can relieve symptoms without slowing resolution of infection. Withholding of antipyretics may be useful, however, in evaluating the effectiveness of a particular antibiotic or in diagnosing conditions with temperature–pulse dissociations or relapsing fevers (e.g., infection with *Plasmodium* or *Borrelia* species).
- Treatment of fever in pts with preexisting impairment of cardiac, pulmonary, or CNS function is recommended to reduce oxygen demand.
- Aspirin, NSAIDs, and glucocorticoids are effective antipyretics. Acetaminophen is preferred because it does not mask signs of inflammation, does not impair platelet function, and is not associated with Reye's syndrome.
- Hyperpyretic pts should be treated with cooling blankets in addition to oral antipyretics.

FEVER OF UNKNOWN ORIGIN

- **Etiology:** FUO is more commonly caused by an atypical presentation of a common disease than by a very rare disease. The most common causes of FUO can be categorized as infections, neoplasms, or noninfectious inflammatory diseases (NIIDs; e.g., "collagen or rheumatic diseases," vasculitis syndromes, and granulomatous disorders). The frequency of each category differs between Western countries and countries in other parts of the world: infections, neoplasms, and NIIDs account for 22%, 11%, and 23% of Western cases, respectively, and for 43%, 16%, and 23% of cases in other geographic regions.

http://internalmedicinebook.com

– Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis represent the more common infectious-disease diagnoses.
– The most common NIIDs that result in FUO are large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still's disease.
– Among the neoplasms, malignant lymphoma is by far the most common cause of FUO. Fever occasionally precedes lymphadenopathy detectable by physical examination.

APPROACH TO THE PATIENT: FUO

A structured approach to the pt with FUO is shown in Fig. 28-1. The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history taking and physical examination. ^{18}F-fluorodeoxyglucose positron emission tomography combined with low-dose CT (FDG-PET/CT) can be used to guide additional diagnostic tests (e.g., targeted biopsies and culture) and aids in final diagnosis of FUO in 54% of cases.

TREATMENT FUO

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a pt's condition is rapidly deteriorating after diagnostic tests have failed to provide a definitive result.

- Hemodynamic instability and neutropenia may prompt earlier empirical anti-infective therapies.
- Use of glucocorticoids and NSAIDs should be avoided unless infection and malignant lymphoma have been largely ruled out and unless inflammatory disease is both probable and debilitating or life-threatening.
- Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, blocks the activity of both IL-1α and IL-1β and is extremely effective in the treatment of many autoinflammatory syndromes. A therapeutic trial with anakinra can be considered in pts whose FUO has not been diagnosed after later-stage diagnostic tests.

Prognosis: When no underlying source of FUO is identified after prolonged observation (>6 months), the prognosis is generally good.

HYPERTHERMIA

- **Etiology:** Exogenous heat exposure (e.g., heat stroke) and endogenous heat production (e.g., drug-induced hyperthermia, malignant hyperthermia) are two mechanisms by which hyperthermia can result in dangerously high internal temperatures.
  – *Heat stroke:* thermoregulatory failure in association with a warm environment; can be categorized as *exertional* (e.g., due to exercise in high heat or humidity) or *classic* (typically occurring in pts with chronic diseases that predispose to heat-related illnesses)
- **Clinical features:** high core temperature in association with an appropriate history (heat exposure, certain drug treatments) and dry skin, hallucinations, delirium, pupil dilation, muscle rigidity, and/or elevated levels of CPK
- **Diagnosis:** It can be difficult to distinguish fever from hyperthermia. The clinical history is often most useful (e.g., a history of heat exposure or of treatment with drugs that interfere with thermoregulation).

http://internalmedicinebook.com

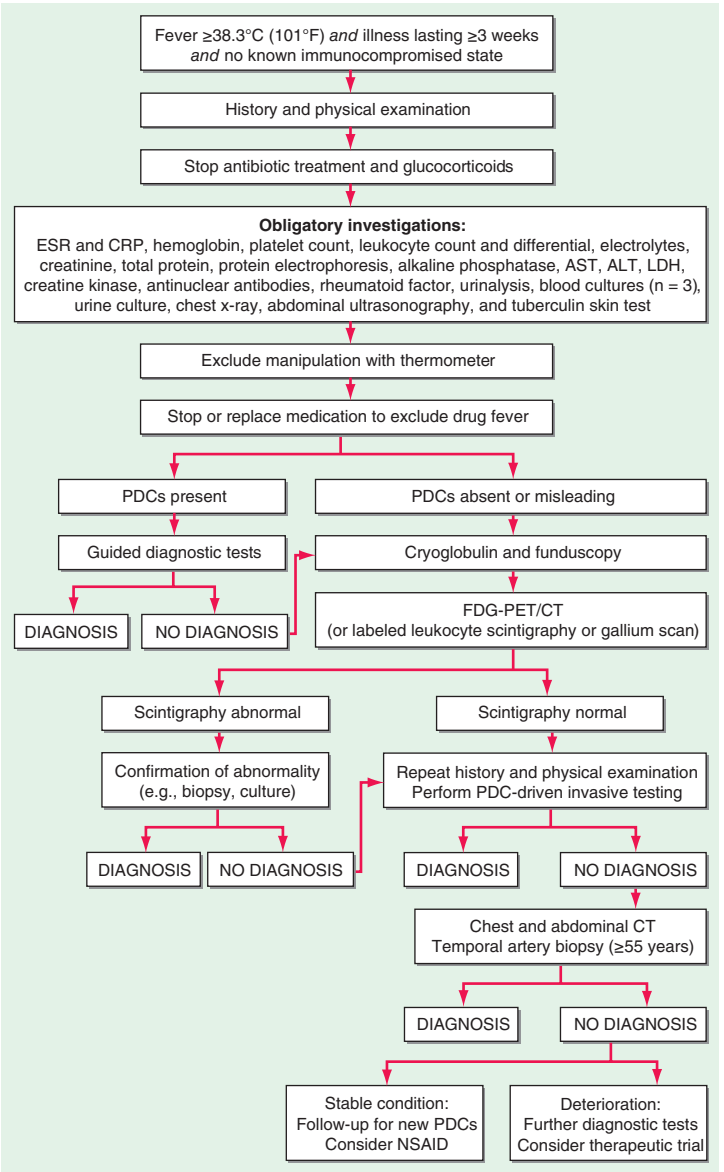


FIGURE 28-1 Structured approach to pts with fever of unknown origin (FUO). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography combined with low-dose computed tomography; LDH, lactate dehydrogenase; PDCs, potentially diagnostic clues (all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis); NSAID, nonsteroidal anti-inflammatory drug.

http://internalmedicinebook.com

–*Hyperthermic* pts have hot, dry skin; antipyretic agents do not lower the body temperature.
–*Febrile* pts can have cold skin (as a result of vasoconstriction) or hot, moist skin; antipyretics usually result in some lowering of the body temperature.

TREATMENT HYPERTHERMIA

- Before cooling is initiated, endotracheal intubation, CVP determination, and continuous core-temperature monitoring should be considered.
- Evaporative cooling (spraying cool water on exposed skin while fans direct continuous airflow over the moistened skin) is the most practical and effective technique for reducing body temperature. Invasive methods (e.g., IV infusion of cold fluids, cold thoracic and peritoneal lavage, cardiopulmonary bypass) are effective but rarely necessary.
- Given the risk of dehydration, IV fluids are necessary or at least appropriate. The CVP, particularly in classic heat stroke, may be deceptively high; rarely, measurement of wedge pressures via a pulmonary artery catheter may be necessary to guide resuscitation.

For a more detailed discussion, see Dinarello CA, Porat R: Fever and Hyperthermia, Chap. 23, p. 123; Kaye ET, Kaye KM: Fever and Rash, Chap. 24, p. 127; Kaye KM, Kaye ET: Atlas of Rashes Associated with Fever, Chap. 25e; Bleeker-Rovers CP, van der Meer JWM: Fever of Unknown Origin, Chap. 26, p. 135; and Danzl DF: Heat-Related Illnesses, Chap. 479e, in HPIM-19.

29 Generalized Fatigue

Fatigue is one of the most common complaints related by pts. It usually refers to nonspecific sense of a low energy level, or the feeling that near exhaustion is reached after relatively little exertion. Fatigue should be distinguished from true neurologic *weakness*, which describes a reduction in the normal power of one or more muscles (Chap. 53). It is not uncommon for pts, especially the elderly, to present with generalized failure to thrive, which may include components of fatigue and weakness, depending on the cause.

CLINICAL MANIFESTATIONS

Because the causes of generalized fatigue are numerous, a thorough history, review of systems (ROS), and physical examination are paramount to narrow the focus to likely causes. The history and ROS should focus on the temporal onset of fatigue and its progression. Has it lasted days, weeks, or months? Activities of daily living, exercise, eating habits/appetite, sexual practices, and sleep habits should be reviewed. Features of depression or dementia should be sought. Travel history and

http://internalmedicinebook.com

possible exposures to infectious agents should be reviewed, along with the medication list. The ROS may elicit important clues as to organ system involvement. The past medical history may elucidate potential precursors to the current presentation, such as previous malignancy or cardiac problems. The physical examination should specifically assess weight and nutritional status, lymphadenopathy, hepatosplenomegaly, abdominal masses, pallor, rash, heart failure, new murmurs, painful joints or trigger points, and evidence of weakness or neurologic abnormalities. A finding of true weakness or paralysis should prompt consideration of neurologic disorders (Chap. 53).

DIFFERENTIAL DIAGNOSIS

Determining the cause of fatigue can be one of the most challenging diagnostic problems in medicine because the differential diagnosis is very broad, including infection, malignancy, cardiac disease, endocrine disorders, neurologic disease, depression, or serious abnormalities of virtually any organ system, as well as side effects of many medications (Table 29-1). Symptoms of fever and weight loss will focus attention on infectious causes, whereas symptoms of progressive dyspnea might point toward cardiac, pulmonary, or renal causes. A presentation that includes arthralgia suggests the possibility of a rheumatologic disorder. A previous malignancy, thought to be

TABLE 29-1 POTENTIAL CAUSES OF GENERALIZED FATIGUE

Disease Category	Examples
Infection	HIV, TB, Lyme disease, endocarditis, hepatitis, sinusitis, fungal, EBV, malaria (chronic phase)
Inflammatory disease	RA, polymyalgia rheumatica, chronic fatigue syndrome, fibromyalgia, sarcoidosis
Cancer	Lung, GI, breast, prostate, leukemia, lymphoma, metastases
Psychiatric	Depression, alcoholism, chronic anxiety
Metabolic	Hypothyroidism, hyperthyroidism, diabetes mellitus, Addison's disease, hyperparathyroidism, hypogonadism, hypopituitarism (TSH, ACTH, growth hormone deficiency), McArdle's disease
Electrolyte imbalance	Hypercalcemia, hypokalemia, hyponatremia, hypomagnesemia
Nutrition, vitamin deficiency	Starvation, obesity, iron deficiency, vitamin B_{12}, folic acid deficiency, vitamin C deficiency (scurvy), thiamine deficiency (beriberi)
Neurologic	Multiple sclerosis, myasthenia gravis, dementia
Cardiac	Heart failure, CAD, valvular disease, cardiomyopathy
Pulmonary	COPD, pulmonary hypertension, chronic pulmonary emboli, sarcoidosis
Sleep disturbances	Sleep apnea, insomnia, restless leg syndrome
Gastrointestinal	Celiac disease, Crohn's, ulcerative colitis, chronic hepatitis, cirrhosis
Hematologic	Anemia
Renal	Renal failure
Medication	Sedatives, antihistamines, narcotics, β blockers, and many other medications

Abbreviations: ACTH, adrenocorticotropin hormone; CAD, coronary artery disease; COPD; chronic obstructive pulmonary disorder; EBV, Epstein-Barr virus; RA, rheumatoid arthritis; TSH, thyroid-stimulating hormone.

http://internalmedicinebook.com

cured or in remission, may have recurred or metastasized widely. A previous history of valvular heart disease or cardiomyopathy may identify a condition that has decompensated. Treatment for Graves' disease may have resulted in hypothyroidism. Sleep apnea is under-recognized and is a common cause of unexplained fatigue. Changes in medication should always be pursued, whether discontinued or recently started. Almost any new medication has the potential to cause fatigue. However, a temporal association with a new medication should not eliminate other causes, because many pts may have received new medications in an effort to address their complaints. Medications and their dosages should be carefully assessed, especially in elderly pts, in whom polypharmacy and inappropriate or misunderstood dosing is a frequent cause of fatigue. The time course for presentation is also valuable. Indolent presentations over months to years are more likely to be associated with slowly progressive organ failure or endocrinopathies, whereas a more rapid course over weeks to months suggests infection or malignancy.

LABORATORY TESTING

Laboratory testing and imaging should be guided by the history and physical examination. However, a CBC with differential, electrolytes, BUN, creatinine, glucose, calcium, and LFTs are useful in most pts with undifferentiated fatigue, because these tests will rule out many causes and may provide clues to unsuspected disorders. Similarly, a CXR is useful to evaluate many possible disorders rapidly, including heart failure, pulmonary disease, or occult malignancy that may be detected in the lungs or bony structures. Subsequent testing should be based on the initial results and clinical assessment of the likely differential diagnoses. For example, a finding of anemia would dictate the need to assess whether it has features of iron deficiency or hemolysis, thereby narrowing potential causes. Hyponatremia might be caused by syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, adrenal insufficiency, or medications or by underlying cardiac, pulmonary, liver, or renal dysfunction. An elevated WBC count would raise the possibility of infection or malignancy. Thus, the approach is generally one of gathering information in a serial but cost-effective manner to narrow the differential diagnosis progressively.

TREATMENT GENERALIZED FATIGUE

Treatment should be based on the diagnosis, if known. Many conditions, such as metabolic, nutritional, or endocrine disorders, can be corrected quickly by appropriate treatment of the underlying causes. Specific treatment can also be initiated for many infections, such as TB, sinusitis, or endocarditis. Pts with chronic conditions such as chronic obstructive pulmonary disorder (COPD), heart failure, renal failure, or liver disease may benefit from interventions that enhance organ function or correct associated metabolic problems, and it may be possible to gradually improve physical conditioning. In pts with cancer, fatigue may be caused by chemotherapy or radiation and may resolve with time; treatment of associated anemia, nutritional deficiency, hyponatremia, or hypercalcemia may increase energy levels. Replacement therapy in endocrine deficiencies typically results in improvement. Treatment of depression or sleep disorders, whether a primary cause of fatigue or secondary to a medical disorder, may be beneficial. A variety of treatments are now available for sleep apnea, including continuous positive airway pressure (CPAP). Withdrawal of medications that potentially contribute to fatigue should be considered, recognizing that other medications may need to be substituted for the underlying condition. In elderly pts, appropriate medication dose adjustments (typically lowering the dose) and restricting the regimen to only essential drugs may improve fatigue.

http://internalmedicinebook.com

CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints. The majority of pts (~75%) are women, generally 30–45 years old. The CDC has developed diagnostic criteria for CFS based upon symptoms and the exclusion of other illnesses (Table 29-2). The cause is uncertain, although clinical manifestations often follow an infectious illness (Q fever, Lyme disease, mononucleosis, or another viral illness). Many studies have attempted, without success, to link CFS to specific infectious agents such as EBV, a retrovirus (including a murine leukemia virus–related retrovirus), or an enterovirus, and many others. CFS might be caused by more than one infectious agent or by postinfectious immune responses. Physical or psychological stress is also often identified as a precipitating factor. Depression is present in half to two-thirds of pts, and some experts believe that CFS is fundamentally a psychiatric disorder.

CFS remains a diagnosis of exclusion, and no laboratory test can establish the diagnosis or measure its severity. CFS does not appear to progress but typically has a protracted course. The median annual recovery rate is 5% (range, 0–31%) with an improvement rate of 39% (range, 8–63%).

The management of CFS commences with acknowledgement by the physician that the pt's daily functioning is impaired. The pt should be informed of the current understanding of CFS (or lack thereof) and be offered general advice about disease management. NSAIDs alleviate headache, diffuse pain, and feverishness. Regular and adequate sleep is important. Antihistamines or decongestants may be helpful for symptoms of rhinitis and sinusitis. Although the pt may be averse to psychiatric diagnoses, features of depression and anxiety may justify treatment. Nonsedating antidepressants may improve mood and disordered sleep and may attenuate the fatigue. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have been found to be effective treatment strategies in some pts.

TABLE 29-2 CDC CRITERIA FOR DIAGNOSIS OF CFS

Consider a diagnosis of CFS if these three criteria are met:

1 The individual has severe chronic fatigue for ≥6 consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue (these other conditions need to be ruled out by a doctor after diagnostic tests have been conducted)

2 The fatigue significantly interferes with daily activities and work.

3 The individual concurrently has four or more of the following eight symptoms:

- postexertion malaise lasting >24 hours
- unrefreshing sleep
- significant impairment of short-term memory or concentration
- muscle pain
- multijoint pain without swelling or redness
- headaches of a new type, pattern, or severity
- tender cervical or axillary lymph nodes
- sore throat that is frequent or recurring

Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome.
Source: www.cdc.gov/cfs/diagnosis/index.html

http://internalmedicinebook.com

For a more detailed discussion, see Aminoff MJ: Neurologic Causes of Weakness and Paralysis, Chap. 30, p. 154; Czeisler CA, Thomas E. Scammell TE, Saper CB: Sleep Disorders, Chap. 38, p. 184; Robertson RG, Jameson LJ: Involuntary Weight Loss, Chap. 80, p. 641; Bleijenberg G, van der Meer JWM: Chronic Fatigue Syndrome, Chap. 464e; Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

30 Weight Loss

Significant unintentional weight loss in a previously healthy individual is often a harbinger of underlying systemic disease. The routine medical history should always include inquiry about changes in weight. Rapid fluctuations of weight over days suggest loss or gain of fluid, whereas long-term changes usually involve loss of tissue mass. Loss of 5% of body weight over 6–12 months should prompt further evaluation. Gradual weight loss is physiologic in persons over age 80, but this demographic group also has a high risk for malignancy or other serious illness.

ETIOLOGY

The principal causes of involuntary weight loss can be assigned to four categories: (1) malignant neoplasms, (2) chronic inflammatory or infectious diseases, (3) metabolic disorders, or (4) psychiatric disorders (Table 30-1). In older persons the most common causes of weight loss are depression, cancer, and benign GI disease. Lung and GI cancers are the most common malignancies in pts presenting with weight loss. In younger individuals, diabetes mellitus, hyperthyroidism, anorexia nervosa, and infection, especially with HIV, should be considered.

CLINICAL FEATURES

Before extensive evaluation is undertaken, it is important to confirm that weight loss has occurred (up to 50% of claims of weight loss cannot be substantiated). In the absence of documentation, changes in belt notch size or the fit of clothing may help to determine loss of weight.

The *history* should include questions about fever, pain, shortness of breath or cough, palpitations, and evidence of neurologic disease. A history of GI symptoms should be obtained, including difficulty eating, dysgeusia, dysphagia, anorexia, nausea, and change in bowel habits. Travel history, use of cigarettes, alcohol, and all medications should be reviewed, and pts should be questioned about previous illness or surgery as well as diseases in family members. Risk factors for HIV should be assessed. Signs of depression, evidence of dementia, and social factors, including isolation, loneliness, and financial issues that might affect food intake, should be considered.

Physical examination should begin with weight determination and documentation of vital signs. The skin should be examined for pallor, jaundice, turgor, surgical scars, and stigmata of systemic disease. Evaluation for oral thrush, dental disease, thyroid gland enlargement, and adenopathy and for respiratory, cardiac, or

http://internalmedicinebook.com

TABLE 30-1 CAUSES OF WEIGHT LOSS

- Cancer
- Endocrine and metabolic causes
  - Hyperthyroidism
  - Diabetes mellitus
  - Pheochromocytoma
  - Adrenal insufficiency
- Gastrointestinal disorders
  - Malabsorption
  - Obstruction
  - Peptic ulcer
  - Celiac disease
  - Inflammatory bowel disease
  - Pancreatitis
  - Pernicious anemia
- Cardiac disorders
  - Chronic ischemia
  - Chronic congestive heart failure
- Respiratory disorders
  - Emphysema
  - Chronic obstructive pulmonary disease
- Renal insufficiency
- Rheumatologic disease
- Infections
  - HIV
  - Tuberculosis
  - Parasitic infection
  - Subacute bacterial endocarditis
- Medications
  - Sedatives
  - Antibiotics
  - Nonsteroidal anti-inflammatory drugs
  - Serotonin reuptake inhibitors
  - Metformin
  - Levodopa
  - ACE inhibitors
  - Other drugs
- Disorders of the mouth and teeth
  - Caries
  - Dysgeusia
- Age-related factors
  - Physiologic changes
  - Decreased taste and smell
  - Functional disabilities
- Neurologic causes
  - Stroke
  - Parkinson's disease
  - Neuromuscular disorders
  - Dementia
- Social causes
  - Isolation
  - Economic hardship
- Psychiatric and behavioral causes
  - Depression
  - Anxiety
  - Bereavement
  - Alcoholism
  - Eating disorders
  - Increased activity or exercise
  - Idiopathic

Abbreviation: ACE, angiotensin-converting enzyme.

abdominal abnormalities should be performed. All men should have a rectal examination, including the prostate; all women should have a pelvic examination; and both should have testing of the stool for occult blood. Neurologic examination should include mental status assessment and screening for depression.

Initial *laboratory evaluation* is shown in Table 30-2, with appropriate treatment based on the underlying cause of the weight loss. If an etiology of weight loss is not found, careful clinical follow-up, rather than persistent undirected testing, is reasonable. The absence of abnormal laboratory tests is a favorable prognostic sign.

http://internalmedicinebook.com

TABLE 30-2 SCREENING TESTS FOR EVALUATION OF INVOLUNTARY WEIGHT LOSS

Initial testing	Additional testing
CBC	HIV test
Electrolytes, calcium, glucose	Upper and/or lower gastrointestinal endoscopy
Renal and liver function tests	Abdominal ultrasound
Urinalysis	
Thyroid-stimulating hormone	
Chest x-ray	
Recommended cancer screening	

Abbreviation: CBC, complete blood cell.

TREATMENT WEIGHT LOSS

Treatment of weight loss should be directed at correcting the underlying physical cause or social circumstance. In specific situations, nutritional supplements and medications (megestrol acetate, dronabinol, or growth hormone) may be effective for stimulating appetite or increasing weight.

For a more detailed discussion, see Robertson RG, Jameson JL: Involuntary Weight Loss, Chap. 56, p. 274, in HPIM-19.

31 Chest Pain

There is little correlation between the severity of chest pain and the seriousness of its cause. The range of disorders that cause chest discomfort is shown in Table 31-1.

POTENTIALLY SERIOUS CAUSES

The differential diagnosis of chest pain is shown in Figs. 31-1 and 31-2. It is useful to characterize the chest pain as (1) new, acute, and ongoing; (2) recurrent, episodic; and (3) persistent, e.g., for days at a time.

Myocardial Ischemia: Angina Pectoris

Substernal pressure, squeezing, constriction, with radiation often to left arm; usually on exertion, especially after meals or with emotional arousal. Characteristically relieved by rest and nitroglycerin.

Acute Myocardial Infarction (Chaps. 119 and 120)

Similar to angina but usually more severe, of longer duration (≥30 min), and not immediately relieved by rest or nitroglycerin. S3 and/or S4 may be present.

http://internalmedicinebook.com

TABLE 31-1 DIFFERENTIAL DIAGNOSES OF PATIENTS ADMITTED TO HOSPITAL WITH ACUTE CHEST PAIN RULED NOT MYOCARDIAL INFARCTION

Diagnosis	Percentage
Gastroesophageal disease[a]	42
Gastroesophageal reflux	
Esophageal motility disorders	
Peptic ulcer	
Gallstones	
Ischemic heart disease	31
Chest wall syndromes	28
Pericarditis	4
Pleuritis/pneumonia	2
Pulmonary embolism	2
Lung cancer	1.5
Aortic aneurysm	1
Aortic stenosis	1
Herpes zoster	1

[a]In order of frequency.
Source: Fruergaard P et al: *Eur Heart J* 17:1028, 1996.

Pulmonary Embolism (Chap. 133)

May be substernal or lateral, pleuritic in nature, and associated with hemoptysis, tachycardia, and hypoxemia.

Aortic Dissection (Chap. 125)

Very severe, in center of chest, a sharp "ripping" quality, radiates to back, not affected by changes in position. May be associated with weak or absent peripheral pulses.

Mediastinal Emphysema

Sharp, intense, localized to substernal region; often associated with audible crepitus.

Acute Pericarditis (Chap. 116)

Usually steady, crushing, substernal; often has pleuritic component aggravated by cough, deep inspiration, supine position, and relieved by sitting upright; pericardial friction rub often audible.

Pleurisy

Due to inflammation; less commonly tumor and pneumothorax. Usually unilateral, knifelike, superficial, aggravated by cough and respiration.

LESS SERIOUS CAUSES

Costochondral Pain

In anterior chest, usually sharply localized, may be brief and darting or a persistent dull ache. Can be reproduced by pressure on costochondral and/or chondrosternal junctions. In Tietze's syndrome (costochondritis), joints are swollen, red, and tender.

Chest Wall Pain

Due to strain of muscles or ligaments from excessive exercise or rib fracture from trauma; accompanied by local tenderness.

Esophageal Pain

Deep thoracic discomfort; may be accompanied by dysphagia and regurgitation.

http://internalmedicinebook.com

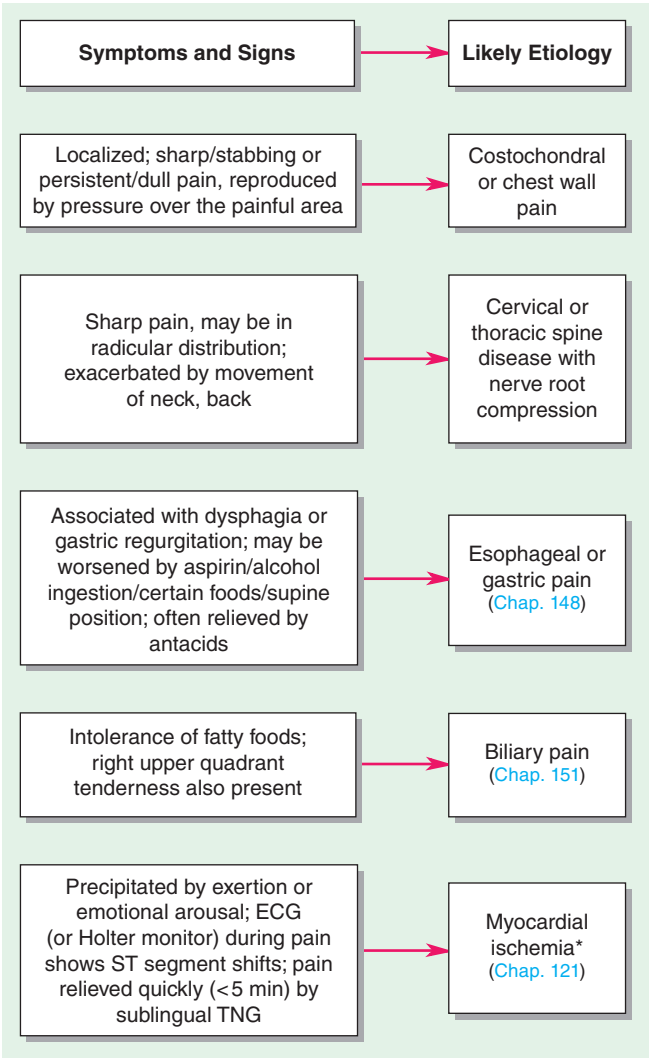


FIGURE 31-1 Differential diagnosis of recurrent chest pain. *If myocardial ischemia suspected, also consider aortic valve disease (**Chap. 114**) and hypertrophic obstructive cardiomyopathy (**Chap. 115**) if systolic murmur present. TNG, trinitroglycerin.

Emotional Disorders

Prolonged ache or dartlike, brief, flashing pain; associated with fatigue, emotional strain.

OTHER CAUSES

(1) Cervical disk disease; (2) osteoarthritis of cervical or thoracic spine; (3) abdominal disorders: peptic ulcer, hiatus hernia, pancreatitis, biliary colic; (4) tracheobronchitis,

http://internalmedicinebook.com

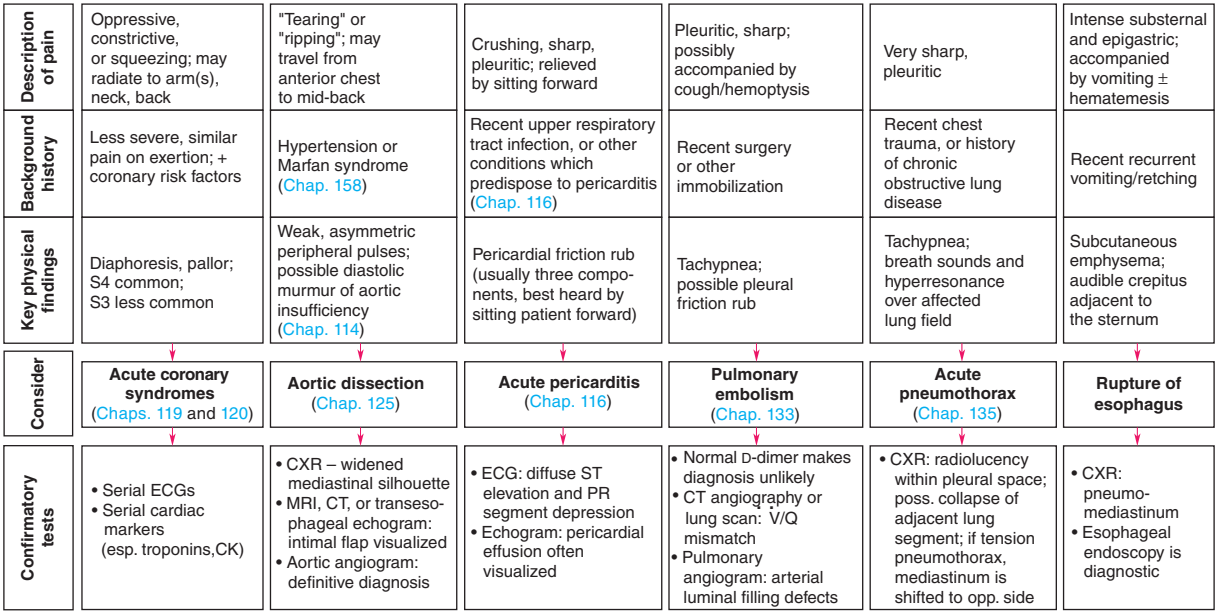


FIGURE 31-2 Differential diagnosis of serious conditions that cause acute chest pain. CK, creatine phosphokinase.

http://internalmedicinebook.com

pneumonia; (5) diseases of the breast (inflammation, tumor); (6) intercostal neuritis (herpes zoster).

APPROACH TO THE PATIENT: Chest Pain

A meticulous history of the behavior of pain, what precipitates it and what relieves it, aids diagnosis of recurrent chest pain. Figure 31-2 presents clues to diagnosis and workup of acute, life-threatening chest pain.

An ECG is key to the initial evaluation to rapidly distinguish pts with acute ST-elevation MI, who typically warrant immediate reperfusion therapies (Chap. 119).



For a more detailed discussion, see Morrow DA: Chest Discomfort, Chap. 19, p. 95, in HPIM-19.

32 Palpitations

Palpitations represent an intermittent or sustained awareness of the heartbeat, often described by the pt as a thumping, pounding, or fluttering sensation in the chest. The symptom may reflect a cardiac etiology, an extracardiac cause (e.g., hyperthyroidism, use of stimulants [e.g., caffeine, cocaine]), or a high catecholamine state (e.g., exercise, anxiety, pheochromocytoma). Contributory cardiac dysrhythmias include atrial or ventricular premature beats or, when sustained and regular, supraventricular or ventricular tachyarrhythmias (Chap. 123). *Irregular* sustained palpitations are often due to atrial fibrillation. Asking the pt to "tap out" the sense of palpitation can help distinguish regular from irregular rhythms.

APPROACH TO THE PATIENT: Palpitations

Palpitations are often benign but may represent an important dysrhythmia if associated with hemodynamic compromise (light-headedness, syncope, angina, dyspnea) or if found in pts with preexisting coronary artery disease (CAD), ventricular dysfunction, hypertrophic cardiomyopathy, aortic stenosis, or other valvular disease.

Helpful diagnostic studies include *electrocardiography* (if symptoms present at time of recording), *exercise testing* (if exertion typically precipitates the sense of palpitation or if underlying CAD is suspected), and *echocardiography* (if structural heart disease is suspected). If symptoms are episodic, ambulatory electrocardiographic monitoring can be diagnostic, including use of a Holter monitor (24–48 h of monitoring), event/loop monitor (for 2–4 weeks), or implantable loop monitor (for 1–2 years). Helpful laboratory studies may include testing for hypokalemia, hypomagnesemia, and/or hyperthyroidism.

http://internalmedicinebook.com

For pts with benign atrial or ventricular premature beats in the absence of structural heart disease, therapeutic strategies include reduction of ethanol and caffeine intake, reassurance, and consideration of beta-blocker therapy for symptomatic suppression. Treatment of more serious dysrhythmias is presented in Chaps. 122 and 123.

For a more detailed discussion, see Loscalzo J: Palpitations, Chap. 52, p. 254, in HPIM-19.

33 Dyspnea

DEFINITION

Dyspnea, a subjective experience of uncomfortable breathing, is a symptom that typically results from cardiopulmonary problems that cause an increased drive to breathe, increased work of breathing, and/or stimulation of specific receptors in the heart, lungs, or vasculature. Assessment begins by determining the quality and intensity of the discomfort.

CAUSES

Respiratory System Dyspnea

- *Airway disease:* Asthma and chronic obstructive pulmonary disorder (COPD) are common causes of dyspnea associated with increased work of breathing. Bronchospasm can cause chest tightness and hyperventilation. Hypoxemia and hypercapnia can result from ventilation-perfusion mismatch.
- *Chest wall disorders:* Chest wall stiffness (e.g., kyphoscoliosis) and neuromuscular weakness (e.g., myasthenia gravis) cause increased work of breathing.
- *Lung parenchymal disorders:* Interstitial lung diseases (Chap. 134) cause reduced lung compliance and increased work of breathing. Ventilation-perfusion mismatch and pulmonary fibrosis may lead to hypoxemia. Stimulation of lung receptors can cause hyperventilation.

Cardiovascular System Dyspnea

- *Left heart disorders:* Elevations of left-ventricular end-diastolic and pulmonary capillary wedge pressures lead to dyspnea related to stimulation of pulmonary receptors and hypoxemia from ventilation-perfusion mismatch.
- *Pulmonary vascular disorders:* Pulmonary emboli, primary pulmonary arterial hypertension, and pulmonary vasculitis stimulate pulmonary receptors via increased pulmonary artery pressures. Hyperventilation and hypoxemia also may contribute to dyspnea.
- *Pericardial diseases:* Constrictive pericarditis and pericardial tamponade cause increased intracardiac and pulmonary arterial pressures, leading to dyspnea.

http://internalmedicinebook.com

Dyspnea with Normal Respiratory and Cardiovascular Systems

Anemia can cause dyspnea, especially with exertion. Obesity is associated with dyspnea due to high cardiac output and impaired ventilatory function. Deconditioning may also cause dyspnea in patients with normal respiratory and cardiovascular systems.

APPROACH TO THE PATIENT: Dyspnea (Fig. 33-1)

History: Obtain description of discomfort, including the impact of position, infections, and environmental exposures. Orthopnea is commonly observed in CHF. Nocturnal dyspnea is seen in CHF and asthma. Acute intermittent dyspnea suggests myocardial ischemia, asthma, or pulmonary embolism.

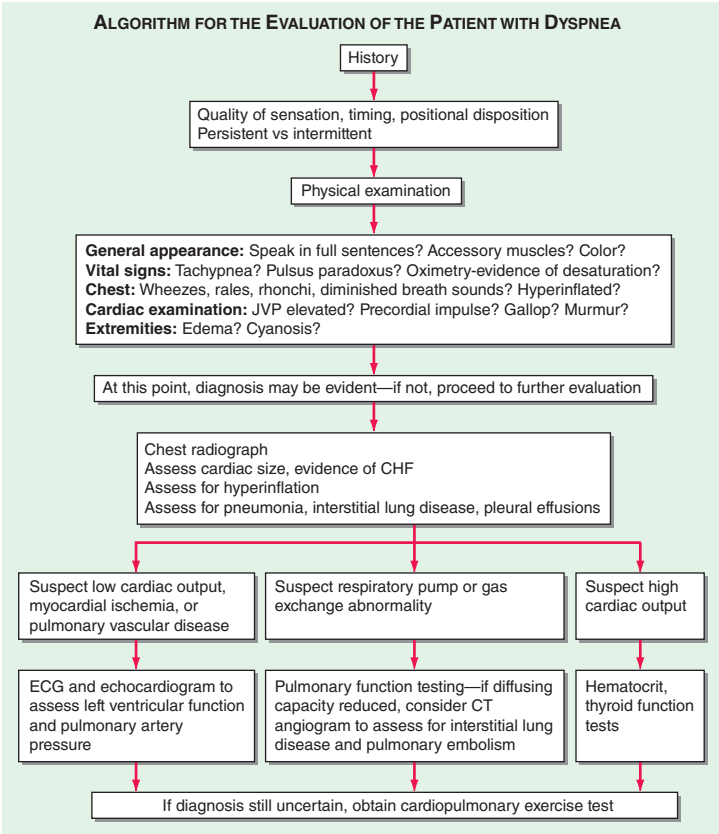


FIGURE 33-1 An algorithm for the evaluation of the pt with dyspnea. CHF, congestive heart failure; ECG, electrocardiogram; JVP, jugular venous pulse. *(Adapted from RM Schwartzstein, D Feller-Kopman, in Primary Cardiology, 2nd ed. E Braunwald, L Goldman [eds]: Philadelphia, Saunders, 2003.)*

http://internalmedicinebook.com

Physical examination: Assess increased work of breathing indicated by accessory ventilatory muscle use. Determine if chest movement is symmetric. Use percussion (dullness or hyperresonance) and auscultation (decreased or adventitious breath sounds) to assess the lungs. Cardiac examination should note jugular venous distention, heart murmurs, and S3 or S4 gallops. Clubbing can relate to interstitial lung disease or lung cancer. To evaluate exertional dyspnea, reproduce the dyspnea with observation while assessing pulse oximetry.

Radiographic studies: Chest radiograph should be obtained as initial evaluation. Chest CT can be used subsequently to assess lung parenchyma (e.g., emphysema or interstitial lung disease) and pulmonary embolism.

Laboratory studies: ECG should be obtained; echocardiography can assess left ventricular dysfunction, pulmonary hypertension, and valvular disease. Pulmonary function tests to consider include spirometry, lung volumes, and diffusing capacity. Methacholine challenge testing can assess for asthma in subjects with normal spirometry. Cardiopulmonary exercise testing can determine whether pulmonary or cardiac disease limits exercise capacity.

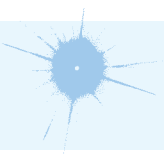
TREATMENT DYSPNEA

Ideally, treatment involves correcting the underlying problem that caused dyspnea. Supplemental oxygen is required for significant oxygen desaturation at rest or with exertion. Pulmonary rehabilitation is helpful to improve exercise tolerance in COPD.

Pulmonary Edema

Cardiogenic pulmonary edema results from cardiac abnormalities that cause increased pulmonary venous pressure leading to interstitial edema; with greater pressures, alveolar edema and pleural effusions develop. Symptoms include exertional dyspnea and orthopnea. Physical examination can reveal S3 gallop, elevated jugular venous pressure, and peripheral edema. Chest radiographs show prominent vascular markings in the upper lung zones. CXRs demonstrate perihilar alveolar opacities progressing to diffuse parenchymal abnormalities as pulmonary edema worsens.

Noncardiogenic pulmonary edema results from damage to the pulmonary capillary lining. Hypoxemia relates to intrapulmonary shunt; decreased pulmonary compliance is observed. Clinical impact can range from mild dyspnea to severe respiratory failure. Normal intracardiac pressures are typically observed. Etiologies may be direct injury (e.g., aspiration, smoke inhalation, pneumonia, oxygen toxicity, or chest trauma), indirect injury (e.g., sepsis, pancreatitis, and transfusion-related acute lung injury), or pulmonary vascular (e.g., high altitude and neurogenic pulmonary edema). Chest radiograph typically shows normal heart size and diffuse alveolar infiltrates; pleural effusions are atypical. Hypoxemia in noncardiogenic pulmonary edema often requires treatment with high concentrations of oxygen.



For a more detailed discussion, see Schwartzstein RM: Dyspnea, Chap. 47e, in HPIM-19.

http://internalmedicinebook.com

34 Cyanosis

Bluish discoloration of the skin and/or mucous membranes are usually due to elevated quantity of reduced hemoglobin (>40 g/L [>4 g/dL]) in the capillary blood vessels. Findings are most apparent in the lips, nail beds, ears, and malar eminences.

CENTRAL CYANOSIS

Results from arterial desaturation or presence of an abnormal hemoglobin. Usually evident when arterial saturation is ≤85%, or ≤75% in dark-skinned individuals. Etiologies include:

1. *Impaired pulmonary function:* Poorly ventilated alveoli or impaired oxygen diffusion; most frequent in pneumonia, pulmonary edema, and chronic obstructive pulmonary disease (COPD); in COPD with cyanosis, secondary polycythemia is often present.
2. *Anatomic vascular shunting:* Shunting of desaturated venous blood into the arterial circulation may result from congenital heart disease or pulmonary atrioventricular (AV) fistula.
3. *Decreased inspired O_2:* Cyanosis may develop in ascents to altitudes >4000 m (>13,000 ft).
4. *Abnormal hemoglobins:* Methemoglobinemia, sulfhemoglobinemia, and mutant hemoglobins with low oxygen affinity (see Chap. 127, HPIM-19).

PERIPHERAL CYANOSIS

Occurs with normal arterial O_2 saturation with increased extraction of O_2 from capillary blood caused by decreased localized blood flow. Contributors include vasoconstriction due to cold exposure, decreased cardiac output (e.g., in shock, Chap. 11), heart failure (Chap. 124), and peripheral vascular disease (Chap. 126) with arterial obstruction or vasospasm (Table 34-1). Local (e.g., thrombophlebitis) or central (e.g., constrictive pericarditis) venous hypertension intensifies cyanosis.

APPROACH TO THE PATIENT: Cyanosis

- Inquire about duration (cyanosis since birth suggests congenital heart disease) and exposures (drugs or chemicals that result in abnormal hemoglobins).
- Differentiate central from peripheral cyanosis by examining nailbeds, lips, and mucous membranes. Peripheral cyanosis is most intense in nailbeds and may resolve with gentle warming of extremities.
- Check for clubbing, i.e., selective enlargement of the distal segments of fingers and toes, due to proliferation of connective tissue. Clubbing may be hereditary, idiopathic, or acquired in association with lung cancer, infective endocarditis, bronchiectasis, or hepatic cirrhosis. Combination of clubbing and cyanosis is frequent in congenital heart disease and occasionally in pulmonary disease (lung abscess, pulmonary AV shunts, but *not* with uncomplicated obstructive lung disease).
- Examine chest for evidence of pulmonary disease, pulmonary edema, or murmurs associated with congenital heart disease.
- If cyanosis is localized to an extremity, evaluate for peripheral vascular obstruction.

http://internalmedicinebook.com

TABLE 34-1 CAUSES OF CYANOSIS

Central Cyanosis
Decreased arterial oxygen saturation
Decreased atmospheric pressure—high altitude
Impaired pulmonary function
Alveolar hypoventilation
Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)
Impaired oxygen diffusion
Anatomic shunts
Certain types of congenital heart disease
Pulmonary arteriovenous fistulas
Multiple small intrapulmonary shunts
Hemoglobin with low affinity for oxygen
Hemoglobin abnormalities
Methemoglobinemia—hereditary, acquired
Sulfhemoglobinemia—acquired
Carboxyhemoglobinemia (not true cyanosis)
Peripheral Cyanosis
Reduced cardiac output
Cold exposure
Redistribution of blood flow from extremities
Arterial obstruction
Venous obstruction

- Obtain arterial blood gas to measure systemic O_2 saturation. Repeat while pt inhales 100% O_2; if saturation fails to increase to >95%, intravascular shunting of blood bypassing the lungs is likely (e.g., right-to-left intracardiac shunts).
- Evaluate for abnormal hemoglobins (e.g., spectroscopy, measurement of methemoglobin level).

For a more detailed discussion, see Loscalzo J: Hypoxia and Cyanosis, Chap. 49, p. 247, in HPIM-19.

35 Cough and Hemoptysis

COUGH

ETIOLOGY

Acute cough, which is defined as duration <21 days, is usually related to respiratory infection, aspiration, or inhalation of respiratory irritants. Subacute cough (present for 3–8 weeks) is often related to persistent inflammation from a tracheobronchitis

http://internalmedicinebook.com

episode. Chronic cough (>8 weeks in duration) can be caused by many pulmonary and cardiac diseases. Chronic bronchitis related to cigarette smoking is a common cause. If the chest radiograph and physical examination are unremarkable, other common causes of chronic cough include cough-variant asthma, gastroesophageal reflux disease (GERD), postnasal drip related to sinus disease, and medications including ACE inhibitors. Irritation of tympanic membranes and chronic eosinophilic bronchitis also can cause chronic cough with a normal chest radiograph. Ineffective cough can predispose to serious respiratory infections due to difficulty clearing lower respiratory secretions; abnormal airway secretions (e.g., due to bronchiectasis) or tracheomalacia can contribute. Weakness or pain limiting abdominal and intercostal muscle use also can lead to ineffective cough.

CLINICAL ASSESSMENT

Key issues in the history include triggers for onset of cough, determinants of increased or decreased cough, and sputum production. Symptoms of nasopharyngeal disease should be assessed, including postnasal drip, sneezing, and rhinorrhea. GERD may be suggested by heartburn, hoarseness, and frequent eructation. Cough-variant asthma is suggested by noting the relationship of cough onset to asthmatic triggers. Usage of ACE inhibitors, but not angiotensin receptor blockers, can cause cough long after treatment is initiated.

On physical examination, signs of cardiopulmonary diseases should be assessed, including adventitious lung sounds and digital clubbing. Examination of the nasal passages, posterior pharyngeal wall, auditory canals, and tympanic membranes should be performed.

Laboratory evaluation should include chest radiography. Spirometry with bronchodilator testing can assess for reversible airflow obstruction. With normal spirometry, methacholine challenge testing can be used to assess for asthma. Purulent sputum should be sent for routine bacterial and possibly mycobacterial cultures. Sputum cytology can reveal malignant cells in lung cancer and eosinophils in eosinophilic bronchitis. Esophageal pH probes or radiotransmitter capsules can be used to assess for GERD. Chest CT should be considered in pts with normal chest radiographs who fail to improve with treatment. Evaluation of hemoptysis is discussed below.

TREATMENT CHRONIC COUGH

In pts with chronic cough and a normal chest x-ray, empiric treatment is directed at the most likely cause based on the history and physical examination. If treatment directed at one empiric cause fails, empiric treatment of an alternative etiology can be considered. Postnasal drip treatment may include antihistamines, nasal corticosteroids, anticholinergics, and/or antibiotics. GERD can be treated with antacids, type 2 histamine blockers, or proton pump inhibitors. Cough-variant asthma is treated with inhaled glucocorticoids and as-needed inhaled β agonists. Pts on ACE inhibitors should be given a 1-month trial of discontinuing this medication. Chronic eosinophilic bronchitis often improves with inhaled glucocorticoid treatment. Symptomatic treatment of cough can include narcotics such as codeine; however, somnolence, constipation, and addiction can result. Dextromethorphan and benzonatate have fewer side effects but reduced efficacy.

HEMOPTYSIS

ETIOLOGY

Hemoptysis, expectoration of blood from the respiratory tract, must be differentiated from expectorated blood originating from the nasopharynx or GI tract. Acute

http://internalmedicinebook.com

bronchitis is the most common cause of hemoptysis in the United States; tuberculosis is the leading cause worldwide.

Hemoptysis originating from the alveoli is known as diffuse alveolar hemorrhage (DAH). DAH can be caused by inflammatory diseases including Wegener granulomatosis, systemic lupus erythematosus, and Goodpasture disease. Within the first 100 days after bone marrow transplant, inflammatory DAH can cause severe hypoxemia. Noninflammatory DAH usually results from inhalational injuries from toxic exposures, such as smoke inhalation or cocaine.

Hemoptysis most commonly originates from small- to medium-sized bronchi. Because the bleeding source is usually bronchial arteries, there is potential for rapid blood loss. Airway hemoptysis is often caused by viral or bacterial bronchitis. Pts with bronchiectasis have increased risk of hemoptysis. Pneumonia can cause hemoptysis, especially if cavitation (e.g., tuberculosis) and/or necrotizing pneumonia (e.g., *Klebsiella pneumoniae* and *Staphylococcus aureus*) develop. Paragonimiasis, a helminthic infection common in pts from Southeast Asia and China, can cause hemoptysis and must be differentiated from tuberculosis. Although only 10% of lung cancer pts have hemoptysis at diagnosis, cancers developing in central airways (e.g., squamous cell carcinoma, small-cell carcinoma, and carcinoid tumors) often cause hemoptysis. Cancers that metastasize to the lungs cause hemoptysis less commonly.

Pulmonary vascular sources of hemoptysis include congestive heart failure, which usually causes pink, frothy sputum. Pulmonary embolism with infarction and pulmonary arteriovenous malformations are additional pulmonary vascular etiologies to consider.

CLINICAL ASSESSMENT

The approaches to assess and treat hemoptysis are shown in Fig. 35-1. History should determine whether the bleeding source is likely the respiratory tract or an alternative source (e.g., nasopharynx, upper GI tract). The quantity of expectorated blood should be estimated, because it influences the urgency of evaluation and treatment. Massive hemoptysis, variably defined as 200–600 mL within 24 h, requires emergent care. The presence of purulent or frothy secretions should be assessed. History of previous hemoptysis episodes and cigarette smoking should be ascertained. Fever and chills should be assessed as potential indicators of acute infection. Recent inhalation of illicit drugs and other toxins should be determined.

Physical examination should include assessment of the nares for epistaxis, and evaluation of the heart and lungs. Pedal edema could indicate congestive heart failure if symmetric, and deep-vein thrombosis with pulmonary embolism if asymmetric. Clubbing could indicate lung cancer or bronchiectasis. Assessment of vital signs and oxygen saturation can provide information about hemodynamic stability and respiratory compromise.

Radiographic evaluation with a chest x-ray should be performed. Chest CT may be helpful to assess for bronchiectasis, pneumonia, lung cancer, and pulmonary embolism. Laboratory studies include a complete blood count and coagulation studies; renal function and urinalysis should be assessed, with additional blood tests including antineutrophil cytoplasmic antibody (ANCA), anti-GBM (glomerular basement membrane), and ANA if DAH is suspected. Sputum should be sent for Gram's stain and routine culture as well as acid-fast bacillus (AFB) smear and culture.

Bronchoscopy is often required to complete the evaluation. In massive hemoptysis, rigid bronchoscopy may be necessary.

TREATMENT HEMOPTYSIS

As shown in Fig. 35-1, massive hemoptysis may require endotracheal intubation and mechanical ventilation to provide airway stabilization. If the source of bleeding can be identified, isolating the bleeding lung with an endobronchial

http://internalmedicinebook.com

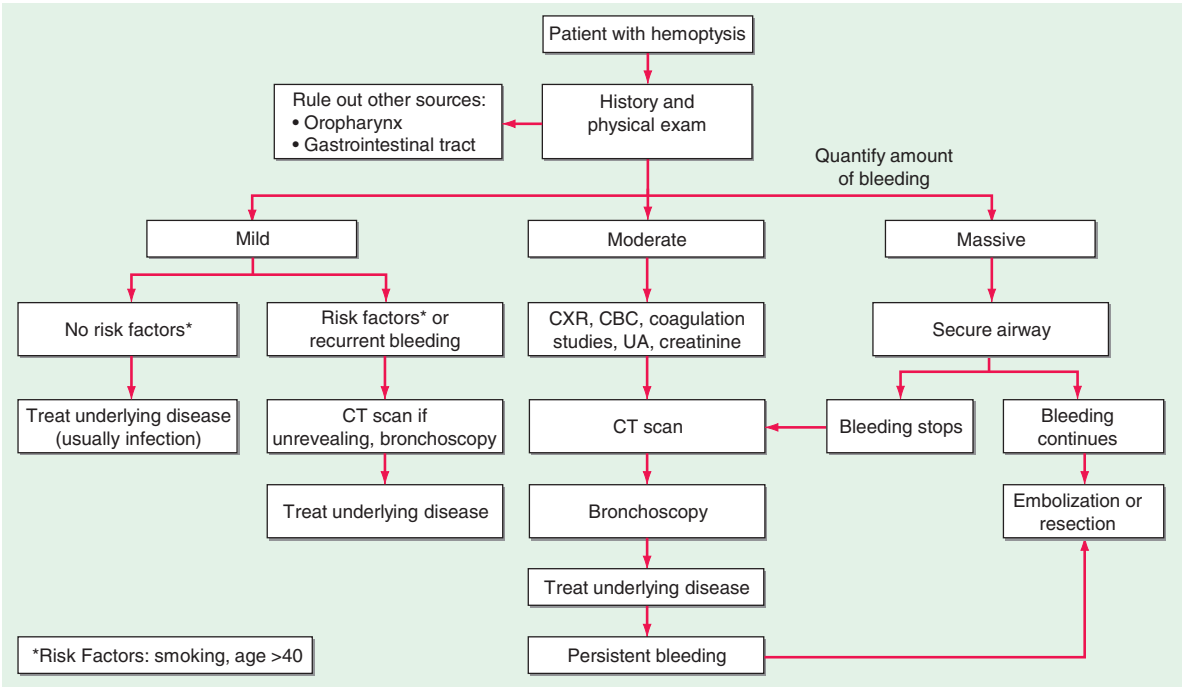


FIGURE 35-1 An algorithm for the evaluation of hemoptysis. CBC, complete blood count; CXR, chest x-ray; UA, urinalysis. *(From Kritek PA, Fanta CH: HPIM-19.)*

http://internalmedicinebook.com

blocker or double-lumen endotracheal tube is optimal. Pts should be positioned with the bleeding side down. If bleeding persists, bronchial arterial embolization by angiography may be beneficial; however, risk of spinal artery embolization is an important potential adverse event. As a last resort, surgical resection can be considered to stop the bleeding. Cough suppression, typically with narcotics, is desirable.

For a more detailed discussion, see Kritek PA, Fanta CH: Cough and Hemoptysis, Chap. 48, p. 243, in HPIM-19.

36 Edema

DEFINITION

Soft tissue swelling due to abnormal expansion of interstitial fluid volume. Edema fluid is a plasma transudate that accumulates when movement of fluid from vascular to interstitial space is favored. Because detectable generalized edema in the adult reflects a gain of ≥3 L, renal retention of salt and water is necessary for edema to occur. Distribution of edema can be an important guide to cause.

Localized Edema

Limited to a particular organ or vascular bed; easily distinguished from generalized edema. Unilateral extremity edema is usually due to venous or lymphatic obstruction (e.g., deep venous thrombosis, tumor obstruction, primary lymphedema). Stasis edema of a paralyzed lower extremity also may occur. Allergic reactions ("angioedema") and superior vena caval obstruction are causes of localized facial edema. Bilateral lower-extremity edema may have localized causes, e.g., inferior vena caval obstruction, compression due to ascites, and abdominal mass. Ascites (fluid in peritoneal cavity) and hydrothorax (in pleural space) also may present as isolated localized edema, due to inflammation or neoplasm.

Generalized Edema

Soft tissue swelling of most or all regions of the body. Bilateral lower-extremity swelling, more pronounced after standing for several hours, and pulmonary edema are usually cardiac in origin. Periorbital edema noted on awakening often results from renal disease and impaired Na excretion. Ascites and edema of lower extremities and scrotum are frequent in cirrhosis, nephrotic syndrome, or CHF.

In *CHF*, diminished cardiac output and arterial underfilling result in both decreased renal perfusion and increased venous pressure with resultant renal Na retention due to renal vasoconstriction, intrarenal blood flow redistribution, direct Na-retentive effects of norepinephrine and angiotensin II, and secondary hyperaldosteronism.

http://internalmedicinebook.com

In *cirrhosis*, arteriovenous shunts and peripheral vasodilation lower renal perfusion, resulting in Na retention. Ascites accumulates when increased intrahepatic vascular resistance produces portal hypertension. As in heart failure, the effects of excess intrarenal and circulating norepinephrine, angiotensin II, and aldosterone lead to renal Na retention and worsening edema. Reduced serum albumin and increased abdominal pressure also promote lower-extremity edema.

In acute or chronic *renal failure*, edema occurs if Na intake exceeds kidneys' ability to excrete Na secondary to marked reductions in glomerular filtration. Severe hypoalbuminemia (<25 g/L [2.5 g/dL]) of any cause (e.g., nephrotic syndrome, nutritional deficiency, chronic liver disease) may lower plasma oncotic pressure, promoting fluid transudation into interstitium; lowering of effective blood volume stimulates renal Na retention and causes edema.

Less common causes of generalized edema: *idiopathic edema*, a syndrome of recurrent rapid weight gain and edema in women of reproductive age; *hypothyroidism*, in which myxedema is typically located in the pretibial region; *drugs* (Table 36-1).

TREATMENT EDEMA

Primary management is to identify and treat the underlying cause of edema (Fig. 36-1).

Dietary Na restriction (<500 mg/d) may prevent further edema formation. Bed rest enhances response to salt restriction in CHF and cirrhosis. Supportive stockings and elevation of edematous lower extremities help to mobilize interstitial fluid. If severe hyponatremia (<132 mmol/L) is present, water intake also should be reduced (<1500 mL/d). Diuretics (Table 36-2) are indicated for marked peripheral edema, pulmonary edema, CHF, and inadequate dietary salt restriction. Complications are

TABLE 36-1 DRUGS ASSOCIATED WITH EDEMA FORMATION

Nonsteroidal anti-inflammatory drugs
Antihypertensive agents
Direct arterial/arteriolar vasodilators
Hydralazine
Clonidine
Methyldopa
Guanethidine
Minoxidil
Calcium channel antagonists
α-Adrenergic antagonists
Thiazolidinediones
Steroid hormones
Glucocorticoids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
Interleukin 2
OKT3 monoclonal antibody

Source: From GM Chertow, in E Braunwald, L Goldman (eds): *Primary Cardiology,* 2nd ed. Philadelphia, Saunders, 2003.

http://internalmedicinebook.com

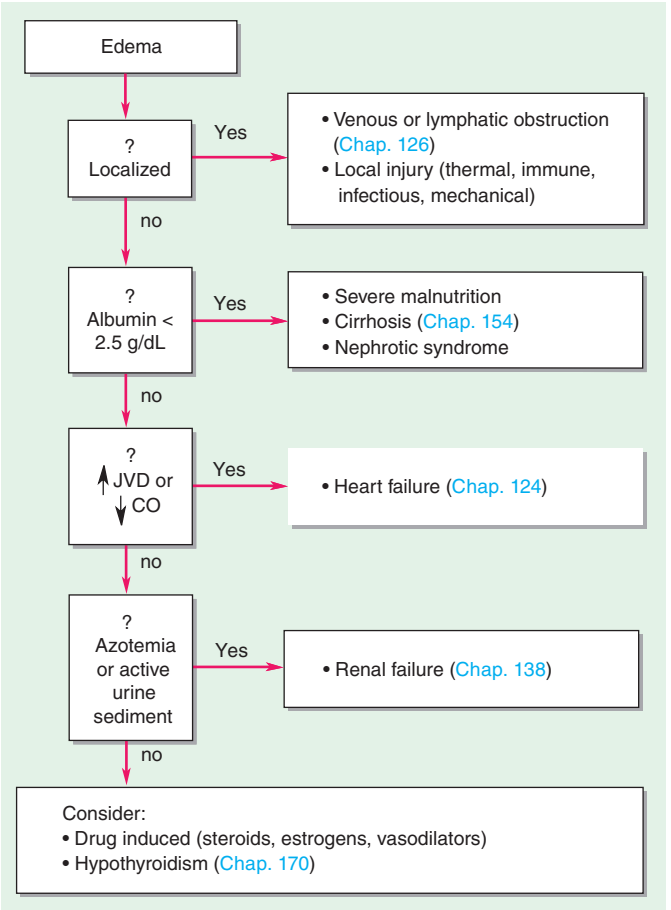


FIGURE 36-1 Diagnostic approach to edema. CO, cardiac output; JVD, jugular venous distention. *(From Chap. 42: HMOM-18.)*

listed in Table 36-3. Weight loss by diuretics should be limited to 1–1.5 kg/d. Distal ("potassium sparing") diuretics or metolazone may be added to loop diuretics for enhanced effect. Note that intestinal edema may impair absorption of oral diuretics and reduce effectiveness. When desired weight is achieved, diuretic doses should be reduced.

In *CHF* (Chap. 124), avoid overdiuresis because it may bring a fall in cardiac output and prerenal azotemia. Avoid diuretic-induced hypokalemia, which predisposes to digitalis toxicity.

In *cirrhosis* and other hepatic causes of edema, spironolactone is the initial diuretic of choice but may produce acidosis and hyperkalemia. Thiazides or small doses of loop diuretics may also be added. However, renal failure may result from volume depletion. Overdiuresis may result in hyponatremia, hypokalemia, and alkalosis, which may worsen hepatic encephalopathy (Chap. 154).

http://internalmedicinebook.com

TABLE 36-2 DIURETICS FOR EDEMA

Drug	Usual Dose	Comments
Loop (May be administered PO or IV)		
Furosemide	20–120 mg qd or bid	Short acting; potent; effective with low GFR
Bumetanide	0.5–2 mg qd or bid	Better oral absorption than furosemide, but shorter duration of action
Torsemide	20–200 mg qd	Better oral absorption than furosemide, longer duration of action
Distal, K-Losing		
Hydrochlorothiazide	12.5–25 mg qd	Causes hypokalemia; need GFR >25 mL/min
Chlorthalidone	12.5–25 mg qd	Long acting (up to 72 h); hypokalemia
Metolazone	1–5 mg qd	Long acting; hypokalemia; effective with low GFR, especially when combined with a loop diuretic
Distal, K-Sparing		
Spironolactone	12.5–100 mg qd	Hyperkalemia; acidosis; blocks aldosterone; gynecomastia, impotence, amenorrhea; onset takes 2–3 days; avoid use in renal failure or in combination with ACE inhibitors or potassium supplement
Eplerenone	25–50 mg qd	Similar side effects to spironolactone, but more specific for mineralocorticoid receptor; lower incidence of gynecomastia and amenorrhea
Amiloride	5–10 mg qd or bid	Hyperkalemia; once daily; less potent than spironolactone
Triamterene	100 mg bid	Hyperkalemia; less potent than spironolactone; renal stones

Abbreviations: ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate.
Source: From Chap. 42, *HMOM-18*.

http://internalmedicinebook.com

TABLE 36-3 COMPLICATIONS OF DIURETICS

Common	Uncommon
Volume depletion	Interstitial nephritis (thiazides, furosemide)
Prerenal azotemia	Pancreatitis (thiazides)
Potassium depletion	Loss of hearing (loop diuretics)
Hyponatremia (thiazides)	Anemia, leukopenia, thrombocytopenia (thiazides)
Metabolic alkalosis	
Hypercholesterolemia	
Hyperglycemia (thiazides)	
Hyperkalemia (K-sparing)	
Hypomagnesemia	
Hyperuricemia	
Hypercalcemia (thiazides)	
GI complaints	
Rash (thiazides)	

Abbreviation: GI, gastrointestinal.
Source: From Chap. 42, *HMOM-18*.

For a more detailed discussion, see Braunwald E, Loscalzo J: Edema, Chap. 50, p. 250, in HPIM-19.

37 Abdominal Pain

Numerous causes, ranging from acute, life-threatening emergencies to chronic functional disease and disorders of several organ systems, can generate abdominal pain. Evaluation of acute pain requires rapid assessment of likely causes and early initiation of appropriate therapy. A more detailed and time-consuming approach to diagnosis may be followed in less acute situations. Table 37-1 lists the common causes of abdominal pain.

APPROACH TO THE PATIENT: **Abdominal Pain**

History: History is of critical diagnostic importance. Physical examination may be unrevealing or misleading, and laboratory and radiologic examinations delayed or unhelpful.

http://internalmedicinebook.com

TABLE 37-1 SOME IMPORTANT CAUSES OF ABDOMINAL PAIN

Pain Originating in the Abdomen	
Parietal peritoneal inflammation	Vascular disturbances
Bacterial contamination	Embolism or thrombosis
Perforated appendix or other perforated viscus	Vascular rupture
Pelvic inflammatory disease	Pressure or torsional occlusion
Chemical irritation	Sickle cell anemia
Perforated ulcer	Abdominal wall
Pancreatitis	Distortion or traction of mesentery
Mittelschmerz	Trauma or infection of muscles
Mechanical obstruction of hollow viscera	Distension of visceral surfaces, e.g., by hemorrhage
Obstruction of the small or large intestine	Hepatic or renal capsules
Obstruction of the biliary tree	Inflammation
Obstruction of the ureter	Appendicitis
	Typhoid fever
	Neutropenic enterocolitis or "typhlitis"
Pain Referred from Extraabdominal Source	
Cardiothoracic	Pleurodynia
Acute myocardial infarction	Pneumothorax
Myocarditis, endocarditis, pericarditis	Empyema
Congestive heart failure	Esophageal disease, including spasm, rupture, or inflammation
Pneumonia (especially lower lobes)	Genitalia
Pulmonary embolus	Torsion of the testis
Metabolic Causes	
Diabetes	Acute adrenal insufficiency
Uremia	Familial Mediterranean fever
Hyperlipidemia	Porphyria
Hyperparathyroidism	C1-esterase-inhibitor deficiency (angioneurotic edema)
Neurologic/Psychiatric Causes	
Herpes zoster	Spinal cord or nerve root compression
Tabes dorsalis	Functional disorders
Causalgia	Psychiatric disorders
Radiculitis from infection or arthritis	
Toxic Causes	
Lead poisoning	
Insect or animal envenomation	
Black widow spider bites	
Snake bites	
Uncertain Mechanisms	
Narcotic withdrawal	
Heat stroke	

http://internalmedicinebook.com

CHARACTERISTIC FEATURES OF ABDOMINAL PAIN

Duration and pattern: These provide clues to nature and severity, although acute abdominal crisis may occasionally present insidiously or on a background of chronic pain.

Type and location provide a rough guide to nature of disease. *Visceral pain* (due to distention of a hollow viscus) localizes poorly and is often perceived in the midline. Intestinal pain tends to be crampy; when originating proximal to the ileocecal valve, it usually localizes above and around the umbilicus. Pain of colonic origin is perceived in the hypogastrium and lower quadrants. Pain from biliary or ureteral obstruction often causes pts to writhe in discomfort. *Somatic pain* (due to peritoneal inflammation) is usually sharper and more precisely localized to the diseased region (e.g., acute appendicitis; capsular distention of liver, kidney, or spleen), exacerbated by movement, causing pts to remain still. Pattern of radiation may be helpful: right shoulder (hepatobiliary origin), left shoulder (splenic), midback (pancreatic), flank (proximal urinary tract), and groin (genital or distal urinary tract).

Factors that precipitate or relieve pain: Ask about its relationship to eating (e.g., upper GI, biliary, pancreatic, ischemic bowel disease), defecation (colorectal), urination (genitourinary or colorectal), respiratory (pleuropulmonary, hepatobiliary), position (pancreatic, gastroesophageal reflux, musculoskeletal), menstrual cycle/menarche (tuboovarian, endometrial, including endometriosis), exertion (coronary/intestinal ischemia, musculoskeletal), medication or specific foods (motility disorders, food intolerance, gastroesophageal reflux, porphyria, adrenal insufficiency, ketoacidosis, toxins), and stress (motility disorders, nonulcer dyspepsia, irritable bowel syndrome).

Associated symptoms: Look for fevers/chills (infection, inflammatory disease, infarction), weight loss (tumor, inflammatory disease, malabsorption, ischemia), nausea/vomiting (obstruction, infection, inflammatory disease, metabolic disease), dysphagia/odynophagia (esophageal), early satiety (gastric), hematemesis (esophageal, gastric, duodenal), constipation (colorectal, perianal, genitourinary), jaundice (hepatobiliary, hemolytic), diarrhea (inflammatory disease, infection, malabsorption, secretory tumors, ischemia, genitourinary), dysuria/hematuria/vaginal or penile discharge (genitourinary), hematochezia (colorectal or, rarely, urinary), and skin/joint/eye disorders (inflammatory disease, bacterial or viral infection).

Predisposing factors: Inquire about family history (inflammatory disease, tumors, pancreatitis), hypertension and atherosclerotic disease (ischemia), diabetes mellitus (motility disorders, ketoacidosis), connective tissue disease (motility disorders, serositis), depression (motility disorders, tumors), smoking (ischemia), recent smoking cessation (inflammatory disease), and ethanol use (motility disorders, hepatobiliary, pancreatic, gastritis, peptic ulcer disease).

Physical examination: Evaluate abdomen for prior trauma or surgery, current trauma; abdominal distention, fluid, or air; direct, rebound, and referred tenderness; liver and spleen size; masses, bruits, altered bowel sounds, hernias, arterial masses. Rectal examination assesses presence and location of tenderness, masses, blood (gross or occult). Pelvic examination in women is essential.

General examination: Evaluate for evidence of hemodynamic instability, acid-base disturbances, nutritional deficiency, coagulopathy, arterial occlusive disease, stigmata of liver disease, cardiac dysfunction, lymphadenopathy, and skin lesions.

Routine laboratory and radiologic studies: Choices depend on clinical setting (esp. severity of pain, rapidity of onset) and may include complete blood count, serum electrolytes, coagulation parameters, serum glucose, and biochemical tests of liver, kidney, and pancreatic function; chest x-ray to determine the presence of diseases involving heart, lung, mediastinum, and pleura; electrocardiogram

http://internalmedicinebook.com

is helpful to exclude referred pain from cardiac disease; plain abdominal radiographs to evaluate bowel displacement, intestinal distention, fluid and gas pattern, free peritoneal air, liver size, and abdominal calcifications (e.g., gallstones, renal stones, chronic pancreatitis).

Special studies: These include abdominal ultrasonography (to visualize biliary ducts, gallbladder, liver, pancreas, and kidneys); CT to identify masses, abscesses, evidence of inflammation (bowel wall thickening, mesenteric "stranding," lymphadenopathy, appendicitis), aortic aneurysm; barium contrast radiographs (barium swallow, upper GI series, small-bowel follow-through, barium enema); upper GI endoscopy, sigmoidoscopy, or colonoscopy; cholangiography (endoscopic, percutaneous, or via MRI), angiography (direct or via CT or MRI), and radionuclide scanning. In selected cases, percutaneous biopsy, laparoscopy, and exploratory laparotomy may be required.

ACUTE, CATASTROPHIC ABDOMINAL PAIN

Intense abdominal pain of acute onset or pain associated with syncope, hypotension, or toxic appearance necessitates rapid yet orderly evaluation. Consider obstruction, perforation, or rupture of hollow viscus; dissection or rupture of major blood vessels (esp. aortic aneurysm); ulceration; abdominal sepsis; ketoacidosis; and adrenal crisis.

BRIEF HISTORY AND PHYSICAL EXAMINATION

Historic features of importance include age; time of onset of the pain; activity of the pt when the pain began; location and character of the pain; radiation to other sites; presence of nausea, vomiting, or anorexia; temporal changes; changes in bowel habits; and menstrual history. Physical examination should focus on the pt's overall appearance (writhing in pain [ureteral lithiasis] vs. still [peritonitis, perforation]), position (a pt leaning forward may have pancreatitis or gastric perforation into the lesser sac), presence of fever or hypothermia, hyperventilation, cyanosis, bowel sounds, direct or rebound abdominal tenderness, pulsating abdominal mass, abdominal bruits, ascites, rectal blood, rectal or pelvic tenderness, and evidence of coagulopathy. Useful laboratory studies include hematocrit (may be normal with acute hemorrhage or misleadingly high with dehydration), WBC with differential count, arterial blood gases, serum electrolytes, BUN, creatinine, glucose, lipase or amylase, and UA. Females of reproductive age should have a pregnancy test. Radiologic studies should include supine and upright abdominal films (left lateral decubitus view if upright unobtainable) to evaluate bowel caliber and presence of free peritoneal air, cross-table lateral film to assess aortic diameter; CT (when available) to detect evidence of bowel perforation, inflammation, solid organ infarction, retroperitoneal bleeding, abscess, or tumor. Abdominal paracentesis (or peritoneal lavage in cases of trauma) can detect evidence of bleeding or peritonitis. Abdominal ultrasound (when available) reveals evidence of abscess, cholecystitis, biliary or ureteral obstruction, or hematoma and is used to determine aortic diameter.

DIAGNOSTIC STRATEGIES

The initial decision point is based on whether the pt is hemodynamically stable. If not, one must suspect a vascular catastrophe such as a leaking abdominal aortic aneurysm. Such pts receive limited resuscitation and move immediately to surgical exploration. If the pt is hemodynamically stable, the next decision point is whether the abdomen is rigid. Rigid abdomens are most often due to perforation or obstruction. The diagnosis can generally be made by a chest and plain abdominal radiograph.

If the abdomen is not rigid, the causes may be grouped based on whether the pain is poorly localized or well localized. In the presence of poorly localized pain, one

http://internalmedicinebook.com

should assess whether an aortic aneurysm is possible. If so, a CT scan can make the diagnosis; if not, early appendicitis, early obstruction, mesenteric ischemia, inflammatory bowel disease, pancreatitis, and metabolic problems are all in the differential diagnosis.

Pain localized to the epigastrium may be of cardiac origin or due to esophageal inflammation or perforation, gastritis, peptic ulcer disease, biliary colic or cholecystitis, or pancreatitis. Pain localized to the right upper quadrant includes those same entities plus pyelonephritis or nephrolithiasis, hepatic abscess, subdiaphragmatic abscess, pulmonary embolus, or pneumonia, or it may be of musculoskeletal origin. Additional considerations with left upper quadrant localization are infarcted or ruptured spleen, splenomegaly, and gastric or peptic ulcer. Right lower quadrant pain may be from appendicitis, Meckel's diverticulum, Crohn's disease, diverticulitis, mesenteric adenitis, rectus sheath hematoma, psoas abscess, ovarian abscess or torsion, ectopic pregnancy, salpingitis, familial fever syndromes, urolithiasis, or herpes zoster. Left lower quadrant pain may be due to diverticulitis, perforated neoplasm, or other entities previously mentioned.

TREATMENT ACUTE, CATASTROPHIC ABDOMINAL PAIN

IV fluids, correction of life-threatening acid-base disturbances, and assessment of need for emergent surgery are the first priority; careful follow-up with frequent reexamination (when possible, by the same examiner) is essential. Relieve the pain. The use of narcotic analgesia is controversial. Traditionally, narcotic analgesics were withheld pending establishment of diagnosis and therapeutic plan, because masking of diagnostic signs may delay needed intervention. However, evidence that narcotics actually mask a diagnosis is sparse.

For a more detailed discussion, see Jacobs DO, Silen W: Abdominal Pain, Chap. 20, p. 103, in HPIM-19.

38 Nausea, Vomiting, and Indigestion

NAUSEA AND VOMITING

Nausea refers to the imminent desire to vomit and often precedes or accompanies vomiting. *Vomiting* refers to the forceful expulsion of gastric contents through the mouth. *Retching* refers to labored rhythmic respiratory activity that precedes emesis. *Regurgitation* refers to the gentle expulsion of gastric contents in the absence of nausea and abdominal diaphragmatic muscular contraction. *Rumination* refers to the regurgitation, rechewing, and reswallowing of food from the stomach.

http://internalmedicinebook.com

PATHOPHYSIOLOGY

Gastric contents are propelled into the esophagus when there is relaxation of the gastric fundus and gastroesophageal sphincter followed by a rapid increase in intraabdominal pressure produced by contraction of the abdominal and diaphragmatic musculature. Increased intrathoracic pressure results in further movement of the material to the mouth. Reflex elevation of the soft palate and closure of the glottis protect the nasopharynx and trachea and complete the act of vomiting. Vomiting is controlled by two brainstem areas, the vomiting center and chemoreceptor trigger zone. Activation of the chemoreceptor trigger zone results in impulses to the vomiting center, which controls the physical act of vomiting.

ETIOLOGY

Nausea and vomiting are manifestations of a large number of disorders (Table 38-1).

TABLE 38-1 CAUSES OF NAUSEA AND VOMITING

Intraperitoneal	Extraperitoneal	Medications/ Metabolic Disorders
Obstructing disorders	Cardiopulmonary disease	Drugs
Pyloric obstruction	Cardiomyopathy	Cancer chemotherapy
Small-bowel obstruction	Myocardial infarction	Antibiotics
Colonic obstruction	Labyrinthine disease	Cardiac antiarrhythmics
Superior mesenteric artery syndrome	Motion sickness	Digoxin
Enteric infections	Labyrinthitis	Oral hypoglycemics
Viral	Malignancy	Oral contraceptives
Bacterial	Intracerebral disorders	Endocrine/ metabolic disease
Inflammatory diseases	Malignancy	Pregnancy
Cholecystitis	Hemorrhage	Uremia
Pancreatitis	Abscess	Ketoacidosis
Appendicitis	Hydrocephalus	Thyroid and parathyroid disease
Hepatitis	Psychiatric illness	Adrenal insufficiency
Altered sensorimotor function	Anorexia and bulimia nervosa	Toxins
Gastroparesis	Depression	Liver failure
Intestinal pseudoobstruction	Postoperative vomiting	Ethanol
Gastroesophageal reflux		
Chronic idiopathic nausea		
Functional vomiting		
Cyclic vomiting syndrome		
Cannabinoid hyperemesis syndrome		
Rumination syndrome		
Biliary colic		
Abdominal irradiation		

http://internalmedicinebook.com

EVALUATION

The history, including a careful drug history, and the timing and character of the vomitus can be helpful. For example, vomiting that occurs predominantly in the morning is often seen in pregnancy, uremia, and alcoholic gastritis; feculent emesis implies distal intestinal obstruction or gastrocolic fistula; projectile vomiting suggests increased intracranial pressure; vomiting during or shortly after a meal may be due to psychogenic causes or peptic ulcer disease. Associated symptoms may also be helpful: vertigo and tinnitus in Ménière's disease, relief of abdominal pain with vomiting in peptic ulcer, and early satiety in gastroparesis. Plain radiographs can suggest diagnoses such as intestinal obstruction. The upper GI series assesses motility of the proximal GI tract as well as the mucosa. Other studies may be indicated, such as gastric emptying scans (diabetic gastroparesis) and CT scan of the brain.

COMPLICATIONS

Rupture of the esophagus (Boerhaave's syndrome), hematemesis from a mucosal tear (Mallory-Weiss syndrome), dehydration, malnutrition, dental caries and erosions, metabolic alkalosis, hypokalemia, and aspiration pneumonitis.

TREATMENT NAUSEA AND VOMITING

Treatment is aimed at correcting the specific cause. The effectiveness of antiemetic medications depends on etiology of symptoms, pt responsiveness, and side effects. Antihistamines such as meclizine and dimenhydrinate are effective for nausea due to inner ear dysfunction. Anticholinergics such as scopolamine are effective for nausea associated with motion sickness. Haloperidol and phenothiazine derivatives such as prochlorperazine are often effective in controlling mild nausea and vomiting, but sedation, hypotension, and parkinsonian symptoms are common side effects. Selective dopamine antagonists such as metoclopramide may be superior to the phenothiazines in treating severe nausea and vomiting and are particularly useful in treatment of gastroparesis. IV metoclopramide may be effective as prophylaxis against nausea when given before chemotherapy. Ondansetron and granisetron, serotonin receptor blockers, and glucocorticoids are used for treating nausea and vomiting associated with cancer chemotherapy. Aprepitant, a neurokinin receptor blocker, is effective at controlling nausea from highly emetic drugs like cisplatin. Erythromycin is effective in some pts with gastroparesis.

INDIGESTION

Indigestion is a nonspecific term that encompasses a variety of upper abdominal complaints including heartburn, regurgitation, and dyspepsia (upper abdominal discomfort or pain). These symptoms are overwhelmingly due to gastroesophageal reflux disease (GERD).

PATHOPHYSIOLOGY

GERD occurs as a consequence of acid reflux into the esophagus from the stomach, gastric motor dysfunction, or visceral afferent hypersensitivity. A wide variety of situations promote GERD: increased gastric contents (from a large meal, gastric stasis, or acid hypersecretion), physical factors (lying down, bending over), increased pressure on the stomach (tight clothes, obesity, ascites, pregnancy), and loss (usually intermittent) of lower esophageal sphincter tone (diseases such as scleroderma, smoking, anticholinergics, calcium antagonists). Hiatal hernia also promotes acid flow into the esophagus.

http://internalmedicinebook.com

NATURAL HISTORY

Heartburn is reported once monthly by 40% of Americans and daily by 7%. Functional dyspepsia is defined as >3 months of dyspepsia without an organic cause. Functional dyspepsia is the cause of symptoms in 60% of pts with dyspeptic symptoms. However, peptic ulcer disease from either *Helicobacter pylori* infection or ingestion of NSAIDs is present in 15% of cases.

In most cases, the esophagus is not damaged, but 5% of pts develop esophageal ulcers and some form strictures; 8–20% develop glandular epithelial cell metaplasia, termed *Barrett's esophagus*, which can progress to adenocarcinoma.

Extraesophageal manifestations include asthma, laryngitis, chronic cough, aspiration pneumonitis, chronic bronchitis, sleep apnea, dental caries, halitosis, and hiccups.

EVALUATION

The presence of dysphagia, odynophagia, unexplained weight loss, recurrent vomiting leading to dehydration, occult or gross bleeding, or a palpable mass or adenopathy are all "alarm" signals that demand directed radiographic, endoscopic, and surgical evaluation. Pts without alarm features are generally treated empirically. Individuals >45 years can be tested for the presence of *H. pylori*. Pts positive for the infection are treated to eradicate the organism. Pts who fail to respond to *H. pylori* treatment, those >45 years old, and those with alarm factors generally undergo upper GI endoscopy.

TREATMENT INDIGESTION

Weight reduction; elevation of the head of the bed; and avoidance of large meals, smoking, caffeine, alcohol, chocolate, fatty food, citrus juices, and NSAIDs may prevent GERD. Antacids are widely used. Clinical trials suggest that proton pump inhibitors (omeprazole) are more effective than histamine receptor blockers (ranitidine) in pts with or without esophageal erosions. *H. pylori* eradication regimens are discussed in Chap. 147. Motor stimulants like metoclopramide and erythromycin may be useful in a subset of pts with postprandial distress.

Surgical techniques (Nissen fundoplication, Belsey procedure) work best in young individuals whose symptoms have improved on proton pump inhibitors and who otherwise may require lifelong therapy. They can be used in the rare pts who are refractory to medical management. Clinical trials have not documented the superiority of one over another.

Dietary exclusion of gas-producing foods (i.e., low FODMAP [fermentable oligosaccharide, disaccharide, monosaccharide, and polyol] diets), and therapies to modify gut flora can reduce symptoms but efficacy is unproven.



For a more detailed discussion, see Hasler WL: Nausea, Vomiting, and Indigestion, Chap. 54, p. 258, in HPIM-19.

http://internalmedicinebook.com

39 Dysphagia

DYSPHAGIA

Dysphagia is difficulty moving food or liquid through the mouth, pharynx, and esophagus. The pt senses swallowed material sticking along the path. *Odynophagia* is pain on swallowing. *Globus pharyngeus* is the sensation of a lump lodged in the throat, with swallowing unaffected.

PATHOPHYSIOLOGY

Dysphagia is caused by two main mechanisms: mechanical obstruction or motor dysfunction. Mechanical causes of dysphagia can be luminal (e.g., large food bolus, foreign body), intrinsic to the esophagus (e.g., inflammation, webs and rings, strictures, tumors), or extrinsic to the esophagus (e.g., cervical spondylitis, enlarged thyroid or mediastinal mass, vascular compression). The motor function abnormalities that cause dysphagia may be related to defects in initiating the swallowing reflex (e.g., tongue paralysis, lack of saliva, lesions affecting sensory components of cranial nerves X and XI), disorders of the pharyngeal and esophageal striated muscle (e.g., muscle disorders such as polymyositis and dermatomyositis, neurologic lesions such as myasthenia gravis, polio, or amyotrophic lateral sclerosis), and disorders of the esophageal smooth muscle (e.g., achalasia, scleroderma, myotonic dystrophy).

APPROACH TO THE PATIENT: **Dysphagia**

History can provide a presumptive diagnosis in about 80% of pts. Difficulty only with solids implies mechanical dysphagia. Difficulty with both solids and liquids may occur late in the course of mechanical dysphagia but is an early sign of motor dysphagia. Pts can sometimes pinpoint the site of food sticking. Weight loss out of proportion to the degree of dysphagia may be a sign of underlying malignancy. Hoarseness may be related to involvement of the larynx in the primary disease process (e.g., neuromuscular disorders), neoplastic disruption of the recurrent laryngeal nerve, or laryngitis from gastroesophageal reflux.

Physical examination may reveal signs of skeletal muscle, neurologic, or oropharyngeal diseases. Neck examination can reveal masses impinging on the esophagus. Skin changes might suggest the systemic nature of the underlying disease (e.g., scleroderma).

Dysphagia is nearly always a symptom of organic disease rather than a functional complaint. If oropharyngeal dysphagia is suspected, video-fluoroscopy of swallowing may be diagnostic. Mechanical dysphagia can be evaluated by barium swallow and esophagogastroscopy with endoscopic biopsy. Barium swallow and esophageal motility studies can show the presence of motor dysphagia. An algorithm outlining an approach to the pt with dysphagia is shown in Fig. 39-1.

OROPHARYNGEAL DYSPHAGIA

Pt has difficulty initiating the swallow; food sticks at the level of the suprasternal notch; nasopharyngeal regurgitation and aspiration may be present.

Causes include the following: for solids only, carcinoma, aberrant vessel, congenital or acquired web (Plummer-Vinson syndrome in iron deficiency), cervical osteophyte; for solids and liquids, cricopharyngeal bar (e.g., hypertensive or hypotensive

http://internalmedicinebook.com

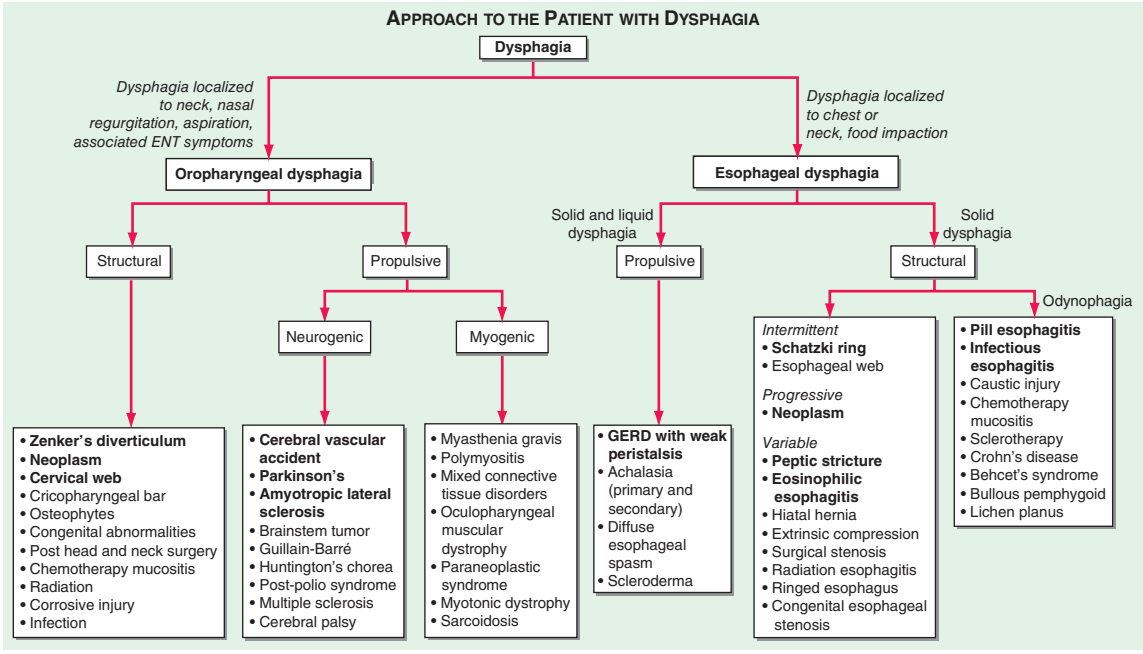


FIGURE 39-1 Approach to the pt with dysphagia. Etiologies in bold print are the most common. ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.

http://internalmedicinebook.com

upper esophageal sphincter), Zenker's diverticulum (outpouching in the posterior midline at the intersection of the pharynx and the cricopharyngeus muscle), myasthenia gravis, glucocorticoid myopathy, hyperthyroidism, hypothyroidism, myotonic dystrophy, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, bulbar palsy, and pseudobulbar palsy.

ESOPHAGEAL DYSPHAGIA

Food sticks in the mid or lower sternal area; can be associated with regurgitation, aspiration, odynophagia. Causes include the following: for solids only, lower esophageal ring (Schatzki's ring—symptoms are usually intermittent), peptic stricture (heartburn accompanies this), carcinoma, lye stricture; for solids and liquids, diffuse esophageal spasm (occurs with chest pain and is intermittent), scleroderma (progressive and occurs with heartburn), achalasia (progressive and occurs without heartburn).

NONCARDIAC CHEST PAIN

Of pts presenting with chest pain, 30% have an esophageal source rather than angina. History and physical examination often cannot distinguish cardiac from noncardiac pain. Exclude cardiac disease first. Causes include the following: gastroesophageal reflux disease, esophageal motility disorders, peptic ulcer disease, gallstones, psychiatric disease (anxiety, panic attacks, depression).

EVALUATION

Consider a trial of antireflux therapy (omeprazole); if no response, 24-h ambulatory luminal pH monitoring; if negative, esophageal manometry may show motor disorder. Trial of imipramine, 50 mg PO qhs, may be worthwhile. Consider psychiatric evaluation in selected cases.

ESOPHAGEAL MOTILITY DISORDERS

Pts may have a spectrum of manometric findings ranging from nonspecific abnormalities to defined clinical entities.

ACHALASIA

Motor obstruction caused by hypertensive lower esophageal sphincter (LES), incomplete relaxation of LES, or loss of peristalsis in smooth-muscle portion of esophagus. Causes include the following: primary (idiopathic) or secondary due to Chagas' disease, lymphoma, carcinoma, chronic idiopathic intestinal pseudoobstruction, ischemia, neurotropic viruses, drugs, toxins, radiation therapy, postvagotomy.

EVALUATION

Chest x-ray shows absence of gastric air bubble. Barium swallow shows dilated esophagus with distal beaklike narrowing and air-fluid level. Endoscopy is done to rule out cancer, particularly in persons >50 years. Manometry shows normal or elevated LES pressure, decreased LES relaxation, absent peristalsis.

TREATMENT ACHALASIA

Pneumatic balloon dilatation is effective in 85%, with 3–5% risk of perforation or bleeding. Injection of botulinum toxin at endoscopy to relax LES is safe and effective in two-thirds of patients, but effects last 6–12 months. Myotomy of LES (Heller procedure) is effective, but 10–30% of pts develop gastroesophageal reflux. Nifedipine, 10–20 mg, or isosorbide dinitrate, 5–10 mg SL ac, may avert need for dilation or surgery. Sildenafil may also augment swallow-induced relaxation of the LES.

http://internalmedicinebook.com

SPASTIC DISORDERS

Diffuse esophageal spasm involves multiple spontaneous and swallow-induced contractions of the esophageal body that are of simultaneous onset and long duration and are recurrent. Causes include the following: primary (idiopathic) or secondary due to gastroesophageal reflux disease, emotional stress, diabetes, alcoholism, neuropathy, radiation therapy, ischemia, or collagen vascular disease.

An important variant is nutcracker esophagus: high-amplitude (>180 mmHg) peristaltic contractions; particularly associated with chest pain or dysphagia, but correlation between symptoms and manometry is inconsistent. Condition may resolve over time or evolve into diffuse spasm; associated with increased frequency of depression, anxiety, and somatization.

EVALUATION

Barium swallow shows corkscrew esophagus, pseudodiverticula, and diffuse spasm. Manometry shows spasm with multiple simultaneous esophageal contractions of high amplitude and long duration. In nutcracker esophagus, the contractions are peristaltic and of high amplitude. If heart disease has been ruled out, edrophonium, ergonovine, or bethanechol can be used to provoke spasm.

TREATMENT SPASTIC DISORDERS

Anticholinergics are usually of limited value; nitrates (isosorbide dinitrate, 5–10 mg PO ac) and calcium antagonists (nifedipine, 10–20 mg PO ac) are more effective. Those refractory to medical management may benefit from balloon dilation. Rare pts require surgical intervention: longitudinal myotomy of esophageal circular muscle. Treatment of concomitant depression or other psychological disturbance may help.

SCLERODERMA

Atrophy of the esophageal smooth muscle and fibrosis can make the esophagus aperistaltic and lead to an incompetent LES with attendant reflux esophagitis and stricture. Treatment of gastroesophageal reflux disease is discussed in Chap. 38.

ESOPHAGEAL INFLAMMATION

VIRAL ESOPHAGITIS

Herpesviruses I and II, varicella-zoster virus, and CMV can all cause esophagitis; particularly common in immunocompromised pts (e.g., AIDS). Odynophagia, dysphagia, fever, and bleeding are symptoms and signs. Diagnosis is made by endoscopy with biopsy, brush cytology, and culture.

TREATMENT VIRAL ESOPHAGITIS

Disease is usually self-limited in the immunocompetent person; viscous lidocaine can relieve pain; in prolonged cases and in immunocompromised hosts, herpes and varicella esophagitis are treated with acyclovir, 400 mg PO five times a day for 14–21 days or valacyclovir 1 g PO tid for 7 days. CMV is treated with ganciclovir, 5 mg/kg IV q12h, until healing occurs, which may take weeks. Oral valganciclovir (900 mg bid) is an effective alternative to parenteral treatment. In nonresponders, foscarnet, 90 mg/kg IV q12h for 21 days, may be effective.

http://internalmedicinebook.com

CANDIDA ESOPHAGITIS

In immunocompromised hosts, or those with malignancy, diabetes, hypoparathyroidism, hemoglobinopathy, systemic lupus erythematosus, corrosive esophageal injury, candidal esophageal infection may present with odynophagia, dysphagia, and oral thrush (50%). Diagnosis is made on endoscopy by identifying yellow-white plaques or nodules on friable red mucosa. Characteristic hyphae are seen on KOH stain. In pts with AIDS, the development of symptoms may prompt an empirical therapeutic trial.

TREATMENT ***CANDIDA*** **ESOPHAGITIS**

In immunocompromised hosts, fluconazole, 200 mg PO on day 1 followed by 100 mg daily for 2–3 weeks, is treatment of choice; alternatives include itraconazole, 200 mg PO bid, or ketoconazole, 200–400 mg PO daily; long-term maintenance therapy is often required. Poorly responsive pts or those who cannot swallow may respond to caspofungin 50 mg IV qd for 7–21 days.

PILL-RELATED ESOPHAGITIS

Doxycycline, tetracycline, aspirin, nonsteroidal anti-inflammatory drugs, KCl, quinidine, ferrous sulfate, clindamycin, alprenolol, and alendronate can induce local inflammation in the esophagus. Predisposing factors include recumbency after swallowing pills with small sips of water and anatomic factors impinging on the esophagus and slowing transit.

TREATMENT **PILL-RELATED ESOPHAGITIS**

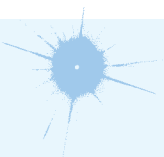
Withdraw offending drug, use antacids, and dilate any resulting stricture.

EOSINOPHILIC ESOPHAGITIS

Mucosal inflammation with eosinophils with submucosal fibrosis can be seen especially in pts with food allergies. This diagnosis relies on the presence of symptoms of esophagitis with the appropriate findings on esophageal biopsy. Eotaxin 3, an eosinophil chemokine, has been implicated in its etiology. IL-5 and TARC (thymus and activation-related chemokine) levels may be elevated. Treatment involves a 12-week course of swallowed fluticasone (440 μg bid) using a metered-dose inhaler.

OTHER CAUSES OF ESOPHAGITIS IN AIDS

Mycobacteria, *Cryptosporidium*, *Pneumocystis*, idiopathic esophageal ulcers, and giant ulcers (possible cytopathic effect of HIV) can occur. Ulcers may respond to systemic glucocorticoids.



For a more detailed discussion, see Hirano I, Kahrilas PJ: Dysphagia, Chap. 53, p. 254; and Kahrilas PJ, Hirano I: Diseases of the Esophagus, Chap. 347, p. 1900, in HPIM-19.

http://internalmedicinebook.com

40 Diarrhea, Malabsorption, and Constipation

NORMAL GASTROINTESTINAL FUNCTION

ABSORPTION OF FLUID AND ELECTROLYTES

Fluid delivery to the GI tract is 8–10 L/d, including 2 L/d ingested; most is absorbed in small bowel. Colonic absorption is normally 0.05–2 L/d, with capacity for 6 L/d if required. Intestinal water absorption passively follows active transport of Na^+, Cl^-, glucose, and bile salts. Additional transport mechanisms include Cl^-/HCO_3^- exchange, Na^+/H^+ exchange, H^+, K^+, Cl^-, and HCO_3^- secretion, Na^+-glucose cotransport, and active Na^+ transport across the basolateral membrane by Na^+,K^+-ATPase.

NUTRIENT ABSORPTION

1. *Proximal small intestine:* iron, calcium, folate, fats (after hydrolysis of triglycerides to fatty acids by pancreatic lipase and colipase), proteins (after hydrolysis by pancreatic and intestinal peptidases), carbohydrates (after hydrolysis by amylases and disaccharidases); triglycerides absorbed as micelles after solubilization by bile salts; amino acids and dipeptides absorbed via specific carriers; sugars absorbed by active transport
2. *Distal small intestine:* vitamin B_{12}, bile salts, water
3. *Colon:* water, electrolytes

INTESTINAL MOTILITY

Allows propulsion of intestinal contents from stomach to anus and separation of components to facilitate nutrient absorption. Propulsion is controlled by neural, myogenic, and hormonal mechanisms; mediated by migrating motor complex, an organized wave of neuromuscular activity that originates in the distal stomach during fasting and migrates slowly down the small intestine. Colonic motility is mediated by local peristalsis to propel feces. Defecation is effected by relaxation of internal anal sphincter in response to rectal distention, with voluntary control by contraction of external anal sphincter.

DIARRHEA

PHYSIOLOGY

Formally defined as fecal output >200 g/d on low-fiber (western) diet; also frequently used to connote loose or watery stools. Mediated by one or more of the following mechanisms:

OSMOTIC DIARRHEA

Nonabsorbed solutes increase intraluminal oncotic pressure, causing outpouring of water; usually ceases with fasting; stool osmolal gap >40 (see below). Causes include disaccharidase (e.g., lactase) deficiencies, pancreatic insufficiency, bacterial overgrowth, lactulose or sorbitol ingestion, polyvalent laxative abuse, celiac or tropical sprue, and short bowel syndrome. Lactase deficiency can be either primary (more prevalent in blacks and Asians, usually presenting in early adulthood) or

http://internalmedicinebook.com

secondary (from viral, bacterial, or protozoal gastroenteritis, celiac or tropical sprue, or kwashiorkor).

SECRETORY DIARRHEA

Active ion secretion causes obligatory water loss; diarrhea is usually watery, often profuse, unaffected by fasting; stool Na^+ and K^+ are elevated with osmolal gap <40. Causes include viral infections (e.g., rotavirus, Norwalk virus), bacterial infections (e.g., cholera, enterotoxigenic *Escherichia coli*, *Staphylococcus aureus*), protozoa (e.g., *Giardia*, *Isospora*, *Cryptosporidium*), AIDS-associated disorders (including mycobacterial and HIV-induced), medications (e.g., theophylline, colchicine, prostaglandins, diuretics), Zollinger-Ellison syndrome (excess gastrin production), vasoactive intestinal peptide (VIP)–producing tumors, carcinoid tumors (histamine and serotonin), medullary thyroid carcinoma (prostaglandins and calcitonin), systemic mastocytosis, basophilic leukemia, distal colonic villous adenomas (direct secretion of potassium-rich fluid), collagenous and microscopic colitis, and choleraic diarrhea (from ileal malabsorption of bile salts).

EXUDATIVE DIARRHEA

Inflammation, necrosis, and sloughing of colonic mucosa; may include component of secretory diarrhea due to prostaglandin release by inflammatory cells; stools usually contain polymorphonuclear leukocytes as well as occult or gross blood. Causes include bacterial infections (e.g., *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, invasive or enterotoxigenic *E. coli*, *Vibrio parahaemolyticus*, *Clostridium difficile* colitis [frequently antibiotic-induced]), colonic parasites (e.g., *Entamoeba histolytica*), Crohn's disease, ulcerative proctocolitis, idiopathic inflammatory bowel disease, radiation enterocolitis, cancer chemotherapeutic agents, and intestinal ischemia.

ALTERED INTESTINAL MOTILITY

Alteration of coordinated control of intestinal propulsion; diarrhea often intermittent or alternating with constipation. Causes include diabetes mellitus, adrenal insufficiency, hyperthyroidism, collagen-vascular diseases, parasitic infestations, gastrin and VIP hypersecretory states, amyloidosis, laxatives (esp. magnesium-containing agents), antibiotics (esp. erythromycin), cholinergic agents, primary neurologic dysfunction (e.g., Parkinson's disease, traumatic neuropathy), fecal impaction, diverticular disease, and irritable bowel syndrome. Blood in intestinal lumen is cathartic, and major upper GI bleeding leads to diarrhea from increased motility.

DECREASED ABSORPTIVE SURFACE

Usually arises from surgical manipulation (e.g., extensive bowel resection or rearrangement) that leaves inadequate absorptive surface for fat and carbohydrate digestion and fluid and electrolyte absorption; occurs spontaneously from enteroenteric fistulas (esp. gastrocolic).

EVALUATION HISTORY

Diarrhea must be distinguished from fecal incontinence, change in stool caliber, rectal bleeding, and small, frequent, but otherwise normal stools. Careful medication history is essential. Alternating diarrhea and constipation suggests fixed colonic obstruction (e.g., from carcinoma) or irritable bowel syndrome. A sudden, acute course, often with nausea, vomiting, and fever, is typical of viral and bacterial infections, diverticulitis, ischemia, radiation enterocolitis, or drug-induced diarrhea and may be the initial presentation of inflammatory bowel disease. More than 90% of acute diarrheal illnesses are infectious in etiology. A longer (>4 weeks), more insidious course suggests malabsorption, inflammatory bowel disease, metabolic or endocrine disturbance, pancreatic insufficiency, laxative abuse, ischemia, neoplasm (hypersecretory state or partial obstruction), or irritable bowel syndrome. Parasitic

http://internalmedicinebook.com

TABLE 40-1 INFECTIOUS CAUSES OF DIARRHEA IN PTS WITH AIDS

Nonopportunistic Pathogens	Opportunistic Pathogens
Shigella	Protozoa
Salmonella	*Cryptosporidium*
Campylobacter	*Isospora belli*
Entamoeba histolytica	Microsporidia
Chlamydia	*Blastocystis hominis*
Neisseria gonorrhoeae	Viruses
Treponema pallidum and other spirochetes	Cytomegalovirus
Giardia lamblia	Herpes simplex
	Adenovirus
	HIV
	Bacteria
	Mycobacterium avium complex

and certain forms of bacterial enteritis can also produce chronic symptoms. Particularly foul-smelling or oily stool suggests fat malabsorption. Fecal impaction may cause apparent diarrhea because only liquids pass partial obstruction. Several infectious causes of diarrhea are associated with an immunocompromised state (Table 40-1).

PHYSICAL EXAMINATION

Signs of dehydration are often prominent in severe, acute diarrhea. Fever and abdominal tenderness suggest infection or inflammatory disease but are often absent in viral enteritis. Evidence of malnutrition suggests chronic course. Certain signs are frequently associated with specific deficiency states secondary to malabsorption (e.g., cheilosis with riboflavin or iron deficiency, glossitis with B_{12}, folate deficiency). Questions to address in pts with chronic diarrhea are shown in Table 40-2.

STOOL EXAMINATION

Culture for bacterial pathogens, examination for leukocytes, measurement of *C. difficile* toxin, and examination for ova and parasites are important components of evaluation of pts with severe, protracted, or bloody diarrhea. Presence of blood (fecal occult blood test) or leukocytes (Wright's stain) suggests inflammation (e.g., ulcerative colitis, Crohn's disease, infection, or ischemia). Gram's stain of stool can

TABLE 40-2 PHYSICAL EXAMINATION IN PTS WITH CHRONIC DIARRHEA

1. Are there general features to suggest malabsorption or IBD such as anemia, dermatitis herpetiformis, edema, or clubbing?
2. Are there features to suggest underlying autonomic neuropathy or collagen-vascular disease in the pupils, orthostasis, skin, hands, or joints?
3. Is there an abdominal mass or tenderness?
4. Are there any abnormalities of rectal mucosa, rectal defects, or altered anal sphincter functions?
5. Are there any mucocutaneous manifestations of systemic disease such as dermatitis herpetiformis (celiac disease), erythema nodosum (ulcerative colitis), flushing (carcinoid), or oral ulcers for IBD or celiac disease?

Abbreviation: IBD, inflammatory bowel disease.

http://internalmedicinebook.com

be diagnostic of *Staphylococcus*, *Campylobacter*, or *Candida* infection. Steatorrhea (determined with Sudan III stain of stool sample or 72-h quantitative fecal fat analysis) suggests malabsorption or pancreatic insufficiency. Measurement of Na^+ and K^+ levels in fecal water helps to distinguish osmotic from other types of diarrhea; osmotic diarrhea is implied by stool osmolal gap > 40, where stool osmolal gap = $osmol_{serum}$ $[2 \times (Na^+ + K^+)_{stool}]$.

LABORATORY STUDIES

Complete blood count may indicate anemia (acute or chronic blood loss or malabsorption of iron, folate, or B_{12}), leukocytosis (inflammation), eosinophilia (parasitic, neoplastic, and inflammatory bowel diseases). Serum levels of calcium, albumin, iron, cholesterol, folate, B_{12}, vitamin D, and carotene; serum iron-binding capacity; and prothrombin time can provide evidence of intestinal malabsorption or maldigestion.

OTHER STUDIES

D-Xylose absorption test is a convenient screen for small-bowel absorptive function. Small-bowel biopsy is especially useful for evaluating intestinal malabsorption. Specialized studies include Schilling test (B_{12} malabsorption), lactose H_2 breath test (carbohydrate malabsorption), [^{14}C]xylose and lactulose H_2 breath tests (bacterial overgrowth), glycocholic breath test (ileal malabsorption), triolein breath test (fat malabsorption), and bentiromide and secretin tests (pancreatic insufficiency). Sigmoidoscopy or colonoscopy with biopsy is useful in the diagnosis of colitis (esp. pseudomembranous, ischemic, microscopic); it may not allow distinction between infectious and noninfectious (esp. idiopathic ulcerative) colitis. Barium contrast x-ray studies may suggest malabsorption (thickened bowel folds), inflammatory bowel disease (ileitis or colitis), tuberculosis (ileocecal inflammation), neoplasm, intestinal fistula, or motility disorders.

TREATMENT DIARRHEA

An approach to the management of acute diarrheal illnesses is shown in Fig. 40-1. Symptomatic therapy includes vigorous rehydration (IV or with oral glucose-electrolyte solutions), electrolyte replacement, binders of osmotically active substances (e.g., kaolin-pectin), and opiates to decrease bowel motility (e.g., loperamide, diphenoxylate); opiates may be contraindicated in infectious or inflammatory causes of diarrhea. An approach to the management of chronic diarrhea is shown in Fig. 40-2.

MALABSORPTION SYNDROMES

Intestinal malabsorption of ingested nutrients may produce osmotic diarrhea, steatorrhea, or specific deficiencies (e.g., iron; folate; B_{12}; vitamins A, D, E, and K). Table 40-3 lists common causes of intestinal malabsorption. Protein-losing enteropathy may result from several causes of malabsorption; it is associated with hypoalbuminemia and can be detected by measuring stool α_1-antitrypsin or radiolabeled albumin levels. Therapy is directed at the underlying disease.

CONSTIPATION

Defined as decrease in frequency of stools to less than one per week or difficulty in defecation; may result in abdominal pain, distention, and fecal impaction, with consequent obstruction or, rarely, perforation. Constipation is a frequent and often

http://internalmedicinebook.com

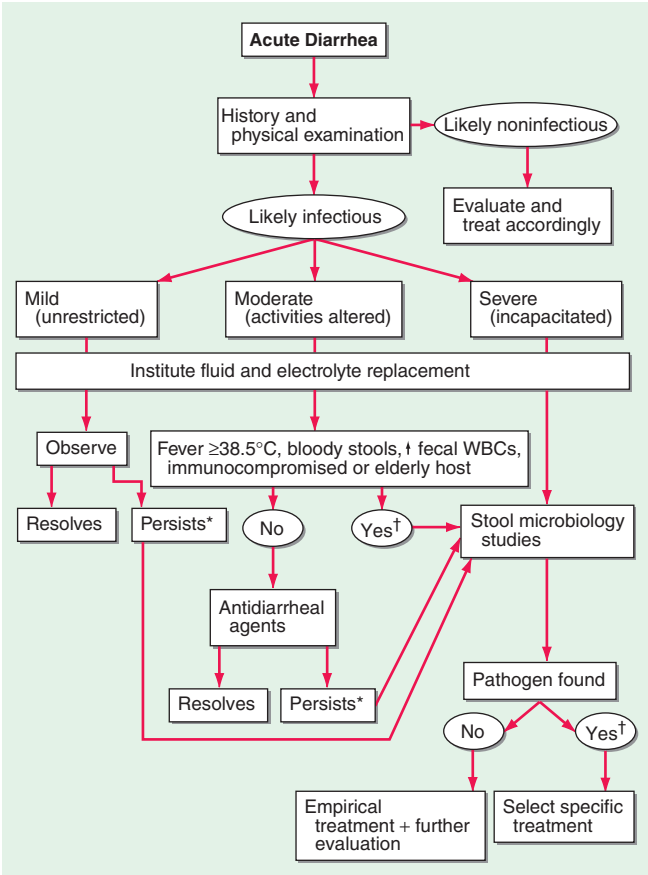


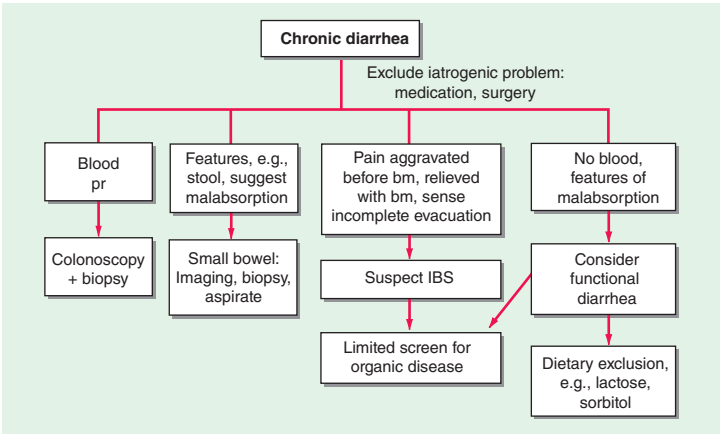
FIGURE 40-1 Algorithm for the management of acute diarrhea. Consider empirical treatment before evaluation with (*) metronidazole and with (†) quinolone. WBCs, white blood cells.

subjective complaint. Contributory factors may include inactivity, low-fiber diet, and inadequate allotment of time for defecation.

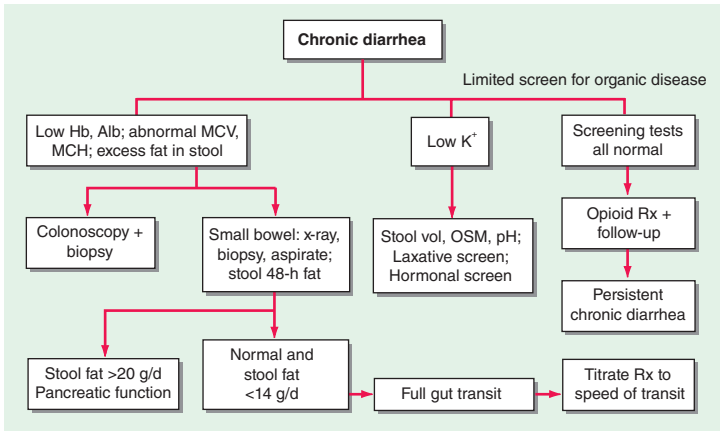
SPECIFIC CAUSES

Altered colonic motility due to neurologic dysfunction (diabetes mellitus, spinal cord injury, multiple sclerosis, Chagas' disease, Hirschsprung's disease, chronic idiopathic intestinal pseudoobstruction, idiopathic megacolon), scleroderma, drugs (esp. anticholinergic agents, opiates, aluminum- or calcium-based antacids, calcium channel blockers, iron supplements, sucralfate), hypothyroidism, Cushing's syndrome, hypokalemia, hypercalcemia, dehydration, mechanical causes (colorectal tumors, diverticulitis, volvulus, hernias, intussusception), and anorectal pain (from fissures, hemorrhoids, abscesses, or proctitis) leading to retention, constipation, and fecal impaction.

http://internalmedicinebook.com



A



B

FIGURE 40-2 Chronic diarrhea. **A.** Initial management based on accompanying symptoms or features. **B.** Evaluation based on findings from a limited age-appropriate screen for organic disease. Alb, albumin; bm, bowel movement; Hb, hemoglobin; IBS, irritable bowel syndrome; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; OSM, osmolality; pr, per rectum. *(Reprinted from M Camilleri: Clin Gastroenterol Hepatol 2:198, 2004.)*

TREATMENT CONSTIPATION

A management approach is shown in Fig. 40-3. In the absence of identifiable cause, constipation may improve with reassurance, exercise, increased dietary fiber, bulking agents (e.g., psyllium), and increased fluid intake. Specific therapies include removal of bowel obstruction (fecalith, tumor), discontinuance of nonessential hypomotility agents (esp. aluminum or calcium-containing antacids, opiates), or substitution of magnesium-based antacids for aluminum-based antacids. For symptomatic relief, magnesium-containing agents or other cathartics are

http://internalmedicinebook.com

TABLE 40-3 COMMON CAUSES OF MALABSORPTION

Maldigestion: Chronic pancreatitis, cystic fibrosis, pancreatic carcinoma

Bile salt deficiency: Cirrhosis, cholestasis, bacterial overgrowth (blind loop syndromes, intestinal diverticula, hypomotility disorders), impaired ileal reabsorption (resection, Crohn's disease), bile salt binders (cholestyramine, calcium carbonate, neomycin)

Inadequate absorptive surface: Massive intestinal resection, gastrocolic fistula, jejunoileal bypass

Lymphatic obstruction: Lymphoma, Whipple's disease, intestinal lymphangiectasia

Vascular disease: Constrictive pericarditis, right-sided heart failure, mesenteric arterial or venous insufficiency

Mucosal disease: Infection (esp. ***Giardia***, Whipple's disease, tropical sprue), inflammatory diseases (esp. Crohn's disease), radiation enteritis, eosinophilic enteritis, ulcerative jejunitis, mastocytosis, tropical sprue, infiltrative disorders (amyloidosis, scleroderma, lymphoma, collagenous sprue, microscopic colitis), biochemical abnormalities (gluten-sensitive enteropathy, disaccharidase deficiency, hypogammaglobulinemia, abetalipoproteinemia, amino acid transport deficiencies), endocrine disorders (diabetes mellitus, hypoparathyroidism, adrenal insufficiency, hyperthyroidism, Zollinger-Ellison syndrome, carcinoid syndrome)

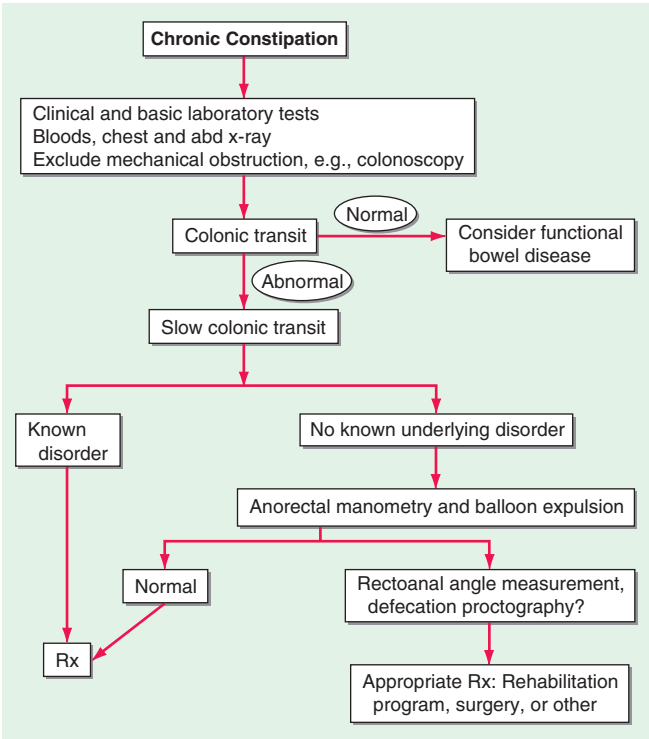
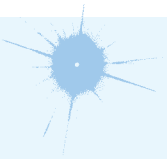


FIGURE 40-3 Algorithm for the management of constipation. abd, abdominal.

http://internalmedicinebook.com

occasionally needed. With severe hypo- or dysmotility or in the presence of opiates, osmotically active agents (e.g., oral lactulose, intestinal polyethylene glycol–containing lavage solutions) and oral or rectal emollient laxatives (e.g., docusate salts) and mineral oil are most effective.



For a more detailed discussion, see Camilleri M, Murray JA: Diarrhea and Constipation, Chap. 55, p. 264; and Binder HJ: Disorders of Absorption, Chap. 349, p. 1932, in HPIM-19.

41 Gastrointestinal Bleeding

PRESENTATION

1. *Hematemesis:* Vomiting of blood or altered blood ("coffee grounds") indicates bleeding proximal to ligament of Treitz.
2. *Melena:* Altered (black) blood per rectum (>100-mL blood required for one melenic stool) usually indicates bleeding proximal to ligament of Treitz but may be as distal as ascending colon; pseudomelena may be caused by ingestion of iron, bismuth, licorice, beets, blueberries, and charcoal.
3. *Hematochezia:* Bright red or maroon rectal bleeding usually implies bleeding beyond ligament of Treitz but may be due to rapid upper GI bleeding (>1000 mL).
4. *Positive fecal occult blood test with or without iron deficiency.*
5. *Symptoms of blood loss:* e.g., light-headedness or shortness of breath.

HEMODYNAMIC CHANGES

Orthostatic drop in bp >10 mmHg usually indicates >20% reduction in blood volume (± syncope, light-headedness, nausea, sweating, thirst).

SHOCK

BP <100 mmHg systolic usually indicates <30% reduction in blood volume (± pallor, cool skin).

LABORATORY CHANGES

Hematocrit may not reflect extent of blood loss because of delayed equilibration with extravascular fluid. Mild leukocytosis and thrombocytosis. Elevated blood urea nitrogen is common in upper GI bleeding.

ADVERSE PROGNOSTIC SIGNS

Age >60 years, associated illnesses, coagulopathy, immunosuppression, presentation with shock, rebleeding, onset of bleeding in hospital, variceal bleeding, endoscopic stigmata of recent bleeding (e.g., "visible vessel" in ulcer base [see below]).

http://internalmedicinebook.com

UPPER GI BLEEDING

CAUSES

Common

Peptic ulcer (accounts for ~50%), gastropathy (alcohol, aspirin, NSAIDs, stress), esophagitis, Mallory-Weiss tear (mucosal tear at gastroesophageal junction due to retching), gastroesophageal varices.

Less Common

Swallowed blood (nosebleed); esophageal, gastric, or intestinal neoplasm; anticoagulant and fibrinolytic therapy; hypertrophic gastropathy (Ménétrier's disease); aortic aneurysm; aortoenteric fistula (from aortic graft); arteriovenous malformation; telangiectases (Osler-Weber-Rendu syndrome); Dieulafoy lesion (ectatic submucosal vessel); vasculitis; connective tissue disease (pseudoxanthoma elasticum, Ehlers-Danlos syndrome); blood dyscrasias; neurofibroma; amyloidosis; hemobilia (biliary origin).

EVALUATION

After hemodynamic resuscitation (see below and Fig. 41-1).

- History and physical examination: Drugs (increased risk of upper and lower GI tract bleeding with aspirin and NSAIDs), prior ulcer, bleeding history, family history, features of cirrhosis or vasculitis, etc. Hyperactive bowel sounds favor upper GI source.
- Nasogastric aspirate for gross blood, if source (upper versus lower) not clear from history; may be falsely negative in up to 16% of pts if bleeding has ceased or duodenum is the source. Testing aspirate for occult blood is meaningless.
- Upper endoscopy: Accuracy >90%; allows visualization of bleeding site and possibility of therapeutic intervention; mandatory for suspected varices, aortoenteric fistulas; permits identification of "visible vessel" (protruding artery in ulcer crater), which connotes high (~50%) risk of rebleeding.
- Upper GI barium radiography: Accuracy ~80% in identifying a lesion, though does not confirm source of bleeding; acceptable alternative to endoscopy in resolved or chronic low-grade bleeding.
- Selective mesenteric arteriography: When brisk bleeding precludes identification of source at endoscopy.
- Radioisotope scanning (e.g., ^{99}Tc tagged to red blood cells or albumin); used primarily as screening test to confirm bleeding is rapid enough for arteriography to be of value or when bleeding is intermittent and of unclear origin.

LOWER GI BLEEDING

CAUSES

Anal lesions (hemorrhoids, fissures), rectal trauma, proctitis, colitis (ulcerative colitis, Crohn's disease, infectious colitis, ischemic colitis, radiation), colonic polyps, colonic carcinoma, angiodysplasia (vascular ectasia), diverticulosis, intussusception, solitary ulcer, blood dyscrasias, vasculitis, connective tissue disease, neurofibroma, amyloidosis, anticoagulation.

EVALUATION (SEE BELOW AND FIG. 41-2)

- History and physical examination.
- In the presence of hemodynamic changes, perform upper endoscopy followed by colonoscopy. In the absence of hemodynamic changes, perform anoscopy and either flexible sigmoidoscopy or colonoscopy: Exclude hemorrhoids, fissure, ulcer, proctitis, neoplasm.

http://internalmedicinebook.com

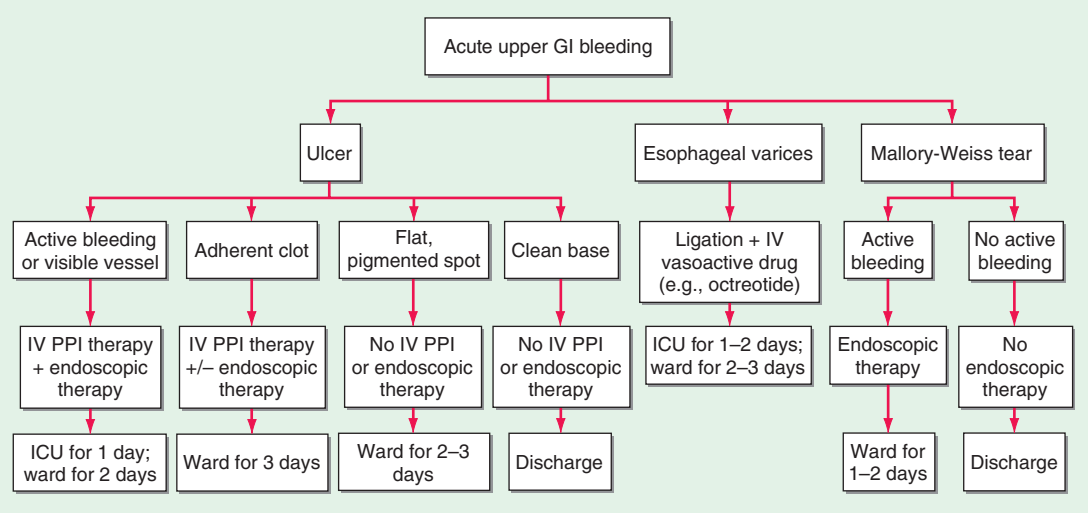


FIGURE 41-1 Suggested algorithm for pts with acute upper GI bleeding. Recommendations on level of care and time of discharge assume pt is stabilized without further bleeding or other concomitant medical problems. PPI, proton pump inhibitor.

http://internalmedicinebook.com

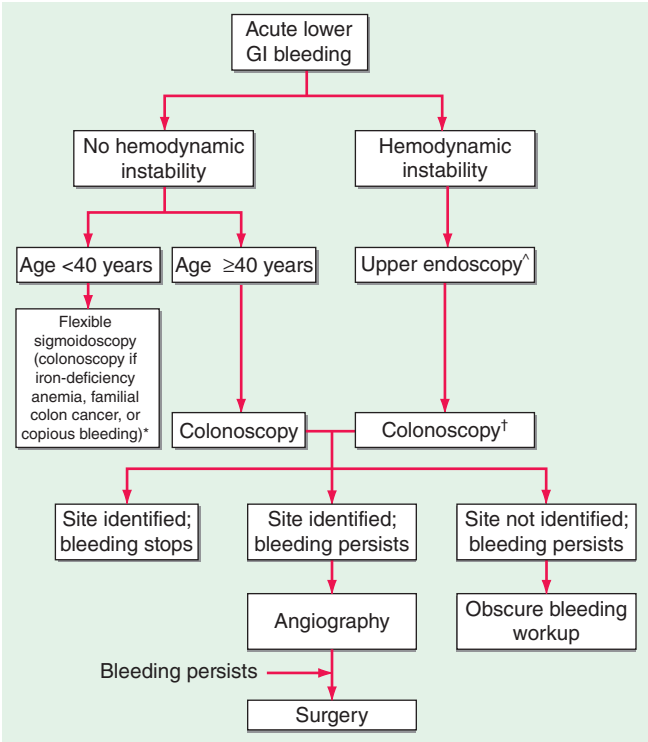


FIGURE 41-2 Suggested algorithm for pts with acute lower GI bleeding. *Some suggest colonoscopy for any degree of rectal bleeding in pts <40 years as well. ^If upper GI endoscopy reveals definite source, no further evaluation is needed. †If massive bleeding does not allow time for colonic lavage, proceed to angiography.

- Colonoscopy: Often test of choice, but may be impossible if bleeding is massive.
- Barium enema: No role in active bleeding.
- Arteriography: When bleeding is severe (requires bleeding rate >0.5 mL/min; may require prestudy radioisotope bleeding scan as above); defines site of bleeding or abnormal vasculature.
- Surgical exploration (last resort).

BLEEDING OF OBSCURE ORIGIN

Often small-bowel source. Consider small-bowel enteroclysis x-ray (careful barium radiography via peroral intubation of small bowel), Meckel's scan, enteroscopy (small-bowel endoscopy), or exploratory laparotomy with intraoperative enteroscopy.

TREATMENT UPPER AND LOWER GI BLEEDING

- Venous access with large-bore IV (14–18 gauge); central venous line for major bleed and pts with cardiac disease; monitor vital signs, urine output, Hct (fall may lag). Gastric lavage of unproven benefit but clears stomach before endoscopy. Iced saline may lyse clots; room-temperature tap water may be preferable. Intubation may be required to protect airway.

http://internalmedicinebook.com

- Type and cross-match blood (six units for major bleed).
- Surgical standby when bleeding is massive.
- Support blood pressure with isotonic fluids (normal saline); albumin and fresh frozen plasma in cirrhotics. Packed red blood cells when available (whole blood if massive bleeding); maintain Hct >25–30. Fresh frozen plasma and vitamin K (10 mg SC or IV) in cirrhotics with coagulopathy.
- IV calcium (e.g., up to 10–20 mL 10% calcium gluconate IV over 10–15 min) if serum calcium falls (due to transfusion of citrated blood). Empirical drug therapy (antacids, H_2 receptor blockers, omeprazole) of unproven benefit.
- Specific measures: *Varices:* octreotide (50-μg bolus, 50-μg/h infusion for 2–5 days), Sengstaken-Blakemore tube tamponade, endoscopic sclerosis, or band ligation; propranolol or nadolol in doses sufficient to cause beta blockade reduces risk of recurrent or initial variceal bleeding (do not use in acute bleed) (Chap. 155); *ulcer with visible vessel or active bleeding*: endoscopic bipolar, heater-probe, or laser coagulation or injection of epinephrine; *gastritis*: embolization or vasopressin infusion of left gastric artery; *GI telangiectases*: ethinylestradiol/norethisterone (0.05/1.0 mg PO qd) may prevent recurrent bleeding, particularly in pts with chronic renal failure; *diverticulosis*: mesenteric arteriography with intraarterial vasopressin; *angiodysplasia*: colonoscopic bipolar or laser coagulation, may regress with replacement of stenotic aortic valve.
- Indications for emergency surgery: Uncontrolled or prolonged bleeding, severe rebleeding, aortoenteric fistula. For intractable variceal bleeding, consider transjugular intrahepatic portosystemic shunt (TIPS).

For a more detailed discussion, see Laine L: Gastrointestinal Bleeding, Chap. 57, p. 276, in HPIM-19.

42 Jaundice and Evaluation of Liver Function

JAUNDICE

Definition

Yellow skin pigmentation caused by elevation in serum bilirubin level (also termed *icterus*); often more easily discernible in sclerae. Scleral icterus becomes clinically evident at a serum bilirubin level of ≥51 μmol/L (≥3 mg/dL); yellow skin discoloration also occurs with elevated serum carotene levels but without pigmentation of the sclerae.

Bilirubin Metabolism

Bilirubin is the major breakdown product of hemoglobin released from senescent erythrocytes. Initially, it is bound to albumin, transported into the liver, conjugated

http://internalmedicinebook.com

to a water-soluble form (glucuronide) by glucuronosyltransferase, excreted into the bile, and converted to urobilinogen in the colon. Urobilinogen is mostly excreted in the stool; a small portion is reabsorbed and excreted by the kidney. Bilirubin can be filtered by the kidney only in its conjugated form (measured as the "direct" fraction); thus, increased *direct* serum bilirubin level is associated with bilirubinuria. Increased bilirubin production and excretion (even without hyperbilirubinemia, as in hemolysis) produce elevated urinary urobilinogen levels.

Etiology

Hyperbilirubinemia occurs as a result of (1) overproduction; (2) impaired uptake, conjugation, or excretion of bilirubin; (3) regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts (Table 42-1).

TABLE 42-1 CAUSES OF ISOLATED HYPERBILIRUBINEMIA

I. Indirect hyperbilirubinemia
  A. Hemolytic disorders
    1. Inherited
      a. Spherocytosis, elliptocytosis, glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies
      b. Sickle cell anemia
    2. Acquired
      a. Microangiopathic hemolytic anemias
      b. Paroxysmal nocturnal hemoglobinuria
      c. Spur cell anemia
      d. Immune hemolysis
      e. Parasitic infections
        1. Malaria
        2. Babesiosis
  B. Ineffective erythropoiesis
    1. Cobalamin, folate, and severe iron deficiencies
    2. Thalassemia
  C. Increased bilirubin production
    1. Massive blood transfusion
    2. Resorption of hematoma
  D. Drugs
    1. Rifampin
    2. Probenecid
    3. Ribavirin
  E. Inherited conditions
    1. Crigler-Najjar types I and II
    2. Gilbert's syndrome
II. Direct hyperbilirubinemia
  A. Inherited conditions
    1. Dubin-Johnson syndrome
    2. Rotor syndrome

http://internalmedicinebook.com

Evaluation

The initial steps in evaluating the pt with jaundice are to determine whether (1) hyperbilirubinemia is conjugated or unconjugated, and (2) other biochemical liver tests are abnormal (Figs. 42-1 and 42-2, Tables 42-2 and 42-3). Essential clinical examination includes history (especially duration of jaundice, pruritus, associated pain, risk factors for parenterally transmitted diseases, medications, ethanol use, travel history, surgery, pregnancy, presence of any accompanying symptoms), physical examination (hepatomegaly, tenderness over liver, palpable gallbladder, splenomegaly, gynecomastia, testicular atrophy, other stigmata of chronic liver disease), blood liver tests (see below), and complete blood count.

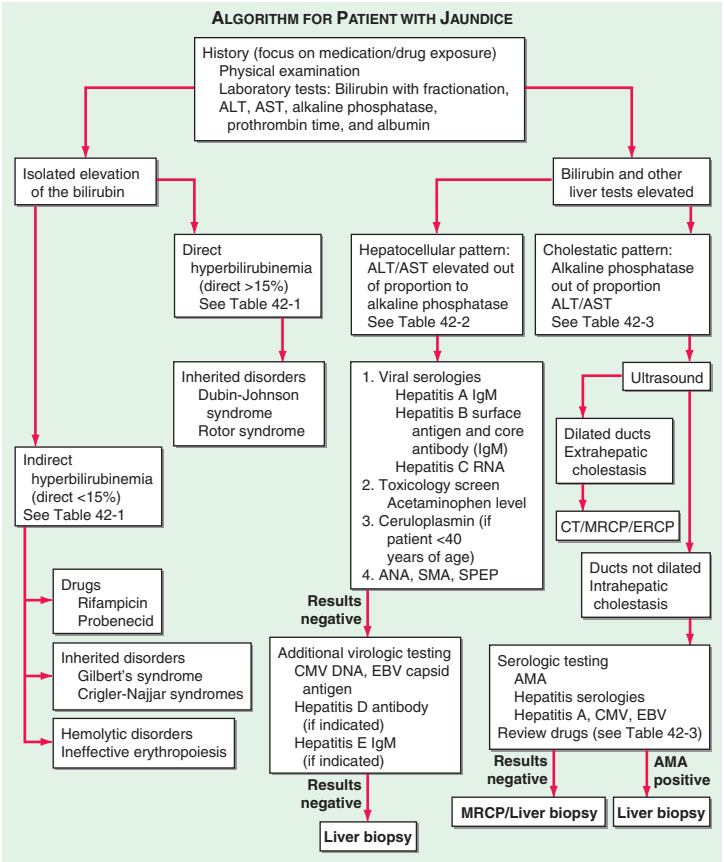


FIGURE 42-1 Evaluation of the pt with jaundice. ALT, alanine aminotransferase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatogram; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis.

http://internalmedicinebook.com

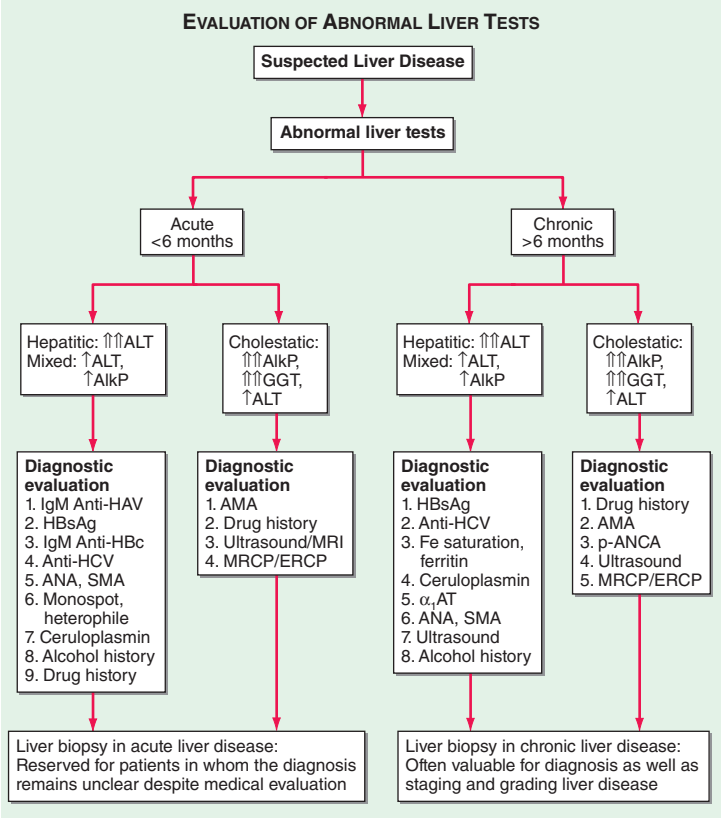


FIGURE 42-2 Algorithm for evaluation of abnormal liver tests. α AT, α1 antitrypsin; AlkP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatogram; GGT, γ-Glutamyl transpeptidase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAG, hepatitis B surface antigen; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SMA, smooth-muscle antibody.

Gilbert Syndrome

Impaired conjugation of bilirubin due to reduced bilirubin UDP glucuronosyltransferase activity. Results in mild unconjugated hyperbilirubinemia, almost always <103 μmol/L (<6 mg/dL). Affects 3–7% of the population; males/females 2–7:1.

BLOOD TESTS OF LIVER FUNCTION

Used to detect presence of liver disease (Fig. 42-2), discriminate among different types of liver disease (Table 42-4), gauge the extent of known liver damage, and follow response to treatment.

Bilirubin

Provides indication of hepatic uptake, metabolic (conjugation) and excretory functions; conjugated fraction (direct) distinguished from unconjugated by chemical assay (Table 42-1).

http://internalmedicinebook.com

TABLE 42-2 HEPATOCELLULAR CONDITIONS THAT MAY PRODUCE JAUNDICE

- Viral hepatitis
  - Hepatitis A, B, C, D, and E
  - Epstein-Barr virus
  - Cytomegalovirus
  - Herpes simplex
- Alcoholic hepatitis
- Drug toxicity
  - Predictable, dose dependent, (e.g., acetaminophen)
  - Unpredictable, idiosyncratic, (e.g., isoniazid)
- Environmental toxins
  - Vinyl chloride
  - Jamaica bush tea—pyrrolizidine alkaloids
  - Kava Kava
  - Wild mushrooms—*Amanita phalloides* or *A. verna*
- Wilson's disease
- Autoimmune hepatitis

TABLE 42-3 CHOLESTATIC CONDITIONS THAT MAY PRODUCE JAUNDICE

I. Intrahepatic
  A. Viral hepatitis
    1. Fibrosing cholestatic hepatitis—hepatitis B and C
    2. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection
  B. Alcoholic hepatitis
  C. Drug toxicity
    1. Pure cholestasis—anabolic and contraceptive steroids
    2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
    3. Chronic cholestasis—chlorpromazine and prochlorperazine
  D. Primary biliary cirrhosis
  E. Primary sclerosing cholangitis
  F. Vanishing bile duct syndrome
    1. Chronic rejection of liver transplants
    2. Sarcoidosis
    3. Drugs
  G. Congestive hepatopathy and ischemic hepatitis
  H. Inherited conditions
    1. Progressive familial intrahepatic cholestasis
    2. Benign recurrent cholestasis
  I. Cholestasis of pregnancy
  J. Total parenteral nutrition
  K. Nonhepatobiliary sepsis
  L. Benign postoperative cholestasis
  M. Paraneoplastic syndrome

(*Continued*)

http://internalmedicinebook.com

TABLE 42-3 CHOLESTATIC CONDITIONS THAT MAY PRODUCE JAUNDICE (*CONTINUED*)

- N. Veno-occlusive disease
- O. Graft-versus-host disease
- P. Infiltrative disease
  - 1. TB
  - 2. Lymphoma
  - 3. Amyloidosis
- Q. Infections
  - 1. Malaria
  - 2. Leptospirosis

II. Extrahepatic

- A. Malignant
  - 1. Cholangiocarcinoma
  - 2. Pancreatic cancer
  - 3. Gallbladder cancer
  - 4. Ampullary cancer
  - 5. Malignant involvement of the porta hepatis lymph nodes
- B. Benign
  - 1. Choledocholithiasis
  - 2. Postoperative biliary strictures
  - 3. Primary sclerosing cholangitis
  - 4. Chronic pancreatitis
  - 5. AIDS cholangiopathy
  - 6. Mirizzi's syndrome
  - 7. Parasitic disease (ascariasis)

Aminotransferases (Transaminases)

Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT); sensitive indicators of liver cell injury; greatest elevations seen in hepatocellular necrosis (e.g., viral hepatitis, toxic or ischemic liver injury, acute hepatic vein obstruction), occasionally with sudden, complete biliary obstruction (e.g., from gallstone); milder abnormalities in cholestatic, cirrhotic, and infiltrative disease; poor correlation between degree of liver cell damage and level of aminotransferases; ALT more specific measure of liver injury, because AST also found in striated muscle and other organs; ethanol-induced liver injury usually produces modest increases with more prominent elevation of AST than ALT.

Alkaline Phosphatase

Sensitive indicator of cholestasis, biliary obstruction (enzyme increases more quickly than serum bilirubin), and liver infiltration; mild elevations in other forms of liver disease; limited specificity because of wide tissue distribution; elevations also seen in normal childhood, pregnancy, and bone diseases; tissue-specific isoenzymes can be distinguished by fractionation or by differences in heat stability (liver enzyme activity stable under conditions that destroy bone enzyme activity).

5′-Nucleotidase (5′-NT)

Pattern of elevation in hepatobiliary disease similar to alkaline phosphatase; has greater specificity for liver disorders; used to determine whether liver is source of

http://internalmedicinebook.com

TABLE 42-4 LIVER TEST PATTERNS IN HEPATOBILIARY DISORDERS

Type of Disorder	Bilirubin	Aminotransferases
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU ALT >AST
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT > 2 suggests alcoholic hepatitis or cirrhosis
Intra- and extra-hepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation
(Obstructive jaundice)	Bilirubinuria	Rarely >500 IU
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation

Alkaline Phosphatase	Albumin	Prothrombin Time
Normal	Normal	Normal
Normal to <3 times normal elevation	Normal	Usually normal. If >5 × above control and not corrected by parenteral vitamin K, suggests poor prognosis
Normal to <3 times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Normal to <3 times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Elevated, often >4 times normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
Elevated, often >4 times normal elevation Fractionate, or confirm liver origin with 5′ nucleotidase or γ-glutamyl transpeptidase	Normal	Normal

http://internalmedicinebook.com

elevation in serum alkaline phosphatase, esp. in children, pregnant women, pts with possible concomitant bone disease.

γ-Glutamyl transpeptidase (GGT)

Correlates with serum alkaline phosphatase activity. Elevation is less specific for cholestasis than alkaline phosphatase or 5′-NT.

Coagulation Factors (See also Chap. 64)

Measure of clotting factor activity; prolongation results from clotting factor deficiency or inactivity; all clotting factors except factor VIII are synthesized in the liver, and deficiency can occur rapidly from widespread liver disease as in hepatitis, toxic injury, or cirrhosis; single best acute measure of hepatic synthetic function; helpful in diagnosis and prognosis of acute liver disease. Clotting factors II, VII, IX, X function only in the presence of the fat-soluble vitamin K; PT prolongation from fat malabsorption distinguished from hepatic disease by rapid and complete response to vitamin K replacement.

Albumin

Decreased serum levels result from decreased hepatic synthesis (chronic liver disease or prolonged malnutrition) or excessive losses in urine or stool; insensitive indicator of acute hepatic dysfunction, because serum half-life is 2–3 weeks; in pts with chronic liver disease, degree of hypoalbuminemia correlates with severity of liver dysfunction.

Globulin

Mild polyclonal hyperglobulinemia often seen in chronic liver diseases; marked elevation frequently seen in *autoimmune* chronic active hepatitis.

Ammonia

Elevated blood levels result from deficiency of hepatic detoxification pathways and portal-systemic shunting, as in fulminant hepatitis, hepatotoxin exposure, and severe portal hypertension (e.g., from cirrhosis); elevation of blood ammonia does not correlate well with hepatic function or the presence or degree of acute encephalopathy.

HEPATOBILIARY IMAGING PROCEDURES

Ultrasonography (US)

Rapid, noninvasive examination of abdominal structures; no radiation exposure; relatively low cost, equipment portable; images and interpretation strongly dependent on expertise of examiner; particularly valuable for detecting biliary duct dilation and gallbladder stones (>95%); much less sensitive for intraductal stones (~60%); most sensitive means of detecting ascites; moderately sensitive for detecting hepatic masses but excellent for discriminating solid from cystic structures; useful in directing percutaneous needle biopsies of suspicious lesions; Doppler US useful to determine patency and flow in portal, hepatic veins and portal-systemic shunts; imaging improved by presence of ascites but severely hindered by bowel gas; endoscopic US less affected by bowel gas and is sensitive for determination of depth of tumor invasion through bowel wall.

CT

Particularly useful for detecting, differentiating, and directing percutaneous needle biopsy of abdominal masses, cysts, and lymphadenopathy; imaging enhanced by intestinal or intravenous contrast dye and unaffected by intestinal gas; somewhat less sensitive than US for detecting stones in gallbladder but more sensitive for choledocholithiasis; may be useful in distinguishing certain forms of diffuse hepatic disease (e.g., fatty infiltration, iron overload).

http://internalmedicinebook.com

MRI

Most sensitive detection of hepatic masses and cysts; allows easy differentiation of hemangiomas from other hepatic tumors; most accurate noninvasive means of assessing hepatic and portal vein patency, vascular invasion by tumor; useful for monitoring iron, copper deposition in liver (e.g., in hemochromatosis, Wilson's disease). Magnetic resonance cholangiopancreatography (MRCP) can be useful for visualizing the head of the pancreas and the pancreatic and biliary ducts.

Radionuclide Scanning

Using various radiolabeled compounds, different scanning methods allow sensitive assessment of biliary excretion (HIDA, PIPIDA, DISIDA scans), parenchymal changes (technetium sulfur colloid liver/spleen scan), and selected inflammatory and neoplastic processes (gallium scan); HIDA and related scans particularly useful for assessing biliary patency and excluding acute cholecystitis in situations where US is not diagnostic; CT, MRI, and colloid scans have similar sensitivity for detecting liver tumors and metastases; CT and combination of colloidal liver and lung scans sensitive for detecting right subphrenic (suprahepatic) abscesses.

Cholangiography

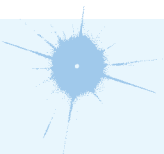
Most sensitive means of detecting biliary ductal calculi, biliary tumors, sclerosing cholangitis, choledochal cysts, fistulas, and bile duct leaks; may be performed via endoscopic (transampullary) or percutaneous (transhepatic) route; allows sampling of bile and ductal epithelium for cytologic analysis and culture; allows placement of biliary drainage catheter and stricture dilation; endoscopic route (endoscopic retrograde cholangiopancreatogram [ERCP]) permits manometric evaluation of sphincter of Oddi, sphincterotomy, and stone extraction.

Angiography

Most accurate means of determining portal pressures and assessing patency and direction of flow in portal and hepatic veins; highly sensitive for detecting small vascular lesions and hepatic tumors (esp. primary hepatocellular carcinoma); "gold standard" for differentiating hemangiomas from solid tumors; most accurate means of studying vascular anatomy in preparation for complicated hepatobiliary surgery (e.g., portal-systemic shunting, biliary reconstruction) and determining resectability of hepatobiliary and pancreatic tumors. Similar anatomic information (but not intravascular pressures) can often be obtained noninvasively by CT- and MR-based techniques.

Percutaneous Liver Biopsy

Most accurate in disorders causing diffuse changes throughout the liver; subject to sampling error in focal infiltrative disorders such as metastasis; should not be the initial procedure in the diagnosis of cholestasis. Contraindications to performing a percutaneous liver biopsy include significant ascites and prolonged international normalized ratio (INR). In such settings, the biopsy can be performed via the transjugular approach.



For a more detailed discussion, see John S, Pratt DS: Jaundice, Chap. 58, p. 279; Ghany MG, Hoofnagle JH: Approach to the Patient with Liver Disease, Chap 357, p. 1989; and Pratt DS: Evaluation of Liver Function, Chap. 358, p. 1995, in HPIM-19.

http://internalmedicinebook.com

43 Ascites

DEFINITION

Accumulation of fluid within the peritoneal cavity. Small amounts may be asymptomatic; increasing amounts cause abdominal distention and discomfort, anorexia, nausea, early satiety, heartburn, flank pain, and respiratory distress.

DETECTION

Physical Examination

Bulging flanks, fluid wave, shifting dullness, "puddle sign" (dullness over dependent abdomen with pt on hands and knees). May be associated with penile or scrotal edema, umbilical or inguinal herniation, pleural effusion. Evaluation should include rectal and pelvic examination, assessment of liver and spleen. Palmar erythema and spider angiomata seen in cirrhosis. Periumbilical nodule (*Sister Mary Joseph's nodule*) or supraclavicular node (*Virchow's node*) suggests an abdominal malignancy.

Ultrasonography/CT

Very sensitive; able to distinguish fluid from cystic masses.

EVALUATION

Diagnostic paracentesis (50–100 mL) essential. Routine evaluation includes gross inspection, protein, albumin, glucose, cell count and differential, Gram's and acid-fast stains, culture, cytology; in selected cases check amylase, LDH, triglycerides, culture for tuberculosis (TB). Rarely, laparoscopy or even exploratory laparotomy may be required. Ascites due to CHF (e.g., pericardial constriction) may require evaluation by right-sided heart catheterization.

Differential Diagnosis

Cirrhosis counts for 84% of cases of ascites. Cardiac ascites, peritoneal carcinomatosis, and "mixed" ascites resulting from cirrhosis and a second disease account for 10–15%.

Diseases of peritoneum: Infections (bacterial, tuberculous, fungal, parasitic), neoplasms, connective tissue disease, miscellaneous (Whipple's disease, familial Mediterranean fever, endometriosis, starch peritonitis, etc.).

Diseases not involving peritoneum: Cirrhosis, CHF, Budd-Chiari syndrome, hepatic venoocclusive disease, hypoalbuminemia (nephrotic syndrome, protein-losing enteropathy, malnutrition), miscellaneous (myxedema, ovarian diseases, pancreatic disease, chylous ascites).

Pathophysiologic Classification Using Serum-Ascites Albumin Gradient (SAAG)

Difference in albumin concentrations between serum and ascites as a reflection of imbalances in hydrostatic pressures and can be used to differentiate between potential causes of ascites (Fig. 43-1).

CIRRHOTIC ASCITES

Pathogenesis

Contributing factors: (1) portal hypertension, (2) hypoalbuminemia, (3) hepatic lymph, (4) renal sodium retention—secondary to hyperaldosteronism, increased sympathetic nervous system activity (renin-angiotensin production). Initiating event may be peripheral arterial vasodilation triggered by endotoxin and cytokines and mediated by nitric oxide.

http://internalmedicinebook.com

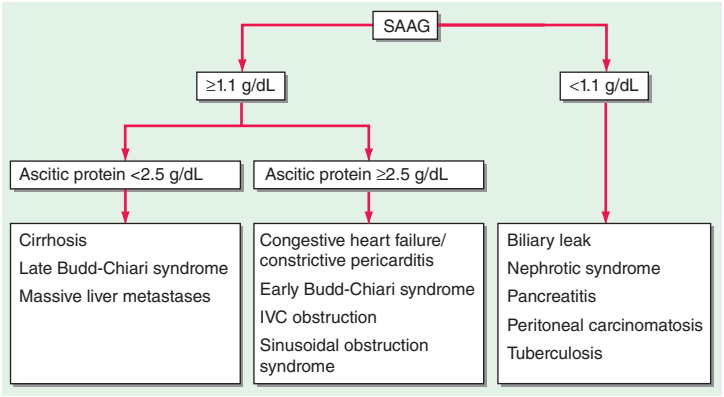


FIGURE 43-1 Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG).

TREATMENT CIRRHOTIC ASCITES

1. Rigid salt restriction (<2 g Na/d).
2. For moderate ascites, diuretics usually necessary; spironolactone 100–200 mg/d PO (can be increased to 400 mg/d if low-sodium diet is confirmed and fluid not mobilized); furosemide 40–80 mg/d PO or IV may be added if necessary (greater risk of hepatorenal syndrome [HRS], encephalopathy), can increase to maximum of 120–160 mg/d until effect achieved or complication occurs.
3. Monitor weight, urinary Na and K, serum electrolytes, and creatinine. If ascites is still present with the above measures, this is defined as *refractory ascites*. Treatment modalities include:
   a. Pharmacologic therapy: add midodrine or clonidine to diuretic therapy
   b. Repeated large-volume paracentesis (5 L) with IV infusions of albumin (6–8 g/L ascites removed)
   c. Consider transjugular intrahepatic portosystemic shunt (TIPS). While TIPS manages the ascites, it has not been found to improve survival and is often associated with encephalopathy.

Prognosis for pts with cirrhotic ascites is poor with <50% survival 2 years after onset of ascites. Consider liver transplantation in appropriate candidates with the onset of ascites (Chap. 154).

COMPLICATIONS

Spontaneous Bacterial Peritonitis

Suspect in cirrhotic pt with ascites and fever, abdominal pain, worsening ascites, ileus, hypotension, worsening jaundice, or encephalopathy; low ascitic protein concentration (low opsonic activity) is predisposing factor. Diagnosis suggested by ascitic fluid PMN cell count >250/μL; confirmed by positive culture (usually *Escherichia coli* and other gut bacteria; however, gram-positive bacteria including *Streptococcus viridans*, *Staphylococcus aureus*, and *Enterococcus* spp. also can be found). Initial treatment: Cefotaxime 2 g IV q8h. Risk is increased in pts with variceal bleeding, and prophylaxis against spontaneous bacterial peritonitis is recommended when a pt presents with upper GI bleeding.

http://internalmedicinebook.com

Hepatorenal Syndrome (HRS)

Functional renal failure without renal pathology; occurs in 10% of pts with advanced cirrhosis or acute liver failure. Thought to result from altered renal hemodynamics. Two types: type 1 HRS—decrease in renal function within 1–2 weeks of presentation; type 2 HRS—associated with a rise in serum creatinine but is associated with a better outcome. Often seen in pts with refractory ascites. Treatment: midodrine along with octreotide and IV albumin. For either type 1 or 2 HRS, prognosis is poor in the absence of liver transplantation.



For a more detailed discussion, see Corey KE, Friedman LS: Abdominal Swelling and Ascites, Chap. 59, p. 285; and Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058, in HPIM-19.

44 Lymphadenopathy and Splenomegaly

LYMPHADENOPATHY

Exposure to antigen through a break in the skin or mucosa results in antigen being taken up by an antigen-presenting cell and carried via lymphatic channels to the nearest lymph node. Lymph channels course throughout the body except for the brain and the bones. Lymph enters the node through the afferent vessel and leaves through an efferent vessel. Because antigen-presenting cells pass through lymph nodes, they present antigen to lymphocytes residing there. Lymphocytes in a node are constantly being replaced by antigen-naïve lymphocytes from the blood. They are retained in the node via special homing receptors. B cells populate the lymphoid follicles in the cortex; T cells populate the paracortical regions. When a B cell encounters an antigen to which its surface immunoglobulin can bind, it stays in the follicle for a few days and forms a germinal center where the immunoglobulin gene is mutated in an effort to make an antibody with higher affinity for the antigen. The B cell then migrates to the medullary region, differentiates into a plasma cell, and secretes immunoglobulin into the efferent lymph.

When a T cell in the node encounters an antigen it recognizes, it proliferates and joins the efferent lymph. The efferent lymph laden with antibodies and T cells specific for the inciting antigen passes through several nodes on its way to the thoracic duct, which drains lymph from most of the body. From the thoracic duct, lymph enters the bloodstream at the left subclavian vein. Lymph from the head and neck and the right arm drains into the right subclavian vein. From the bloodstream, the antibody and T cells localize to the site of infection.

Lymphadenopathy may be caused by infections, immunologic diseases, malignancies, lipid storage diseases, or other disorders of uncertain etiology (e.g., sarcoidosis, Castleman's disease; **Table 44-1**). The two major mechanisms of lymphadenopathy are *hyperplasia*, in response to immunologic or infectious stimuli, and *infiltration*, by cancer cells or lipid- or glycoprotein-laden macrophages.

http://internalmedicinebook.com

TABLE 44-1 DISEASES ASSOCIATED WITH LYMPHADENOPATHY

1. Infectious diseases
   a. Viral—infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus 6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus 8
   b. Bacterial—streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy
   c. Fungal—histoplasmosis, coccidioidomycosis, paracoccidioidomycosis
   d. Chlamydial—lymphogranuloma venereum, trachoma
   e. Parasitic—toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis
   f. Rickettsial—scrub typhus, rickettsialpox, Q fever
2. Immunologic diseases
   a. Rheumatoid arthritis
   b. Juvenile rheumatoid arthritis
   c. Mixed connective tissue disease
   d. Systemic lupus erythematosus
   e. Dermatomyositis
   f. Sjögren's syndrome
   g. Serum sickness
   h. Drug hypersensitivity—diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc.
   i. Angioimmunoblastic lymphadenopathy
   j. Primary biliary cirrhosis
   k. Graft-versus-host disease
   l. Silicone-associated
   m. Autoimmune lymphoproliferative syndrome
3. Malignant diseases
   a. Hematologic—Hodgkin's lymphoma, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, histiocytic and dendritic cell neoplasms, amyloidosis
   b. Metastatic—from numerous primary sites
4. Lipid storage diseases—Gaucher's, Niemann-Pick, Fabry, Tangier
5. Endocrine diseases—hyperthyroidism
6. Other disorders
   a. Unicentric and multicentric Castleman's disease (giant lymph node hyperplasia)
   b. Sarcoidosis
   c. Dermatopathic lymphadenitis
   d. Lymphomatoid granulomatosis
   e. Histiocytic necrotizing lymphadenitis (Kikuchi's disease)
   f. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
   g. Mucocutaneous lymph node syndrome (Kawasaki's disease)
   h. Familial Mediterranean fever
   i. Severe hypertriglyceridemia
   j. Vascular transformation of sinuses
   k. Inflammatory pseudotumor of lymph node
   l. Congestive heart failure

http://internalmedicinebook.com

APPROACH TO THE PATIENT: **Lymphadenopathy**

HISTORY Age, occupation, animal exposures, sexual orientation, substance abuse history, medication history, and concomitant symptoms influence diagnostic workup. Adenopathy is more commonly malignant in origin in those over age 40 years. Farmers have an increased incidence of brucellosis and lymphoma. Male homosexuals may have AIDS-associated adenopathy. Alcohol and tobacco abuse increase risk of malignancy. Phenytoin may induce adenopathy. The concomitant presence of cervical adenopathy with sore throat or with fever, night sweats, and weight loss suggests particular diagnoses (mononucleosis in the former instance, Hodgkin's disease in the latter).

PHYSICAL EXAMINATION Location of adenopathy, size, node texture, and the presence of tenderness are important in differential diagnosis. Generalized adenopathy (three or more anatomic regions) implies systemic infection or lymphoma. Subclavian or scalene adenopathy is always abnormal and should be biopsied. Nodes >4 cm should be biopsied immediately. Rock-hard nodes fixed to surrounding soft tissue are usually a sign of metastatic carcinoma. Tender nodes are most often benign.

LABORATORY TESTS Usually laboratory tests are not required in the setting of localized adenopathy. If generalized adenopathy is noted, an excisional node biopsy should be performed for diagnosis, rather than a panoply of laboratory tests.

TREATMENT LYMPHADENOPATHY

Pts over age 40 years, those with scalene or supraclavicular adenopathy, those with lymph nodes >4 cm in diameter, and those with hard nontender nodes should undergo immediate excisional biopsy. In younger pts with smaller nodes that are rubbery in consistency or tender, a period of observation for 7–14 days is reasonable. Empirical antibiotics are not indicated. If the nodes shrink, no further evaluation is necessary. If they enlarge, excisional biopsy is indicated.

SPLENOMEGALY

Just as the lymph nodes are specialized to fight pathogens in the tissues, the spleen is the lymphoid organ specialized to fight bloodborne pathogens. It has no afferent lymphatics. The spleen has specialized areas like the lymph node for making antibodies (follicles) and amplifying antigen-specific T cells (periarteriolar lymphatic sheath, or PALS). In addition, it has a well-developed reticuloendothelial system for removing particles and antibody-coated bacteria. The flow of blood through the spleen permits it to filter pathogens from the blood and to maintain quality control over erythrocytes (RBCs)—those that are old and nondeformable are destroyed, and intracellular inclusions (sometimes including pathogens such as *Babesia* and *Plasmodium*) are culled from the cells in a process called *pitting*. Under certain conditions, the spleen can generate hematopoietic cells in place of the marrow.

The normal spleen is about 12 cm in length and 7 cm in width and is not normally palpable. Dullness from the spleen can be percussed between the ninth and eleventh ribs with the pt lying on the right side. Palpation is best performed with the pt supine with knees flexed. The spleen may be felt because it descends when the pt inspires. Physical diagnosis is not sensitive. CT or ultrasound is a superior test.

http://internalmedicinebook.com

Spleen enlargement occurs by three basic mechanisms: (1) hyperplasia or hypertrophy due to an increase in demand for splenic function (e.g., hereditary spherocytosis where demand for removal of defective RBCs is high or immune hyperplasia in response to systemic infection or immune diseases); (2) passive vascular congestion due to portal hypertension; and (3) infiltration with malignant cells, lipid- or glycoprotein-laden macrophages, or amyloid (**Table 44-2**). Massive enlargement, with spleen palpable >8 cm below the left costal margin, usually signifies a lymphoproliferative or myeloproliferative disorder.

TABLE 44-2 DISEASES ASSOCIATED WITH SPLENOMEGALY GROUPED BY PATHOGENIC MECHANISM

Enlargement Due to Increased Demand for Splenic Function	
Reticuloendothelial system hyperplasia (for removal of defective erythrocytes)	Leishmaniasis
Spherocytosis	Trypanosomiasis
Early sickle cell anemia	Ehrlichiosis
Ovalocytosis	Disordered immunoregulation
Thalassemia major	Rheumatoid arthritis (Felty's syndrome)
Hemoglobinopathies	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria	Collagen vascular diseases
Pernicious anemia	Serum sickness
Immune hyperplasia	Immune hemolytic anemias
Response to infection (viral, bacterial, fungal, parasitic)	Immune thrombocytopenias
Infectious mononucleosis	Immune neutropenias
AIDS	Drug reactions
Viral hepatitis	Angioimmunoblastic lymphadenopathy
Cytomegalovirus	Sarcoidosis
Subacute bacterial endocarditis	Thyrotoxicosis (benign lymphoid hypertrophy)
Bacterial septicemia	Interleukin-2 therapy
Congenital syphilis	Extramedullary hematopoiesis
Splenic abscess	Myelofibrosis
Tuberculosis	Marrow damage by toxins, r adiation, strontium
Histoplasmosis	Marrow infiltration by tumors, leukemias, Gaucher's disease
Malaria	
Enlargement Due to Abnormal Splenic or Portal Blood Flow	
Cirrhosis	Splenic artery aneurysm
Hepatic vein obstruction	Hepatic schistosomiasis
Portal vein obstruction, intrahepatic or extrahepatic	Congestive heart failure
Cavernous transformation of the portal vein	Hepatic echinococcosis
Splenic vein obstruction	Portal hypertension (any cause including the above): "Banti's disease"

(*Continued*)

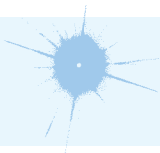
http://internalmedicinebook.com

TABLE 44-2 DISEASES ASSOCIATED WITH SPLENOMEGALY GROUPED BY PATHOGENIC MECHANISM (*CONTINUED*)

Infiltration of the Spleen	
Intracellular or extracellular depositions	Hodgkin's lymphoma
Amyloidosis	Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis)
Gaucher's disease	Angiosarcomas
Niemann-Pick disease	Metastatic tumors (melanoma is most common)
Tangier disease	Eosinophilic granuloma
Hurler's syndrome and other mucopolysaccharidoses	Histiocytic and dendritic cell neoplasms (Histiocytosis X)
Hyperlipidemias	Hamartomas
Benign and malignant cellular infiltrations	Hemangiomas, fibromas, lymphangiomas
Leukemias (acute, chronic, lymphoid, myeloid, monocytic, hairy cell)	Splenic cysts
Lymphomas	
Unknown Etiology	
Idiopathic splenomegaly	Iron-deficiency anemia
Berylliosis	

Peripheral blood RBC count, white blood cell count, and platelet count may be normal, decreased, or increased depending on the underlying disorder. Decreases in one or more cell lineages could indicate hypersplenism, increased destruction. In cases with hypersplenism, the spleen is removed and the cytopenia is generally reversed. In the absence of hypersplenism, most causes of splenomegaly are diagnosed on the basis of signs and symptoms and laboratory abnormalities associated with the underlying disorder. Splenectomy is rarely performed for diagnostic purposes.

Individuals who have had splenectomy are at increased risk of sepsis from a variety of organisms including pneumococcus and *Haemophilus influenzae*. Vaccines for these agents should be given before splenectomy is performed. Splenectomy compromises the immune response to T-independent polysaccharide antigens. Newer vaccine formulations are T dependent and are more effective in splenectomized persons.



For a more detailed discussion, see Henry PH, Longo DL: Enlargement of Lymph Nodes and Spleen, Chap. 79, p. 407, in HPIM-19.

http://internalmedicinebook.com

45 Anemia and Polycythemia

ANEMIA

According to World Health Organization criteria, anemia is defined as blood hemoglobin (Hb) concentration <130 g/L (<13 g/dL) or hematocrit (Hct) <39% in adult males; Hb <120 g/L (<12 g/dL) or Hct <37% in adult females.

Signs and symptoms of anemia are varied, depending on the level of anemia and the time course over which it developed. Acute anemia is nearly always due to blood loss or hemolysis. In acute blood loss, hypovolemia dominates the clinical picture; hypotension and decreased organ perfusion are the main issues. Symptoms associated with more chronic onset vary with the age of the pt and the adequacy of blood supply to critical organs. Moderate anemia is associated with fatigue, loss of stamina, breathlessness, and tachycardia. The pt's skin and mucous membranes may appear pale. If the palmar creases are lighter in color than the surrounding skin with the fingers extended, Hb level is often <80 g/L (8 g/dL). In pts with coronary artery disease, anginal episodes may appear or increase in frequency and severity. In pts with carotid artery disease, light-headedness or dizziness may develop.

A physiologic approach to anemia diagnosis is based on the understanding that a decrease in circulating RBCs can be related to either inadequate production of RBCs or increased RBC destruction or loss. Within the category of inadequate production, erythropoiesis can be either ineffective, due to an erythrocyte maturation defect (which usually results in RBCs that are too small or too large), or hypoproliferative (which usually results in RBCs of normal size, but too few of them).

Basic evaluations include (1) reticulocyte index (RI), and (2) review of blood smear and RBC indices (chiefly mean corpuscular volume [MCV]) (Fig. 45-1).

The RI is a measure of RBC production. The reticulocyte count is corrected for the Hct level and for early release of marrow reticulocytes into the circulation, which leads to an increase in the lifespan of the circulating reticulocyte beyond the usual 1 day. Thus, RI = (% reticulocytes × pt Hct/45%) × (1/shift correction factor). The shift correction factor varies with the Hct: 1.5 for Hct = 35%, 2 for Hct = 25%, 2.5 for Hct = 15%. RI <2–2.5% implies inadequate RBC production for the particular level of anemia; RI >2.5% implies excessive RBC destruction or loss.

If the anemia is associated with a low RI, RBC morphology helps distinguish a maturation disorder from hypoproliferative marrow states. Cytoplasmic maturation defects such as iron deficiency or Hb synthesis problems produce smaller RBCs, MCV < 80; nuclear maturation defects such as B_{12} and folate deficiency and drug effects produce larger RBCs, MCV >100. In hypoproliferative marrow states, RBCs are generally normal in morphology but too few are produced. Bone marrow examination is often helpful in the evaluation of anemia but is done most frequently to diagnose hypoproliferative marrow states.

Other laboratory tests indicated to evaluate particular forms of anemia depend on the initial classification based on the pathophysiology of the defect. These are discussed in more detail in Chap. 62.

POLYCYTHEMIA (ERYTHROCYTOSIS)

Polycythemia is an increase above the normal range of RBCs in the circulation. Concern that the Hb level may be abnormally high should be triggered at a level of 170 g/L (17 g/dL) in men and 150 g/L (15 g/dL) in women. Polycythemia is usually

http://internalmedicinebook.com

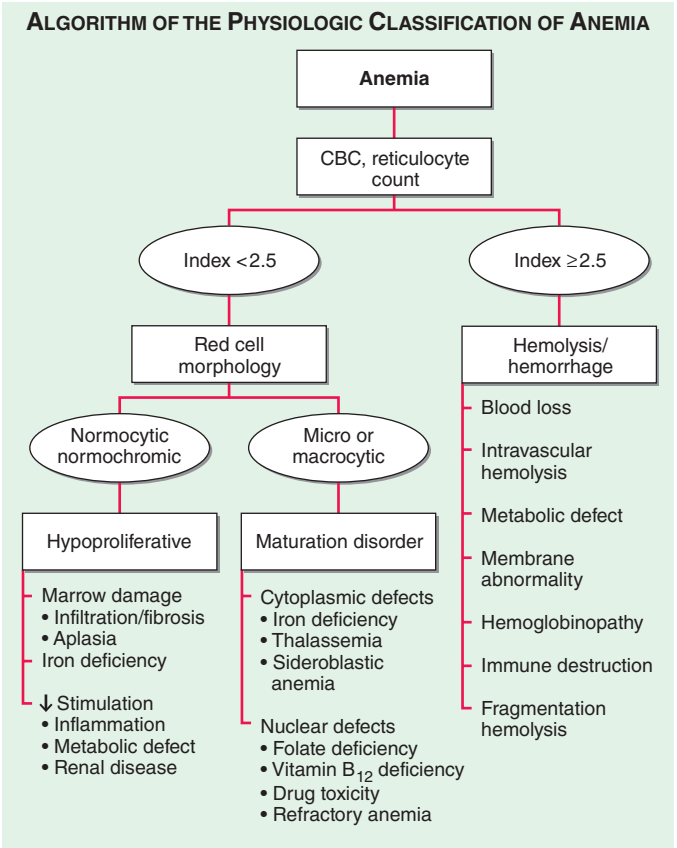


FIGURE 45-1 The physiologic classification of anemia.

found incidentally at routine blood count. Relative erythrocytosis, due to plasma volume loss (e.g., severe dehydration, burns), does not represent a true increase in total RBC mass. Absolute erythrocytosis is a true increase in total RBC mass.

CAUSES

Polycythemia vera (a clonal myeloproliferative disorder), erythropoietin-producing neoplasms (e.g., renal cancer, cerebellar hemangioma), chronic hypoxemia (e.g., high altitude, pulmonary disease), carboxyhemoglobin excess (e.g., smokers), high-affinity Hb variants, Cushing's syndrome, androgen excess. Polycythemia vera is distinguished from secondary polycythemia by the presence of splenomegaly, leukocytosis, thrombocytosis, and elevated vitamin B_{12} levels, and by decreased erythropoietin levels and the presence of a mutation in the JAK2 kinase (V617F). An approach to evaluate polycythemic pts is shown in Fig. 45-2.

COMPLICATIONS

Hyperviscosity (with diminished O_2 delivery) with risk of ischemic organ injury and thrombosis (venous or arterial) are most common.

http://internalmedicinebook.com

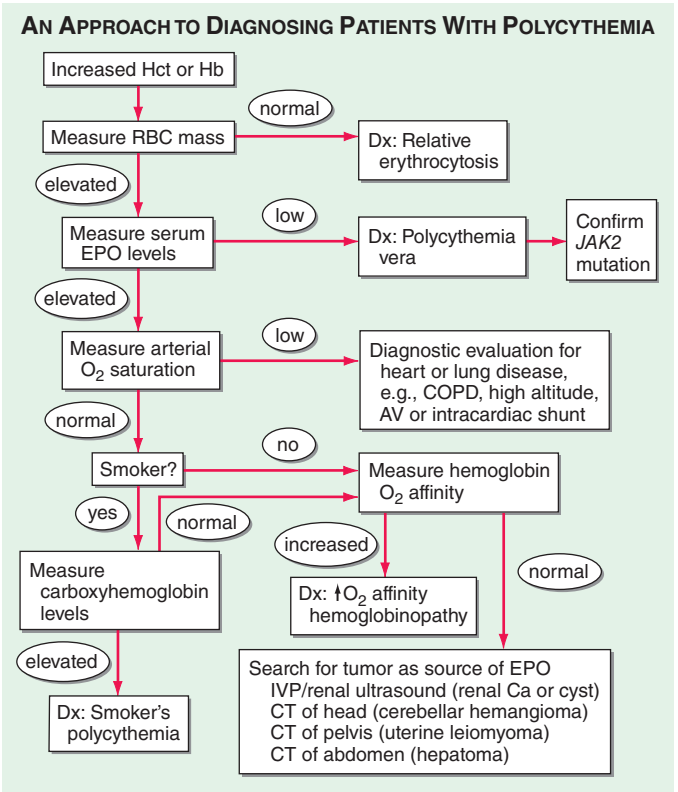


FIGURE 45-2 An approach to the differential diagnosis of pts with an elevated hemoglobin (possible polycythemia). AV, atrioventricular; COPD, chronic obstructive pulmonary disease; EPO, erythropoietin.

TREATMENT POLYCYTHEMIA

Phlebotomy recommended for Hct ≥55%, regardless of cause, to low-normal range. Aspirin is routinely given to lower the thrombosis risk.

For a more detailed discussion, see Adamson JW, Longo DL: Anemia and Polycythemia, Chap. 77, p. 392, in HPIM-19.

http://internalmedicinebook.com

46 Azotemia and Urinary Abnormalities

ABNORMALITIES OF RENAL FUNCTION, AZOTEMIA

Azotemia is the retention of nitrogenous waste products excreted by the kidney. Increased levels of blood urea nitrogen (BUN) (>10.7 mmol/L [>30 mg/dL]) and creatinine (>133 μmol/L [>1.5 mg/dL]) are ordinarily indicative of impaired renal function. Renal function can be estimated by determining the clearance of creatinine (CL_{cr}) (normal >100 mL/min); this can be directly measured from a 24-h urine collection using the following equation:

$$\text{Creatinine clearance (mL/min)} = (\text{uCr} \times \text{uV})/(\text{sCr} \times 1440)$$

1. Where uCr is urine creatinine in mg/dL
2. Where sCr is serum creatinine in mg/dL
3. Where uV is 24-h urine volume in mL
4. Where 1440 represents number of minutes in 24 h

The "adequacy" or "completeness" of the collection is estimated by the urinary volume and creatinine content; creatinine is produced from muscle and excreted at a relatively constant rate. For a 20- to 50-year-old man, creatinine excretion should be 18.5–25.0 mg/kg body weight; for a woman of the same age, it should be 16.5–22.4 mg/kg body weight. For example, an 80-kg man should excrete between ~1500 and 2000 mg of creatinine in an "adequate" collection. Creatinine excretion is also influenced by age and muscle mass. Notably, creatinine is an imperfect measure of glomerular filtration rate (GFR), because it is both filtered by glomeruli and secreted by proximal tubular cells; the relative contribution of tubular secretion increases with advancing renal dysfunction, such that creatinine clearance will provide an overestimate of the "true" GFR in pts with chronic kidney disease. Isotopic markers that are filtered and not secreted (e.g., iothalamate) provide more accurate estimates of GFR.

A formula that allows for an estimate of creatinine clearance in men that accounts for age-related decreases in GFR, body weight, and sex has been derived by Cockcroft-Gault:

$$\text{Creatinine clearance (mL/min)} = (140\text{-age}) \times \text{lean body weight (kg)}/\text{plasma creatinine (mg/dL)} \times 72$$

This value should be multiplied by 0.85 for women.

GFR may also be estimated using serum creatinine–based equations derived from the Modification of Diet in Renal Disease Study. This "eGFR" (estimated glomerular filtration rate) is now reported with serum creatinine by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of chronic kidney disease (Table 46-1).

Manifestations of impaired renal function include volume overload, hypertension, electrolyte abnormalities (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia), metabolic acidosis, and hormonal disturbances (e.g., insulin resistance, functional vitamin D deficiency, secondary hyperparathyroidism). When severe, the symptom complex of "uremia" may develop, encompassing one or more of the following symptoms and signs: anorexia, dysgeusia, nausea, vomiting, lethargy, confusion, asterixis, pleuritis, pericarditis, enteritis, pruritus, sleep and taste disturbance, nitrogenous fetor.

An approach to the pt with azotemia is shown in Fig. 46-1.

http://internalmedicinebook.com

TABLE 46-1 THE CLASSIFICATION OF CHRONIC KIDNEY DISEASE (NATIONAL KIDNEY FOUNDATION GUIDELINES)

Kidney Damage Stage	Description	eGFR (mL/min per 1.73 m²)
0	With risk factors for CKD[a]	>90
1	With evidence of kidney damage[b]	>90
2	Mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure	<15

[a]Diabetes, high blood pressure, family history, older age, African ancestry.
[b]Abnormal urinalysis, hematuria, proteinuria, albuminuria.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

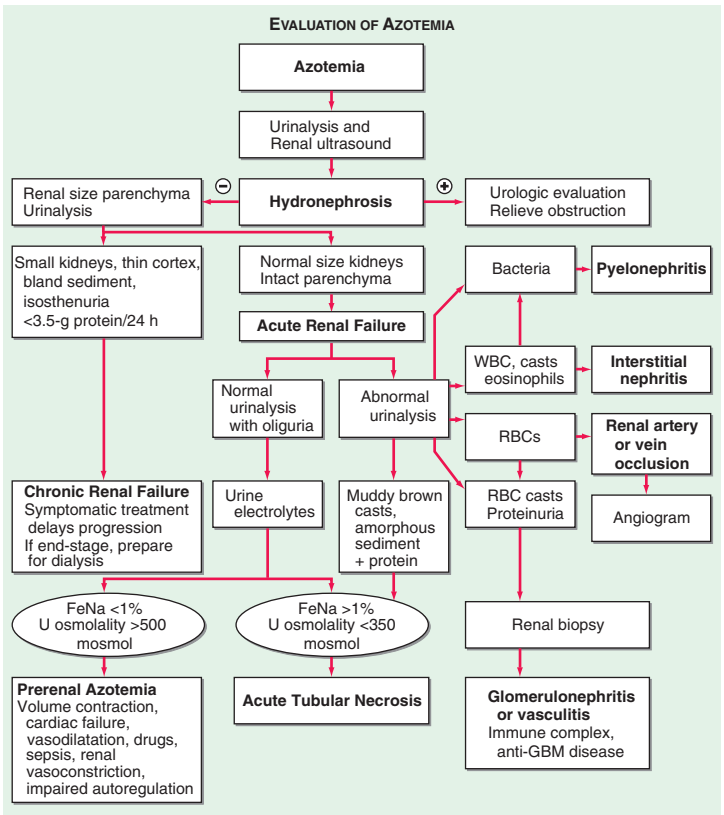


FIGURE 46-1 Approach to the pt with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

http://internalmedicinebook.com

ABNORMALITIES OF URINE VOLUME

Oliguria

This refers to reduced urine output, usually defined as <400 mL/d. *Oligoanuria* refers to a more marked reduction in urine output, i.e., <100 mL/d. *Anuria* indicates the complete absence of urine output. Oliguria most often occurs in the setting of volume depletion and/or renal hypoperfusion, resulting in "prerenal azotemia" and acute renal failure (Chap. 137). Anuria can be caused by complete bilateral urinary tract obstruction; a vascular catastrophe (dissection or arterial occlusion); renal vein thrombosis; renal cortical necrosis; severe acute tubular necrosis; nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers; and hypovolemic, cardiogenic, or septic shock. Oliguria is never normal, because at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load.

Polyuria

Polyuria is defined as a urine output >3 L/d. It is often accompanied by nocturia and urinary frequency and must be differentiated from other more common conditions associated with lower urinary tract pathology and urinary urgency or frequency (e.g., cystitis, prostatism). It is often accompanied by hypernatremia (Chap. 1). Polyuria (Table 46-2) can occur as a response to a solute load (e.g., hyperglycemia) or to an abnormality in arginine vasopressin (AVP; also known as antidiuretic hormone [ADH]) action. Diabetes insipidus is termed *central* if due to the insufficient hypothalamic production of AVP and *nephrogenic* if the result of renal insensitivity to the action of AVP. Excess fluid intake can lead to polyuria, but primary polydipsia rarely results in changes in plasma osmolality unless urinary diluting capacity is impaired. Tubulointerstitial diseases, lithium therapy, and resolving acute tubular necrosis or urinary tract obstruction can be associated with nephrogenic diabetes insipidus, which is more rarely caused by mutations in the V2 AVP receptor, the aquaporin-1 water channel in the descending thin limb of the loop of Henle, and the AVP-regulated water channel in principal cells, aquaporin 2.

The approach to the pt with polyuria is shown in Fig. 46-2.

ABNORMALITIES OF URINE COMPOSITION

Proteinuria

This is the hallmark of glomerular disease. Levels up to 150 mg/d are considered within normal limits. Typical measurements are semiquantitative, using a

TABLE 46-2 MAJOR CAUSES OF POLYURIA

Excessive fluid intake	Nephrogenic diabetes insipidus
Primary polydipsia	Lithium exposure
Iatrogenic (IV fluids)	Urinary tract obstruction
Therapeutic	Papillary necrosis
Diuretic agents	Reflux nephropathy
Osmotic diuresis	Interstitial nephritis
Hyperglycemia	Hypercalcemia
	Hereditary (V2R, AQP-1/2)
Azotemia	Central diabetes insipidus
Mannitol	Tumor
Radiocontrast	Postoperative
	Head trauma
	Basilar meningitis
	Neurosarcoidosis

Abbreviations: AQP, aquaporin; V2R, vasopressin type 2 receptor.

http://internalmedicinebook.com

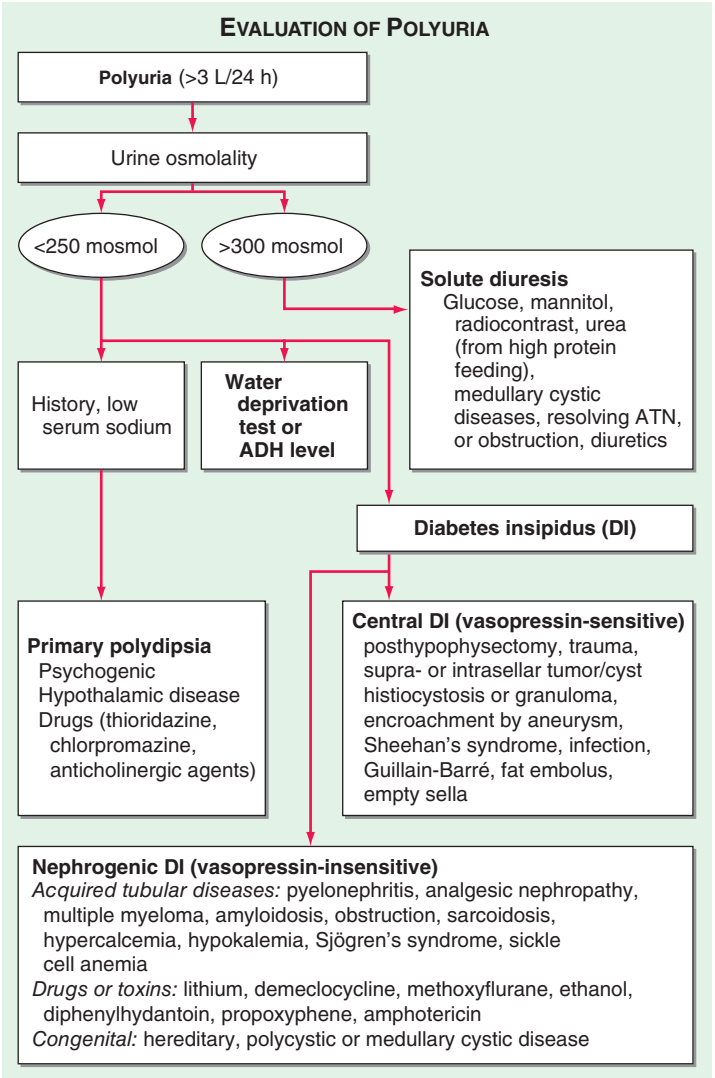


FIGURE 46-2 Approach to the pt with polyuria. ADH, antidiuretic hormone; ATN, acute tubular necrosis. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

moderately sensitive dipstick that estimates protein concentration; therefore, the degree of hydration may influence the dipstick protein determination. Most commercially available urine dipsticks detect albumin and do not detect smaller proteins, such as light chains, that require testing with sulfosalicylic acid. More sensitive assays can in turn be used to detect microalbuminuria, an important screening tool for diabetic nephropathy. A urine albumin to creatinine ratio >30 mg/g defines the presence of microalbuminuria.

Formal assessment of urinary protein excretion requires a 24-h urine protein collection (see "Abnormalities of Renal Function, Azotemia," above). The ratio of

http://internalmedicinebook.com

protein to creatinine in a random, "spot" urine can also provide a rough estimate of protein excretion; e.g., a protein/creatinine ratio of 3.0 correlates to ~3.0 g of proteinuria per day.

Urinary protein excretion rates between 500 mg/d and 3 g/d are nonspecific and can be seen in a variety of renal diseases (including hypertensive nephrosclerosis, interstitial nephritis, vascular disease, and other primary renal diseases with little or no glomerular involvement). Transient, lesser degrees of proteinuria (500 mg/d–1.5 g/d) may be seen after vigorous exercise, changes in body position, fever, or congestive heart failure. Protein excretion rates >3 g/d are termed *nephrotic range proteinuria* in that they may be accompanied by hypoalbuminemia, hypercholesterolemia, and edema (the nephrotic syndrome). Nephrotic syndrome can be associated with a variety of extrarenal complications (Chap. 141). Massive degrees of proteinuria (>10 g/d) can be seen with minimal change disease, primary focal segmental glomerulosclerosis (FSGS), membranous nephropathy, diabetic nephropathy, collapsing glomerulopathy (a subtype of primary FSGS), and HIV-associated nephropathy.

Pharmacologic inhibition of ACE or blockade of angiotensin II should be employed to reduce proteinuria; successful reduction of proteinuria decreases the rate of progression to end-stage renal disease in diabetic nephropathy and other glomerulopathies. Specific therapy for a variety of causes of nephrotic syndrome is discussed in Chap. 141.

Hematuria

Gross hematuria refers to the presence of frank blood in the urine and is more characteristic of lower urinary tract disease and/or bleeding diatheses than intrinsic renal disease (Table 46-3). Cyst rupture in polycystic kidney disease and postpharyngitic flares of IgA nephropathy are exceptions. Microscopic hematuria (>1–2 red blood cells [RBCs] per high-powered field), accompanied by proteinuria, hypertension, and an active urinary sediment (the "nephritic syndrome") is most likely related to an inflammatory glomerulonephritis, classically poststreptococcal glomerulonephritis (Chap. 141).

TABLE 46-3 MAJOR CAUSES OF HEMATURIA

Lower Urinary Tract
Bacterial cystitis
Interstitial cystitis
Urethritis (infectious or inflammatory)
Passed or passing kidney stone
Transitional cell carcinoma of bladder or structures proximal to it
Squamous cell carcinoma of bladder (e.g., following schistosomiasis)
Upper Urinary Tract
Renal cell carcinoma
Age-related renal cysts
Other neoplasms (e.g., oncocytoma, hamartoma)
Acquired renal cystic disease
Congenital cystic disease, including autosomal dominant form
Glomerular diseases
Interstitial renal diseases, including interstitial nephritis
Nephrolithiasis
Pyelonephritis
Renal infarction
Hypercalciuria
Hyperuricosuria

http://internalmedicinebook.com

Free hemoglobin and myoglobin are detected by dipstick; a negative urinary sediment with strongly heme-positive dipstick is characteristic of either hemolysis or rhabdomyolysis, which can be differentiated by clinical history and laboratory testing. RBC casts are not a sensitive finding but when seen are highly specific for glomerulonephritis. Specificity of urinalysis can be enhanced by examining urine with a phase contrast microscope capable of detecting dysmorphic red cells ("acanthocytes") associated with glomerular disease.

The approach to the pt with hematuria is shown in Fig. 46-3.

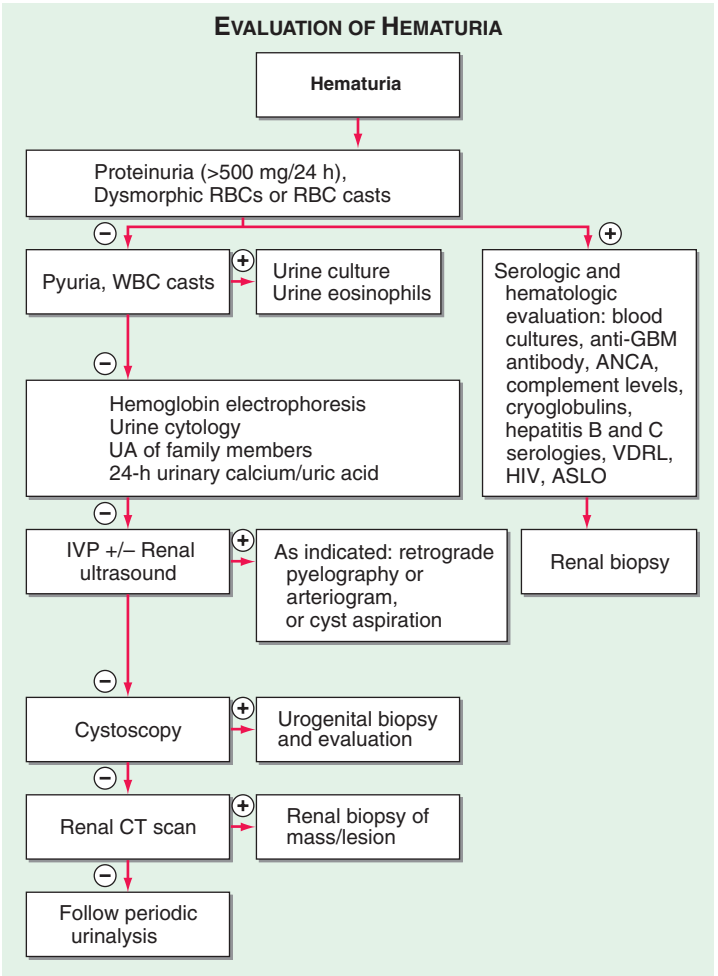


FIGURE 46-3 Approach to the pt with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; GBM, glomerular basement membrane; VDRL, Venereal Disease Research Laboratory. *(From Lin J and Denker BM: Chap. 61, p. 289, HPIM-19.)*

http://internalmedicinebook.com

PYURIA

This may accompany hematuria in inflammatory glomerular diseases. Isolated pyuria is most commonly observed in association with an infection of the upper or lower urinary tract. Pyuria may also occur with allergic interstitial nephritis (often with a preponderance of eosinophils), transplant rejection, and noninfectious, nonallergic tubulointerstitial diseases, including atheroembolic renal disease. The finding of "sterile" pyuria (i.e., urinary white blood cells without bacteria) in the appropriate clinical setting should raise suspicion of renal tuberculosis.

For a more detailed discussion, see Lin J, Denker BM: Azotemia and Urinary Abnormalities, Chap. 61, p. 289, in HPIM-19.

47 Pain and Swelling of Joints

Musculoskeletal complaints are extremely common in outpatient medical practice and are among the leading cause of disability and absenteeism from work. Pain in the joints must be evaluated in a uniform, thorough, and logical fashion to ensure the best chance of accurate diagnosis and to plan appropriate follow-up testing and therapy. Joint pain and swelling may be manifestations of disorders affecting primarily the musculoskeletal system or may reflect systemic disease.

INITIAL ASSESSMENT OF A MUSCULOSKELETAL COMPLAINT (FIG. 47-1)

1. *Articular versus nonarticular:* Is the pain located in a joint or in a periarticular structure such as soft tissue or muscle?
2. *Inflammatory versus noninflammatory:* Inflammatory disease is suggested by local signs of inflammation (erythema, warmth, swelling); systemic features (morning stiffness, fatigue, fever, weight loss); or laboratory evidence of inflammation (thrombocytosis, elevated ESR or C-reactive protein).
3. *Acute (≤6 weeks) versus chronic.*
4. *Localized versus systemic.*

HISTORIC FEATURES

- Age, sex, race, and family history
- Symptom onset (abrupt or gradual), evolution (chronic constant, intermittent, migratory, additive), and duration (acute versus chronic)
- Number and distribution of involved structures: monarticular (one joint), oligoarticular (two to three joints), polyarticular (more than three joints); symmetry
- Other articular features: morning stiffness, effect of movement, features that improve/worsen Sx

http://internalmedicinebook.com

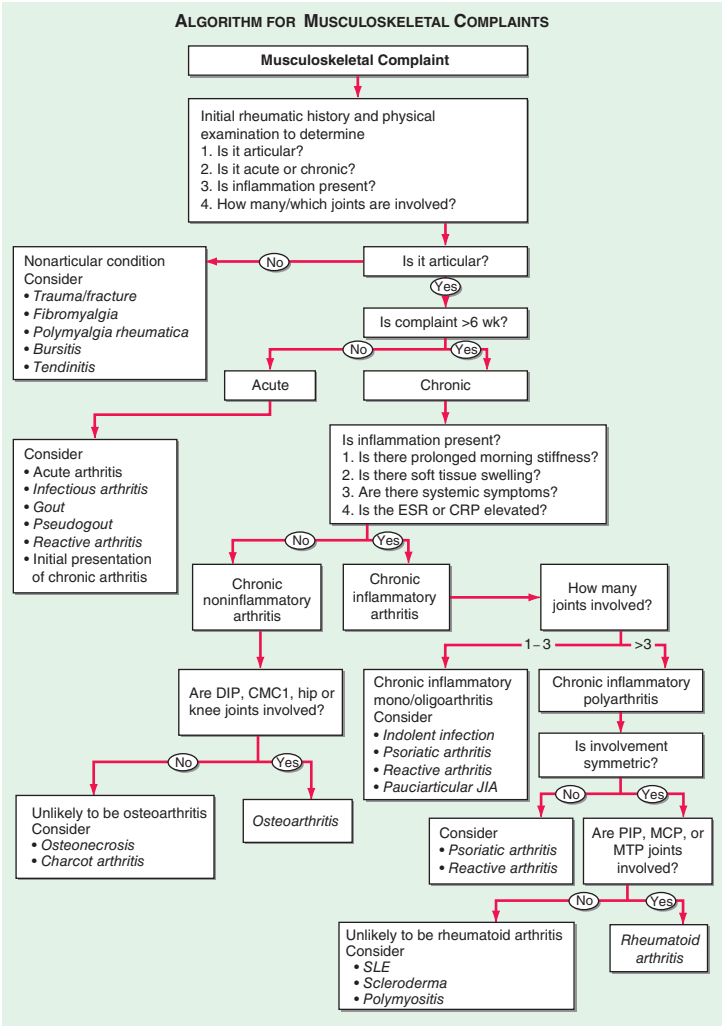


FIGURE 47-1 Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

- Extraarticular Sx: e.g., fever, rash, weight loss, visual change, dyspnea, diarrhea, dysuria, numbness, weakness
- Recent events: e.g., trauma, drug administration, travel, other illnesses

PHYSICAL EXAMINATION

Complete examination is essential: particular attention to skin, mucous membranes, nails (may reveal characteristic pitting in psoriasis), eyes. Careful and thorough

http://internalmedicinebook.com

examination of involved and uninvolved joints and periarticular structures; this should proceed in an organized fashion from head to foot or from extremities inward toward axial skeleton; special attention should be paid to identifying the presence or absence of:

- Warmth and/or erythema
- Swelling
- Synovial thickening
- Subluxation, dislocation, joint deformity
- Joint instability
- Limitations to active and passive range of motion
- Crepitus
- Periarticular changes
- Muscular changes including weakness, atrophy

LABORATORY INVESTIGATIONS

Additional evaluation usually indicated for monarticular, traumatic, inflammatory, or chronic conditions or for conditions accompanied by neurologic changes or systemic manifestations.

- For all evaluations: include CBC, ESR, or C-reactive protein
- Where there are suggestive clinical features, include: rheumatoid factor, antibodies to cyclic citrullinated peptides (anti-CCPs), ANA, antineutrophil cytoplasmic antibodies (ANCA), antistreptolysin O titer, Lyme antibodies
- Where systemic disease is present or suspected: renal/hepatic function tests, UA
- Uric acid: useful only when gout diagnosed and therapy contemplated
- CPK, aldolase: consider with muscle pain, weakness
- Synovial fluid aspiration and analysis: always indicated for acute monarthritis or when infectious or crystal-induced arthropathy is suspected. Should be examined for (1) appearance, viscosity; (2) cell count and differential (suspect septic joint if WBC count >50,000/μL); (3) crystals using polarizing microscope; (4) Gram's stain, cultures (Fig. 47-2).

DIAGNOSTIC IMAGING

Conventional radiography using plain x-rays is a valuable tool in the diagnosis and staging of articular disorders (Table 47-1).

Additional imaging procedures, including ultrasound, radionuclide scintigraphy, CT, and MRI, may be helpful in selected clinical settings.

SPECIAL CONSIDERATIONS IN THE ELDERLY PATIENT

The evaluation of joint and musculoskeletal disorders in the elderly pt presents a special challenge given the frequently insidious onset and chronicity of disease in this age group, the confounding effect of other medical conditions, and the increased variability of many diagnostic tests in the geriatric population. Although virtually all

TABLE 47-1 APPLICATIONS FOR CONVENTIONAL RADIOGRAPHY IN ARTICULAR DISEASE

Trauma
Suspected chronic joint or bone infection
Progressive joint disability
Monarticular involvement
Baseline assessment of a chronic articular process
When therapeutic alterations are considered (such as for rheumatoid arthritis)

http://internalmedicinebook.com

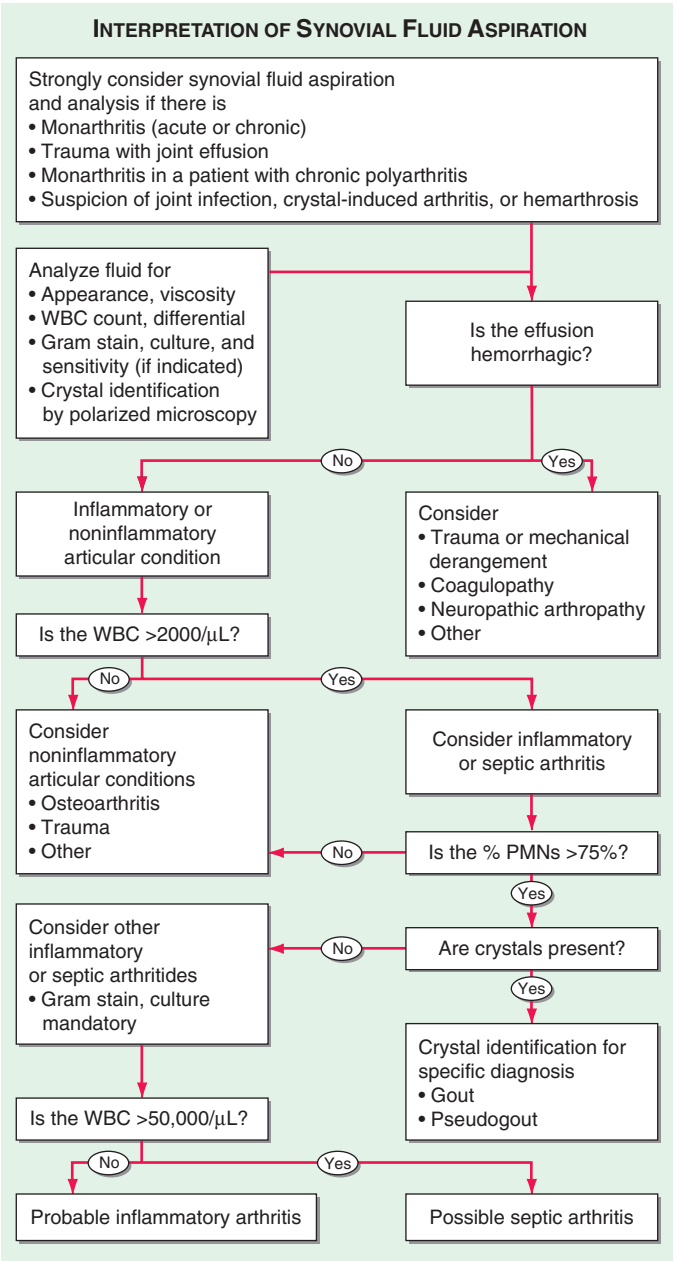


FIGURE 47-2 Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear leukocytes.

http://internalmedicinebook.com

musculoskeletal conditions may afflict the elderly, certain disorders are especially frequent. Special attention should be paid to identifying the potential rheumatic consequences of intercurrent medical conditions and therapies when evaluating the geriatric pt with musculoskeletal complaints.

For a more detailed discussion, see Cush JJ: Approach to Articular and Musculoskeletal Disorders, Chap. 393, p. 2216, in HPIM-19.

48 Back and Neck Pain

LOW BACK PAIN

Cost of low back pain (LBP) in the United States is ~$100 billion annually. Back symptoms are most common cause of disability in those <45 years; LBP is the second most common cause of visiting a physician in the United States; 70% of people will have LBP at some point in their lives.

TYPES OF LOW BACK PAIN

- *Local pain*: caused by injury to pain-sensitive structures that compress or irritate sensory nerve endings; pain located near the affected part of the back.
- *Pain referred to the back*: abdominal or pelvic origin; back pain unaffected by posture.
- *Pain of spine origin*: restricted to the back or referred to lower limbs or buttock. Diseases of upper lumbar spine refer pain to upper lumbar region, groin, or anterior thighs. Diseases of lower lumbar spine refer pain to buttocks, posterior thighs, calves, or feet.
- *Radicular back pain*: radiates from spine to leg in specific nerve root territory. Coughing, sneezing, lifting heavy objects, or straining may elicit pain.
- *Pain associated with muscle spasm*: diverse causes; accompanied by tense paraspinal muscles, dull or aching pain in the paraspinal region, and abnormal posture.

EXAMINATION

Include abdomen and rectum to search for visceral sources of pain. Inspection may reveal scoliosis or muscle spasm. Palpation may elicit pain over a diseased spine segment. Pain from hip may be confused with spine pain; manual internal/external rotation of leg at hip (with knee and hip in flexion) reproduces the hip pain.

Straight leg raising (SLR) sign—elicited by passive flexion of leg at the hip with pt in supine position; maneuver stretches L5/S1 nerve roots and sciatic nerve passing posterior to the hip; SLR sign is positive if maneuver reproduces the pain. Crossed SLR sign—positive when SLR on one leg reproduces symptoms in opposite leg or buttocks; nerve/nerve root lesion is on the painful side. Reverse SLR sign—passive

http://internalmedicinebook.com

TABLE 48-1 LUMBOSACRAL RADICULOPATHY: NEUROLOGIC FEATURES

Lumbosacral Nerve Roots	Examination Findings			Pain Distribution
	Reflex	Sensory	Motor	
L2[a]	—	Upper anterior thigh	Psoas (hip flexors)	Anterior thigh
L3[a]	—	Lower anterior thigh Anterior knee	Psoas (hip flexors) Quadriceps (knee extensors) Thigh adductors	Anterior thigh, knee
L4[a]	Quadriceps (knee)	Medial calf	Quadriceps (knee extensors)[b] Thigh adductors	Knee, medial calf Anterolateral thigh
L5[c]	—	Dorsal surface—foot Lateral calf	Peronei (foot evertors)[b] Tibialis anterior (foot dorsiflexors) Gluteus medius (hip abductors) Toe dorsiflexors	Lateral calf, dorsal foot, posterolateral thigh, buttocks
S1[c]	Gastrocnemius/soleus (ankle)	Plantar surface—foot Lateral aspect—foot	Gastrocnemius/soleus (foot plantar flexors)[b] Abductor hallucis (toe flexors)[b] Gluteus maximus (hip extensors)	Bottom foot, posterior calf, posterior thigh, buttocks

[a]Reverse straight leg–raising sign present—see "Examination of the Back."
[b]These muscles receive the majority of innervation from this root.
[c]Straight leg–raising sign present—see "Examination of the Back" in Engstrom JW, Deyo RA: Back and Neck Pain, Chap. 22, p. 111, in *HPIM-19*.

extension of leg backward with pt standing; maneuver stretches L2–L4 nerve roots, lumbosacral plexus, and femoral nerve passing anterior to the hip.

Neurologic examination—search for focal atrophy, weakness, reflex loss, diminished sensation in a dermatomal distribution. Findings with radiculopathy are summarized in Table 48-1.

LABORATORY EVALUATION

"Routine" laboratory studies and lumbar spine x-rays are rarely needed for nonspecific acute LBP (<3 months) but indicated when risk factors for serious underlying disease are present (Table 48-2). MRI and CT-myelography are tests of choice for

http://internalmedicinebook.com

TABLE 48-2 ACUTE LOW BACK PAIN: RISK FACTORS FOR AN IMPORTANT STRUCTURAL CAUSE

History
Pain worse at rest or at night
Prior history of cancer
History of chronic infection (especially lung, urinary tract, skin)
History of trauma
Incontinence
Age >70 years
Intravenous drug use
Glucocorticoid use
History of a rapidly progressive neurologic deficit
Examination
Unexplained fever
Unexplained weight loss
Percussion tenderness over the spine
Abdominal, rectal, or pelvic mass
Internal/external rotation of the leg at the hip; heel percussion sign
Straight leg– or reverse straight leg–raising signs
Progressive focal neurologic deficit

anatomic definition of spine disease. Electromyography (EMG) and nerve conduction studies useful for functional assessment of peripheral nervous system.

ETIOLOGY

Lumbar Disk Disease

Common cause of low back and leg pain; usually at L4–L5 or L5–S1 levels. Dermatomal sensory loss, reduction or loss of deep tendon reflexes, or myotomal pattern of weakness more informative than pain pattern for localization. Usually unilateral; can be bilateral with large central disk herniations compressing multiple nerve roots and causing cauda equina syndrome (Chap. 188).

Indications for lumbar disk surgery:

- Progressive motor weakness on examination or progressive nerve root injury is demonstrated on EMG.
- Cauda equina syndrome or spinal cord compression is usually indicated by abnormal bowel or bladder function.
- Incapacitating nerve root pain despite conservative treatment for at least 6–8 weeks: Trials indicate surgery leads to more rapid pain relief but no difference at 1–2 years compared with nonsurgical treatment.

Spinal Stenosis

A narrowed spinal canal producing neurogenic claudication, i.e., back, buttock, and/or leg pain induced by walking or standing and relieved by sitting. Symptoms are usually bilateral. Unlike vascular claudication, symptoms are provoked by standing without walking. Unlike lumbar disk disease, symptoms are relieved by sitting. Focal neurologic deficits common; severe neurologic deficits (paralysis, incontinence) rare. Stenosis results from acquired (75%), congenital, or mixed acquired/congenital factors.

- Symptomatic treatment adequate for mild disease
- Surgery indicated when medical therapy does not allow for activities of daily living

http://internalmedicinebook.com

or if focal neurologic signs are present. Most pts treated surgically experience relief of back and leg pain; 25% develop recurrent stenosis within 7–10 years.

Trauma

Low back strain or *sprain* used to describe minor, self-limited injuries associated with LBP. *Vertebral fractures* from trauma result in anterior wedging or compression of vertebral bodies; burst fractures involving vertebral body and posterior spine elements can occur. Neurologic impairment common with vertebral fractures; early surgical intervention indicated. CT scans used to screen for spine disease in moderate to severe trauma; superior to routine x-rays for bony disease. Most common cause of *nontraumatic fracture* is osteoporosis; others include osteomalacia, hyperparathyroidism, hyperthyroidism, multiple myeloma, or metastatic carcinoma.

Spondylolisthesis

Slippage of anterior spine forward, leaving posterior elements behind; L4–L5 > L5–S1 levels; can produce LBP or radiculopathy/cauda equina syndrome (Chap. 188).

Osteoarthritis (Spondylosis)

Back pain induced by spine movement and associated with stiffness. Increases with age; radiologic findings do not correlate with severity of pain. Osteophytes or combined disc-osteophytes may cause or contribute to central spinal canal stenosis, lateral recess stenosis, or neural foraminal narrowing.

Vertebral Metastases (Chap. 20)

Back pain most common neurologic symptom in pts with systemic cancer and may be presenting complaint (20%); pain typically not relieved by rest and worse at night. MRI or CT-myelography demonstrates vertebral body metastasis; disk space is spared.

Vertebral Osteomyelitis

Back pain unrelieved by rest; focal spine tenderness, elevated ESR. Primary source of infection usually urinary tract, skin, or lung; IV drug abuse a risk factor. Destruction of the vertebral bodies and disk space common. Lumbar spinal epidural abscess presents as back pain and fever; examination may be normal or show radicular findings, spinal cord involvement, or cauda equina syndrome. Extent of abscess best defined by MRI.

Lumbar Adhesive Arachnoiditis

May follow inflammation within subarachnoid space; fibrosis results in clumping of nerve roots, best seen by MRI; treatment is unsatisfactory.

Immune Disorders

Ankylosing spondylitis, rheumatoid arthritis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease.

Osteoporosis

Loss of bone substance resulting from immobilization, hyperparathyroidism, chronic glucocorticoid use, other medical disorders, or increasing age (particularly in females). Sole manifestation may be back pain exacerbated by movement. Can also occur in the upper back.

Visceral Diseases

Pelvis refers pain to sacral region, lower abdomen to mid-lumbar region, upper abdomen to lower thoracic or upper lumbar region. Local signs are absent; normal movements of the spine are painless. Rupture of an abdominal aortic aneurysm may produce isolated back pain.

http://internalmedicinebook.com

Other

Chronic LBP with no clear cause; psychiatric disorders, substance abuse may be associated.

TREATMENT LOW BACK PAIN

ACUTE LOW BACK PAIN (ALBP)

- Pain of <3 months duration.
- Spine infections, fractures, tumors, or rapidly progressive neurologic deficits require urgent diagnostic evaluation.
- If "risk factors" (Table 48-2) are absent, initial treatment is symptomatic and no diagnostic tests necessary.
- When leg pain absent, prognosis is excellent; full recovery in 85%.
- Clinical trials do not show benefit from bed rest >2 days. Possible benefits of early activity—cardiovascular conditioning, disk and cartilage nutrition, bone and muscle strength, increased endorphin levels.
- Spinal manipulation appears to be equivalent to conventional medical therapies and may be a useful alternative for some patients.
- Proof lacking to support physical therapy, massage, acupuncture, ultrasound, laser therapy, corsets, or traction.
- Self-application of ice or heat or use of shoe insoles is optional given low cost and risk.
- Drug treatment of ALBP includes NSAIDs and acetaminophen (Chap. 5).
- Muscle relaxants (cyclobenzaprine) may be useful but sedation is a common side effect.
- Opioids are not clearly superior to NSAIDs or acetaminophen for ALBP.
- No evidence to support oral or injected epidural glucocorticoids.

CHRONIC LOW BACK PAIN (CLBP)

- Pain lasting >12 weeks; differential diagnosis includes most conditions described above.
- Cause can be clarified by neuroimaging and EMG/nerve conduction studies; diagnosis of radiculopathy secure when results concordant with findings on neurologic examination. Treatment should not be based on neuroimaging alone: up to one-third of asymptomatic young adults have a herniated lumbar disk by CT or MRI.
- Management based on identification of underlying cause; when specific cause not found, conservative management necessary.
- Treatment measures include acetaminophen, NSAIDs, and tricyclic antidepressants.
- Evidence supports the use of exercise therapy; effective in returning some pts to work, diminishing pain, and improving walking distances.
- Cognitive-behavioral therapy may have some use; long-term results unclear.
- Alternative therapies including spinal manipulation, acupuncture, and massage are frequently tried; trials are mixed as to their effectiveness.
- Epidural glucocorticoids and facet joint injections are not effective in the absence of radiculopathy.
- Surgical intervention for chronic LBP without radiculopathy is controversial, and clinical trials do not support its use.

http://internalmedicinebook.com

NECK AND SHOULDER PAIN

Usually arises from diseases of the cervical spine and soft tissues of the neck; typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion.

ETIOLOGY

Trauma to the Cervical Spine

Trauma to the cervical spine (fractures, subluxation) places spine at risk for compression; immediate immobilization of the neck is essential to minimize movement of unstable cervical spine segments.

Whiplash injury is due to trauma (usually automobile accidents) causing cervical musculoligamentous injury due to hyperflexion or hyperextension. This diagnosis is not applied to pts with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness.

Cervical Disk Disease

Herniation of a lower cervical disk is a common cause of neck, shoulder, arm, or hand pain or tingling. Neck pain (worse with movement), stiffness, and limited range of motion are common. With nerve root compression, pain may radiate into shoulder or arm. Extension and lateral rotation of the neck narrows the intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young individuals, acute radiculopathy from a ruptured disk is often traumatic. *Subacute radiculopathy* is less likely to be related to a specific traumatic incident and may involve both disk disease and spondylosis. Clinical features of cervical nerve root lesions are summarized in Table 48-3.

Cervical Spondylosis

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms; can also be source of headaches in the posterior occipital region. A combined radiculopathy and myelopathy may occur. An electrical sensation elicited by neck flexion and radiating down the spine from the neck (Lhermitte's symptom) usually indicates spinal cord involvement. MRI or CT-myelography can define the anatomic abnormalities, and EMG and nerve conduction studies can quantify the severity and localize the levels of nerve root injury.

Other Causes of Neck Pain

Includes *rheumatoid arthritis* of the cervical facet joints, ankylosing spondylitis, *herpes zoster* (shingles), *neoplasms* metastatic to the spine, *infections* (osteomyelitis and epidural abscess), and *metabolic bone diseases*. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

Thoracic Outlet

An anatomic region containing the first rib, subclavian artery and vein, brachial plexus, clavicle, and lung apex. Injury may result in posture- or movement-induced pain around the shoulder and supraclavicular region. *True neurogenic thoracic outlet syndrome* is uncommon and results from compression of the lower trunk of the brachial plexus by an anomalous band of tissue; treatment is surgical division of the band. *Arterial thoracic outlet syndrome* results from compression of the subclavian artery by a cervical rib; treatment is thrombolysis or anticoagulation, plus surgical excision of the cervical rib. *Venous thoracic outlet syndrome* is due to subclavian vein thrombosis producing swelling of the arm and pain. The vein may be compressed by a cervical rib or anomalous scalene muscle. *Disputed thoracic outlet syndrome* includes a large number of pts with chronic arm and shoulder pain of unclear cause; surgery is controversial and treatment is often unsuccessful.

http://internalmedicinebook.com

TABLE 48-3 CERVICAL RADICULOPATHY: NEUROLOGIC FEATURES

Cervical Nerve Roots	Examination Findings			Pain Distribution
	Reflex	Sensory	Motor	
C5	Biceps	Lateral deltoid	Rhomboids[a] (elbow extends backward with hand on hip) Infraspinatus[a] (arm rotates externally with elbow flexed at the side) Deltoid[a] (arm raised laterally 30–45° from the side)	Lateral arm, medial scapula
C6	Biceps	Thumb/index finger Dorsal hand/lateral forearm	Biceps[a] (arm flexed at the elbow in supination) Pronator teres (forearm pronated)	Lateral forearm, thumb/index fingers
C7	Triceps	Middle fingers Dorsal forearm	Triceps[a] (forearm extension, flexed at elbow) Wrist/finger extensors[a]	Posterior arm, dorsal forearm, dorsal hand
C8	Finger flexors	Palmar surface of little finger Medial hand and forearm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Fourth and fifth fingers, medial hand and forearm
T1	Finger flexors	Axilla and medial arm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Medial arm, axilla

[a]These muscles receive the majority of innervation from this root.

Brachial Plexus and Nerves

Pain from injury to the brachial plexus or peripheral nerves can mimic pain of cervical spine origin. *Neoplastic infiltration* can produce this syndrome, as can *postradiation fibrosis* (pain less often present). *Acute brachial neuritis* consists of acute onset of severe shoulder or scapular pain followed over days by weakness of proximal arm

http://internalmedicinebook.com

and shoulder girdle muscles innervated by the upper brachial plexus; onset often preceded by an infection or immunization.

Shoulder

If signs of radiculopathy are absent, differential diagnosis includes mechanical shoulder pain (tendinitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, and cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast [apical lung] tumor). Mechanical pain is often worse at night, associated with shoulder tenderness, and aggravated by abduction, internal rotation, or extension of the arm.

TREATMENT NECK AND SHOULDER PAIN

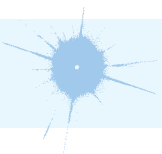
- Indications for cervical disk surgery are similar to those for lumbar disk; however, with cervical disease, an aggressive approach is indicated if spinal cord injury is threatened.

NECK PAIN WITHOUT RADICULOPATHY

- Spontaneous improvement is expected for most acute neck pain.
- Symptomatic treatment includes analgesic medications.
- If not related to trauma, supervised exercise appears to be effective.
- No valid clinical evidence to support cervical fusion or cervical disk arthroplasty.
- Low-level laser therapy may be effective but additional trials are needed.
- No evidence to support radiofrequency neurotomy or cervical facet injections.

NECK PAIN WITH RADICULOPATHY

- Natural history is favorable and many will improve without specific therapy.
- NSAIDs, acetaminophen, or both with or without muscle relaxants is appropriate initial therapy.
- Soft cervical collars are modestly helpful in limiting movements that exacerbate pain.
- Indications for surgery include a progressive radicular motor deficit, pain that limits function and fails to respond to conservative management, or spinal cord compression.
- *Cervical spondylosis* with bony, compressive cervical radiculopathy is generally treated with surgical decompression to interrupt the progression of neurologic signs although it is unclear if long-term outcomes are improved over medical therapy.
- Surgical options for *cervical herniated disks* consist of anterior cervical diskectomy alone, laminectomy with diskectomy, or diskectomy with fusion. The cumulative risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to the fusion is ~3% per year and 26% per decade.



For more detailed discussion, see Engstrom JW, Deyo RA: Back and Neck Pain, Chap. 22, p. 111, in HPIM-19.

http://internalmedicinebook.com

49 Headache

APPROACH TO THE PATIENT: Headache

Among the most common reasons that pts seek medical attention; can be either primary or secondary (Table 49-1). First step—distinguish serious from benign etiologies. Symptoms that raise suspicion for a serious cause are listed in Table 49-2. Intensity of head pain rarely has diagnostic value; most pts who present with worst headache of their lives have migraine. Headache location can suggest involvement of local structures (temporal pain in giant cell arteritis, facial pain in sinusitis). Ruptured aneurysm (instant onset), cluster headache (peak over 3–5 min), and migraine (pain increases over minutes to hours) differ in time to peak intensity. Provocation by environmental factors suggests a benign cause.

Complete neurologic examination is important in evaluation of headache. If examination is abnormal or if serious underlying cause is suspected, an imaging study (CT or MRI) is indicated as a first step. Lumbar puncture (LP) is required when meningitis (stiff neck, fever) or subarachnoid hemorrhage (following negative imaging) is a possibility. The psychological state of the pt should also be evaluated because a relationship exists between pain and depression.

MIGRAINE

A benign, episodic syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures. Second to tension-type as most common cause of headache; afflicts ~15% of women and 6% of men annually. Diagnostic criteria are listed in Table 49-3. Onset usually in childhood, adolescence, or early adulthood; however, initial attack may occur at any age. Family history is often present. Women may have increased sensitivity to attacks during menstrual cycle. Classic triad: premonitory visual (scotoma or scintillations), sensory, or motor symptoms; unilateral throbbing headache; and nausea and vomiting. Most pts do not have visual aura or other premonitory symptoms. Photo- and phonophobia common. Vertigo may occur. Focal neurologic disturbances without headache or vomiting (migraine equivalents) may also occur. An attack lasting 4–72 h is typical, as is relief after sleep. Attacks may be triggered by glare, bright lights, sounds, hunger, stress, physical exertion, hormonal fluctuations, lack of sleep, alcohol, or other chemical stimulation.

TABLE 49-1 COMMON CAUSES OF HEADACHE

Primary Headache		Secondary Headache	
Type	**%**	**Type**	**%**
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: After J Olesen et al: *The Headaches*. Philadelphia, Lippincott Williams & Wilkins, 2005.

http://internalmedicinebook.com

TABLE 49-2 HEADACHE SYMPTOMS THAT SUGGEST A SERIOUS UNDERLYING DISORDER

Sudden-onset headache
First severe headache
"Worst" headache ever
Vomiting that precedes headache
Subacute worsening over days or weeks
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55 years
Fever or unexplained systemic signs
Abnormal neurologic examination
Pain associated with local tenderness, e.g., region of temporal artery

TREATMENT MIGRAINE

- Three approaches to migraine treatment: nonpharmacologic (such as the avoidance of pt-specific triggers; information for pts is available at *www.achenet.org*); drug treatment of acute attacks (Tables 49-4 and 49-5); and prophylaxis (Table 49-6).
- Drug treatment necessary for most migraine pts, but avoidance or management of environmental triggers alone is sufficient for some.
- General principles of pharmacologic treatment:
  - Response rates vary from 50% to 70%.
  - Initial drug choice is empirical and individualized—influenced by age, coexisting illnesses, and side effect profile.
  - Efficacy of prophylactic treatment may take several months to assess with each drug.
  - When an acute attack requires additional medication 60 min after the first dose, then the initial drug dose should be increased for subsequent attacks or another class of drug tried.
- Mild to moderate acute migraine attacks often respond to over-the-counter (OTC) NSAIDs when taken early.
- Triptans are widely used and have many formulations.

TABLE 49-3 SIMPLIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE

Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:	
At Least Two of the Following Features:	**Plus at Least One of the Following Features:**
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2013).

http://internalmedicinebook.com

TABLE 49-4 TREATMENT OF ACUTE MIGRAINE

Drug	Trade Name	Dosage
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max eight per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg PO bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg PO q3–4h
Tolfenamic acid	Clotam Rapid	200 mg PO; may repeat ×1 after 1–2 h
Diclofenac K	Cambia	50 mg PO with water
5-HT$_1$ Receptor Agonists		
Oral		
Ergotamine 1 mg, caffeine 100 mg	Cafergot	One or two tablets at onset, then one tablet q½h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5-mg tablet at onset; may repeat once after 4 h
Rizatriptan	Maxalt Maxalt-MLT	5- to 10-mg tablet at onset; may repeat after 2 h (max 30 mg/d)
Sumatriptan	Imitrex	50- to 100-mg tablet at onset; may repeat after 2 h (max 200 mg/d)
Frovatriptan	Frova	2.5-mg tablet at onset, may repeat after 2 h (max 5 mg/d)
Almotriptan	Axert	12.5-mg tablet at onset, may repeat after 2 h (max 25 mg/d)
Eletriptan	Relpax	40 or 80 mg
Zolmitriptan	Zomig Zomig Rapimelt	2.5-mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed four times; one spray (0.5 mg) is administered, followed in 15 min by a second spray
Sumatriptan	Imitrex Nasal Spray	5- to 20-mg intranasal spray as four sprays of 5 mg or a single 20-mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
Zolmitriptan	Zomig	5-mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d)
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection Alsuma Sumavel DosePro	6 mg SC at onset (may repeat once after 1 h for max of two doses in 24 h)

(*Continued*)

http://internalmedicinebook.com

TABLE 49-4 TREATMENT OF ACUTE MIGRAINE (*CONTINUED*)

Drug	Trade Name	Dosage
Dopamine Receptor Antagonists		
Oral		
Metoclopramide	Reglan,[a] generic[a]	5–10 mg/d
Prochlorperazine	Compazine,[a] generic[a]	1–25 mg/d
Parenteral		
Chlorpromazine	Generic[a]	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan,[a] generic	10 mg IV
Prochlorperazine	Compazine,[a] generic[a]	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, *plus* dichloralphenazone, 100 mg, *plus* isometheptene, 65 mg	Midrin, generic	Two capsules at onset followed by one capsule q1h (max five capsules)
Nasal		
Butorphanol	Generic	1 mg (one spray in one nostril), may repeat if necessary in 1–2 h
Parenteral		
Opioids	Generic[a]	Multiple preparations and dosages; see Table 5-2

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.
Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.
Abbreviations: 5-HT, 5-hydroxytryptamine.

- There is likely less frequent headache recurrence when using ergots, but more frequent nausea.
- For prophylaxis, tricyclic antidepressants are a good first choice for young people with difficulty falling asleep; verapamil is often a first choice for prophylaxis in the elderly.

Tension-Type Headache

Common in all age groups. Pain is described as bilateral tight, bandlike discomfort. May persist for hours or days; usually builds slowly.

- Pain can be managed generally with simple analgesics such as acetaminophen, aspirin, or NSAIDs.
- Often related to stress; responds to behavioral approaches including relaxation.
- Amitriptyline may be helpful for chronic (>15 days per month) tension-type headache prophylaxis.

http://internalmedicinebook.com

TABLE 49-5 CLINICAL STRATIFICATION OF ACUTE SPECIFIC MIGRAINE TREATMENTS

Clinical Situation	Treatment Options
Failed NSAIDs/analgesics	**First tier** Sumatriptan 50 or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eletriptan 40 mg PO Zolmitriptan 2.5 mg PO **Slower effect/better tolerability** Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO **Infrequent headache** Ergotamine/caffeine 1–2/100 mg PO Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5-mg nasal spray Sumatriptan 20-mg nasal spray Rizatriptan 10-mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg
Early vomiting	Zolmitriptan 5-mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC
Menses-related headache	**Prevention** Ergotamine PO at night Estrogen patches **Treatment** Triptans Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5-mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM

Cluster Headache

Rare form of primary headache; population frequency 0.1%. Characterized by episodes of recurrent, deep, unilateral, retroorbital searing pain. Unilateral lacrimation and nasal and conjunctival congestion may be present. Visual complaints, nausea, or vomiting is rare. Unlike migraine, pts with cluster tend to move about during attacks. A core feature is periodicity. Typically, daily bouts of one to two attacks of relatively short-duration unilateral pain for 8–10 weeks a year; usually followed by a pain-free interval that averages a little less than a year. Alcohol may provoke attacks.

- Prophylaxis with verapamil (40–80 mg twice daily to start), lithium (400–800 mg/d), or prednisone (60 mg/d for 7 days followed by a taper over 21 days).
- High-flow oxygen (10–12 L/min for 15–20 min) or sumatriptan (6 mg SC or 20-mg nasal spray) is useful for the acute attack.

http://internalmedicinebook.com

TABLE 49-6 PREVENTIVE TREATMENTS IN MIGRAINE[a]

Drug	Dose	Selected Side Effects
Pizotifen[b]	0.5–2 mg qd	Weight gain Drowsiness
β Blocker		
Propranolol	40–120 mg bid	Reduced energy
Metoprolol	25–100 mg bid	Tiredness Postural symptoms Contraindicated in asthma
Antidepressants		
Amitriptyline	10–75 mg at night	Drowsiness
Dosulepin	25–75 mg at night	
Nortriptyline	25–75 mg at night	***Note:*** Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required
Venlafaxine	75–150 mg/d	
Anticonvulsants		
Topiramate	25–200 mg/d	Paresthesias Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities
Serotonergic drugs		
Methysergide[c]	1–4 mg qd	Drowsiness Leg cramps Hair loss Retroperitoneal fibrosis (1-month drug holiday is required every 6 months)
Other classes		
Flunarizine[b]	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
Candesartan	16 mg daily	Dizziness
Chronic migraine		
Onabotulinum toxin type A	155 U	Loss of brow furrow
No convincing evidence from controlled trials		
Verapamil		

(*Continued*)

http://internalmedicinebook.com

TABLE 49-6 PREVENTIVE TREATMENTS IN MIGRAINE[a] (*CONTINUED*)

Drug	Dose	Selected Side Effects
Controlled trials demonstrate *no effect*		
Nimodipine		
Clonidine		
Selective serotonin reuptake inhibitors: fluoxetine		

[a]Commonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.
[b]Not available in the United States.
[c]Not currently available worldwide.

- Deep-brain stimulation of the posterior hypothalamic gray matter is successful for refractory cases as is the less-invasive approach of occipital nerve stimulation.

Post-Concussion Headache

Common following motor vehicle collisions, other head trauma; severe injury, or loss of consciousness often not present. Symptoms of headache, dizziness, vertigo, impaired memory, poor concentration, irritability; typically remits after several weeks to months. Neurologic examination and neuroimaging studies normal. Not a functional disorder; cause unknown and treatment usually not satisfactory.

Lumbar Puncture Headache

Typical onset within 48 h after LP; follows 10–30% of LPs. Positional: onset when pt sits or stands, relief by lying flat. Most cases remit spontaneously in ≤1 week. Oral or IV caffeine (500 mg IV over 2 h) successful in many; epidural blood patch effective immediately in refractory cases.

Indomethacin-Responsive Headaches

A diverse set of disorders that respond often exquisitely to indomethacin (25 mg two to three times daily). Includes:

- *Paroxysmal hemicrania:* Frequent unilateral, severe, short-lasting episodes of headache that are often retroorbital and associated with autonomic phenomena such as lacrimation and nasal congestion.
- *Hemicrania continua:* Moderate and continuous unilateral pain associated with fluctuations of severe pain that may be associated with autonomic features.
- *Primary stabbing headache:* Stabbing pain confined to the head or rarely the face lasting from 1 to many seconds or minutes.
- *Primary cough headache:* Transient severe head pain with coughing, bending, lifting, sneezing, or stooping; lasts for several minutes. Usually benign, but posterior fossa mass lesion in some pts; therefore consider brain MRI.
- *Primary exertional headache:* Features similar to cough headache and migraine, but precipitated by any form of exercise.

FACIAL PAIN

Most common cause of facial pain is dental; triggered by hot, cold, or sweet foods. Exposure to cold repeatedly induces dental pain. Trigeminal neuralgia consists of paroxysmal, electric shock—like episodes of pain in the distribution of trigeminal nerve; occipital neuralgia presents as lancinating occipital pain. These disorders are discussed in Chap. 187.

http://internalmedicinebook.com

For a more detailed discussion, see Goadsby PJ, Raskin NH: Headache, Chap. 21, p. 107; and Goadsby PJ, Raskin NH: Migraine and Other Primary Headache Disorders, Chap. 447, p. 2586, in HPIM-19.

50 Syncope

Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. It may occur suddenly, without warning, or may be preceded by presyncopal symptoms such as light-headedness or faintness, weakness, fatigue, nausea, dimming vision, ringing in ears, or sweating. The syncopal pt appears pale and has a faint, rapid, or irregular pulse. Breathing may be almost imperceptible; transient myoclonic or clonic movements may occur. Recovery of consciousness is prompt and complete if pt is maintained in a horizontal position and cerebral perfusion is restored.

APPROACH TO THE PATIENT: Syncope

The cause may be apparent only at the time of the event, leaving few, if any, clues when the pt is seen by the physician. Other disorders must be distinguished from syncope, including seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia (see below). First consider serious underlying etiologies; among these are massive internal hemorrhage, myocardial infarction (can be painless), and cardiac arrhythmias. In elderly pts, a sudden faint without obvious cause should raise the question of complete heart block or a tachyarrhythmia. Loss of consciousness in particular situations, such as during venipuncture or micturition, suggests a benign abnormality of vascular tone. The position of the pt at the time of the syncopal episode is important; syncope in the supine position is unlikely to be vasovagal and suggests arrhythmia or seizure. Medications must be considered, including nonprescription drugs or health store supplements, with particular attention to recent changes. Symptoms of impotence, bowel and bladder difficulties, disturbed sweating, or an abnormal neurologic examination suggest a primary neurogenic cause. An algorithmic approach is presented in Fig. 50-1.

ETIOLOGY

Syncope is usually due to a neurally mediated disorder, orthostatic hypotension, or an underlying cardiac condition (Table 50-1). Not infrequently the cause is multifactorial.

Neurocardiogenic (Vasovagal and Vasodepressor) Syncope

The common faint, experienced by normal persons, accounts for approximately half of all episodes of syncope. It is frequently recurrent and may be provoked by hot or

http://internalmedicinebook.com

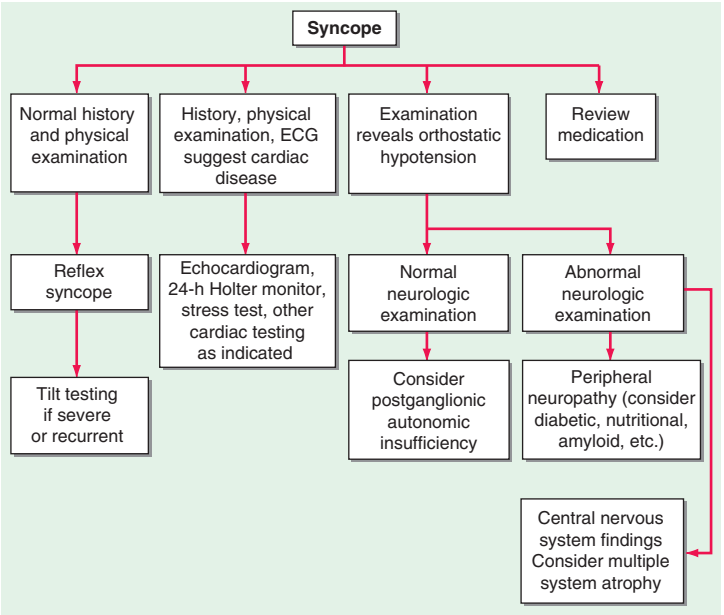


FIGURE 50-1 Approach to the pt with syncope.

TABLE 50-1 CAUSES OF SYNCOPE

A. Neurally Mediated Syncope
Vasovagal syncope
Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress
Situational reflex syncope
Pulmonary
Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"[a] and "fainting lark,"[b] sneeze syncope, airway instrumentation
Urogenital
Postmicturition syncope, urogenital tract instrumentation, prostatic massage
Gastrointestinal
Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope
Cardiac
Bezold-Jarisch reflex, cardiac outflow obstruction
Carotid sinus
Carotid sinus sensitivity, carotid sinus massage
Ocular
Ocular pressure, ocular examination, ocular surgery

(*Continued*)

http://internalmedicinebook.com

TABLE 50-1 CAUSES OF SYNCOPE (*CONTINUED*)

B. Orthostatic Hypotension
Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies"
Lewy body diseases
Parkinson's disease
Lewy body dementia
Pure autonomic failure
Multiple system atrophy (the Shy-Drager syndrome)
Secondary autonomic failure due to autonomic peripheral neuropathies
Diabetes
Hereditary amyloidosis (familial amyloid polyneuropathy)
Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated)
HSAN (especially type III—familial dysautonomia)
Idiopathic immune-mediated autonomic neuropathy
Autoimmune autonomic ganglionopathy
Sjögren's syndrome
Paraneoplastic autonomic neuropathy
HIV neuropathy
Postprandial hypotension
Iatrogenic (drug-induced)
Volume depletion
C. Cardiac Syncope
Arrhythmias
Sinus node dysfunction
Atrioventricular dysfunction
Supraventricular tachycardias
Ventricular tachycardias
Inherited channelopathies
Cardiac structural disease
Valvular disease
Myocardial ischemia
Obstructive and other cardiomyopathies
Atrial myxoma
Pericardial effusions and tamponade

[a]Hyperventilation for ~1 min, followed by sudden chest compression.
[b]Hyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.
Abbreviation: HSAN, Hereditary sensory and autonomic neuropathies.

crowded environment, alcohol, fatigue, pain, hunger, prolonged standing, or stressful situations.

Postural (Orthostatic) Hypotension

Sudden rising from a recumbent position or standing quietly is a precipitating circumstance. Cause of syncope in many elderly and incidence rises with age; polypharmacy with antihypertensive or antidepressant drugs often a contributor; physical deconditioning may also play a role. Also occurs with autonomic nervous system disorders, either peripheral (diabetes, nutritional, or amyloid polyneuropathy) or central (multiple system atrophy, Parkinson's disease). Some cases are idiopathic.

http://internalmedicinebook.com

DIFFERENTIAL DIAGNOSIS

Seizures

The differential diagnosis is often between syncope and a generalized seizure. Syncope is more likely if the event was provoked by acute pain or emotion or occurred immediately after arising from a lying or sitting position; seizures are typically not related to posture. Pts with syncope often describe a stereotyped transition from consciousness to unconsciousness that develops over a few seconds. Seizures either occur very abruptly without a transition or are preceded by premonitory symptoms such as an epigastric rising sensation, perception of odd odors, or racing thoughts. Pallor is seen during syncope; cyanosis is usually seen during a seizure. The duration of unconsciousness is usually very brief (i.e., seconds) in syncope and more prolonged (i.e., >5 min) in a seizure. Injury from falling and incontinence are common in seizure, rare in syncope. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also occur in up to 90% of syncopal episodes and eyewitnesses will often have a difficult time distinguishing between the two etiologies.

Hypoglycemia

Severe hypoglycemia is usually due to a serious disease or insulin use. Hunger is a premonitory feature that is not typical in syncope. The glucose level at the time of a spell is diagnostic.

Cataplexy

Abrupt partial or complete loss of muscular tone triggered by strong emotions; occurs in 60–75% of narcolepsy pts. Unlike syncope, consciousness is maintained throughout the attacks that typically last between 30 s and 2 min. No premonitory symptoms.

Psychiatric Disorders

Apparent loss of consciousness can be present in generalized anxiety, panic disorders, major depression, and somatization disorder. Frequently resembles presyncope, although the symptoms are not accompanied by prodromal symptoms and are not relieved by recumbency. Attacks can often be reproduced by hyperventilation and have associated symptoms of panic attacks such as a feeling of impending doom, air hunger, palpitations, and tingling of the fingers and perioral region. Such pts are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes.

TREATMENT SYNCOPE

Therapy is determined by the underlying cause.

- Pts with neurally mediated syncope should be reassured and instructed to avoid situations or stimuli that provoke attacks. Plasma volume expansion should occur with fluid and salt.
- Drug therapy may be necessary for resistant neurally medicated syncope. Fludrocortisone, vasoconstricting agents, and β-adrenergic antagonists are widely used although there is no consistent evidence from randomized trials.
- Pts with orthostatic hypotension should first be treated with removal of vasoactive medications. Then consider nonpharmacologic (pt education regarding moves from supine to upright, increasing fluids and salt in diet) and finally pharmacologic methods such as fludrocortisone and vasoconstricting agents such as midodrine, L-dihydroxyphenylserine, and pseudoephedrine.
- Management of cardiac causes depends in the underlying disorder. Cardiac pacing or cardioverter-defibrillator implantation is sometimes necessary.
- Management of refractory orthostatic hypotension is discussed in Chap. 186.

http://internalmedicinebook.com

For a more detailed discussion, see Freeman R: Syncope, Chap. 27, p. 142, in HPIM-19.

51 Dizziness and Vertigo

APPROACH TO THE PATIENT: Dizziness or Vertigo

The term *dizziness* is used by pts to describe a variety of sensations or gait unsteadiness. With a careful history, distinguishing between *faintness* (presyncope; Chap. 50) and *vertigo* (a sense of movement of the body or the environment, most often a feeling of spinning) is usually possible.

When the meaning of *dizziness* is uncertain, provocative tests to reproduce the symptoms may be helpful. Valsalva maneuver, hyperventilation, or postural changes leading to orthostasis may reproduce faintness. Rapid rotation in a swivel chair is a simple provocative test to reproduce vertigo.

Benign positional vertigo is identified by the Dix-Hallpike maneuver to elicit vertigo and the characteristic nystagmus; the pt begins in a sitting position with head turned 45°; holding the back of the head, examiner gently lowers pt to supine position with head extended backward 20° and observes for nystagmus; after 30 s the pt is raised to sitting position and after 1 min rest the maneuver is repeated on other side.

If a central cause for the vertigo is suspected (e.g., no signs of peripheral vertigo, no hearing loss, no ear sensations, or the presence of other neurologic abnormalities indicating central nervous system [CNS] disease), then prompt evaluation for central pathology is required. The initial test is usually an MRI scan of the posterior fossa. Distinguishing between central and peripheral etiologies can be accomplished with vestibular function tests, including videonystagmography and simple bedside examinations including the *head impulse test* (rapid, small amplitude head rotations while pt instructed to fixate on the examiner's face; if peripheral, a catch-up saccade is seen at the end of the rotation) and *dynamic visual acuity* (measure acuity at rest and with head rotated back and forth by examiner; a drop in acuity of more than one line on a near card or Snellen chart indicates vestibular dysfunction).

FAINTNESS

Faintness is usually described as light-headedness followed by visual blurring and postural swaying along with a feeling of warmth, diaphoresis, and nausea. It is a symptom of insufficient blood, oxygen, or, rarely, glucose supply to the brain. It can occur prior to a syncopal event of any etiology (Chap. 50) and with hyperventilation

http://internalmedicinebook.com

TABLE 51-1 FEATURES OF PERIPHERAL AND CENTRAL VERTIGO

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in BPPV, but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a pt with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

Abbreviation: BPPV, benign paroxysmal positional vertigo.

or hypoglycemia. Light-headedness can rarely occur during an aura before a seizure. Chronic light-headedness is a common somatic complaint with depression.

VERTIGO

Usually due to a disturbance in the vestibular system; abnormalities in the visual or somatosensory systems may also contribute to vertigo. Frequently accompanied by nausea, postural unsteadiness, and gait ataxia; may be provoked or worsened by head movement.

Physiologic vertigo results from unfamiliar head movement (seasickness) or a mismatch between visual-proprioceptive-vestibular system inputs (height vertigo, visual vertigo during motion picture chase scenes). *Pathologic vertigo* may be caused by a peripheral (labyrinth or eighth nerve) or central CNS lesion. Distinguishing between these causes is the essential first step in diagnosis (Table 51-1) as only central lesions require urgent imaging, usually with MRI.

Peripheral Vertigo

Usually severe, accompanied by nausea and emesis. Tinnitus, a feeling of ear fullness, or hearing loss may occur. A characteristic jerk nystagmus is almost always present. The nystagmus does not change direction with a change in direction of gaze; it is usually horizontal with a torsional component and has its fast phase away from the side of the lesion. It is inhibited by visual fixation. The pt senses spinning motion away from the lesion and tends to have difficulty walking, with falls toward the side of the lesion, particularly in the darkness or with eyes closed. No other neurologic abnormalities are present.

Acute prolonged vertigo may be caused by infection, trauma, or ischemia. Often no specific etiology is found, and the term *acute labyrinthitis* (or *vestibular neuritis*) is used to describe the event. Acute bilateral labyrinthine dysfunction is usually due to drugs (aminoglycoside antibiotics), alcohol, or a neurodegenerative disorder. Recurrent labyrinthine dysfunction with signs and symptoms of cochlear disease is usually due to *Ménière's disease* (recurrent vertigo accompanied by tinnitus and deafness). Positional vertigo is usually precipitated by a recumbent head position; *benign paroxysmal positional vertigo* (BPPV) of the posterior semicircular canal is particularly common; the pattern of nystagmus is distinctive. BPPV may follow trauma but is usually idiopathic; it generally abates spontaneously after weeks or months. *Vestibular schwannomas* of the eighth cranial nerve (acoustic neuroma) usually present with hearing loss and tinnitus, sometimes accompanied by facial weakness and sensory loss due to involvement of cranial nerves VII and V. *Psychogenic vertigo* should be suspected in pts with chronic incapacitating vertigo who also have agoraphobia, panic attacks, a normal neurologic examination, and no nystagmus.

http://internalmedicinebook.com

Central Vertigo

Identified by associated brainstem or cerebellar signs such as dysarthria, diplopia, dysphagia, hiccups, other cranial nerve abnormalities, weakness, or limb ataxia; depending on the cause, headache may be present. The nystagmus can take almost any form (i.e., vertical or multidirectional) but is often purely horizontal without a torsional component and changes direction with different directions of gaze. Central nystagmus is not inhibited by fixation. Central vertigo may be chronic, mild, and is usually not accompanied by tinnitus or hearing loss. It may be due to vascular, demyelinating, neurodegenerative, or neoplastic disease. Vertigo may be a manifestation of migraine or, rarely, of temporal lobe epilepsy.

TREATMENT VERTIGO

- Treatment of acute vertigo consists of vestibular suppressant drugs for short-term relief (Table 51-2). They may hinder central compensation, prolonging the duration of symptoms, and therefore should be used sparingly.

TABLE 51-2 TREATMENT OF VERTIGO

Agent[a]	Dose[b]
Antihistamines	
Meclizine	25–50 mg three times daily
Dimenhydrinate	50 mg one to two times daily
Promethazine	25 mg two to three times daily (also can be given rectally and IM)
Benzodiazepines	
Diazepam	2.5 mg one to three times daily
Clonazepam	0.25 mg one to three times daily
Anticholinergic	
Scopolamine transdermal[c]	Patch
Physical therapy	
Repositioning maneuvers[d]	
Vestibular rehabilitation	
Other	
Diuretics and/or low-sodium (1000 mg/d) diet[e]	
Antimigrainous drugs[f]	
Methylprednisolone[g]	100 mg daily days 1–3; 80 mg daily days 4–6; 60 mg daily days 7–9; 40 mg daily days 10–12; 20 mg daily days 13–15; 10 mg daily days 16–18, 20, 22
Selective serotonin reuptake inhibitors[h]	

[a]All listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo.
[b]Usual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase.
[c]For motion sickness only.
[d]For benign paroxysmal positional vertigo.
[e]For Ménière's disease.
[f]For vestibular migraine.
[g]For acute vestibular neuritis (started within 3 days of onset).
[h]For psychosomatic vertigo.

http://internalmedicinebook.com

- Vestibular rehabilitation promotes central adaptation processes and may habituate motion sensitivity and other symptoms of psychosomatic dizziness.
- BPPV may respond dramatically to repositioning exercises such as the Epley maneuver designed to empty particulate debris from the posterior semicircular canal (*www.dizziness-and-balance.com/disorders/bppv/bppv.html*).
- For vestibular neuritis, antiviral medications are of no proven benefit unless herpes zoster oticus is present. Some data suggest that glucocorticoids improve the likelihood of recovery in vestibular neuritis if given within 3 days of symptom onset.
- Ménière's disease may respond to a low-salt diet (1 g/d) or to a diuretic. Otolaryngology referral is recommended.
- Recurrent episodes of migraine-associated vertigo should be treated with antimigraine therapy (**Chap. 49**).



For a more detailed discussion, see Walker MF, Daroff RB: Dizziness, and Vertigo, Chap. 28, p. 148, in HPIM-19.

52 Acute Visual Loss and Double Vision

APPROACH TO THE PATIENT: **Acute Visual Loss or Double Vision**

Accurate measurement of visual acuity in each eye (with glasses or contact lenses) is of primary importance. Additional assessments include testing of pupils, eye movements, ocular alignment, and visual fields. Slit-lamp examination can exclude corneal infection, trauma, glaucoma, uveitis, and cataract. Ophthalmoscopic examination to inspect the optic disc and retina often requires pupillary dilation using 1% tropicamide and 2.5% phenylephrine; risk of provoking an attack of narrow-angle glaucoma is remote.

Visual field mapping by finger confrontation localizes lesions in the visual pathway (Fig. 52-1); formal testing using a perimeter may be necessary. The goal is to determine whether the lesion is anterior to, at, or posterior to the optic chiasm. A scotoma confined to one eye is caused by an anterior lesion affecting the optic nerve or globe; swinging flashlight test may reveal an afferent pupil defect. History and ocular examination are usually sufficient for diagnosis. If a bitemporal hemianopia is present, lesion is located at optic chiasm (e.g., pituitary adenoma, meningioma). Homonymous visual field loss signals a retrochiasmal lesion affecting the optic tract, lateral geniculate body, optic radiations, or visual cortex (e.g., stroke, tumor, abscess). Neuroimaging is recommended for any pt with a bitemporal or homonymous hemianopia.

http://internalmedicinebook.com

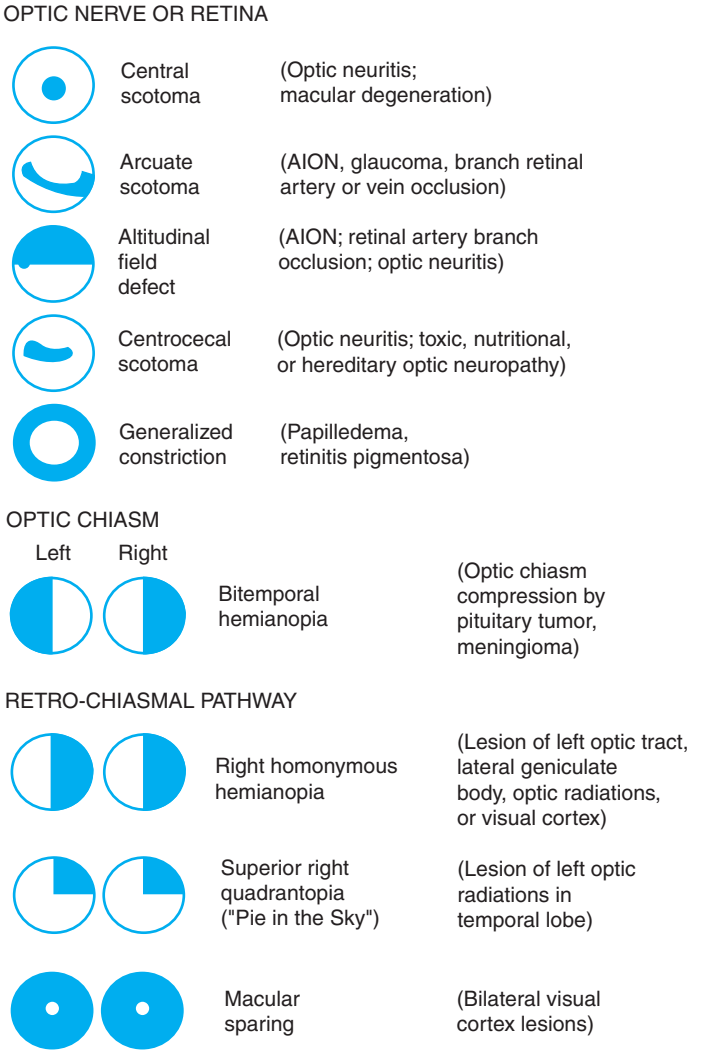


FIGURE 52-1 Deficits in visual fields caused by lesions affecting visual pathways.

TRANSIENT OR SUDDEN VISUAL LOSS

Amaurosis fugax (*transient monocular blindness*; a TIA of the retina) usually occurs from a retinal embolus often arising from ipsilateral carotid stenosis or the heart. Prolonged occlusion of the central retinal artery results in classic fundus appearance of a milky, infarcted retina with cherry red fovea. Any pt with compromise of the retinal circulation should be evaluated promptly for stroke risk factors (e.g., carotid atheroma, heart disease, atrial fibrillation). *Occipital cortex lesions* can be confused with amaurosis fugax because many pts mistakenly ascribe symptoms to their left or right eye, when in fact they are occurring in the left or right hemifield of both eyes. Interruption of blood flow to the visual cortex causes sudden graying of vision, occasionally with flashing

http://internalmedicinebook.com

lights or other symptoms that mimic *migraine*. The history may be the only guide to the correct diagnosis. Pts should be questioned about the precise pattern and duration of visual loss and other neurologic symptoms, especially those of posterior circulation dysfunction such as diplopia, vertigo, numbness, or weakness.

Marked *systemic hypertension* can cause visual loss from exudates, hemorrhages, cotton-wool spots (focal nerve fiber layer infarcts), and optic disc edema.

In central or branch *retinal vein occlusion*, the fundus examination reveals engorged, phlebitic veins with extensive retinal hemorrhages.

In age-related *macular degeneration*, characterized by extensive drusen and scarring of the pigment epithelium, leakage of blood or fluid from subretinal neovascular membranes can produce sudden central visual loss.

Flashing lights and floaters may indicate a fresh *vitreous detachment*. Separation of the vitreous from the retina is a frequent involutional event in the elderly. It is not harmful unless it creates sufficient traction to produce a *retinal detachment*. *Vitreous hemorrhage* may occur in diabetic pts from retinal neovascularization.

Papilledema refers to optic disc edema from raised intracranial pressure. Transient visual obscurations are common, but visual acuity is not affected unless the papilledema is severe, long-standing, or accompanied by macular exudates or hemorrhage. Enlarged blind spots and peripheral constriction are typical. Neuroimaging should be obtained to exclude an intracranial mass. If negative, a LP is required to confirm elevation of the intracranial pressure. *Pseudotumor cerebri* (idiopathic intracranial hypertension) is a diagnosis of exclusion. Most pts are young, female, and obese; some are found to have occult cerebral venous sinus thrombosis. Treatment is with acetazolamide, repeated LPs, and weight loss (via bariatric surgery if necessary); some pts require lumboperitoneal shunting to prevent blindness.

Optic neuritis is a common cause of monocular optic disc swelling and visual loss. If site of inflammation is retrobulbar, fundus will appear normal on initial examination. The typical pt is female, age 15–45, with pain provoked by eye movements. Glucocorticoids, typically IV methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days), may hasten recovery in severely affected pts but make no difference in final acuity (measured 6 months after the attack). If an MRI shows multiple demyelinating lesions, treatment for multiple sclerosis (**Chap. 190**) should be considered. Optic neuritis involving both eyes simultaneously or sequentially suggests neuromyelitis optica.

Anterior ischemic optic neuropathy (AION) is an infarction of the optic nerve head due to inadequate perfusion via the posterior ciliary arteries. Pts have sudden visual loss, often noted on awakening, and painless swelling of the optic disc. It is important to differentiate between nonarteritic (idiopathic) AION and arteritic AION. There is no treatment for nonarteritic AION. In contrast, arteritic AION is caused by *giant cell (temporal) arteritis* and requires immediate glucocorticoid therapy to prevent blindness; temporal artery biopsy establishes the diagnosis. The ESR and C-reactive protein should be checked in any elderly pt with acute optic disc swelling or symptoms suggestive of polymyalgia rheumatica (associated with arteritic AION).

DOUBLE VISION (DIPLOPIA)

First step: clarify whether diplopia persists in either eye after covering the opposite eye; if it does the diagnosis is monocular diplopia usually caused by disease intrinsic to the eye with no dire implications for the pt. Occasionally it is a symptom of malingering or psychiatric disease.

If pt has diplopia while being examined, motility testing will usually reveal an abnormality in ocular excursions. However, if the degree of angular separation between the double images is small, the limitation of eye movements may be subtle and difficult to detect. In this situation, the cover test is useful. While the pt is fixating upon a distant target, one eye is covered while observing the other eye for a movement of redress as it takes up fixation. If none is seen, the procedure is repeated with the other eye. With genuine diplopia, this test should reveal ocular malalignment,

http://internalmedicinebook.com

TABLE 52-1 COMMON CAUSES OF DIPLOPIA

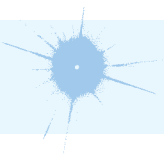
Brainstem stroke (skew deviation, nuclear or fascicular palsy)
Microvascular infarction (III, IV, VI nerve palsy)
Tumor (brainstem, cavernous sinus, superior orbital fissure, orbit)
Multiple sclerosis (internuclear ophthalmoplegia, ocular motor nerve palsy)
Aneurysm (III nerve)
Raised intracranial pressure (VI nerve)
Postviral inflammation
Meningitis (bacterial, fungal, granulomatosis, neoplastic)
Carotid-cavernous fistula or thrombosis
Herpes zoster
Tolosa-Hunt syndrome
Wernicke-Korsakoff syndrome
Botulism
Myasthenia gravis
Guillain-Barré or Fisher syndrome
Graves' disease
Orbital pseudotumor
Orbital myositis
Trauma
Orbital cellulitis

especially if the head is turned or tilted in the position that gives rise to the worst symptoms.

Common causes of diplopia are summarized in Table 52-1. The physical findings in isolated ocular motor nerve palsies are:

- CN III: Ptosis and deviation of the eye down and outwards, causing vertical and horizontal diplopia. A dilated pupil suggests direct compression of the third nerve; if present, the possibility of an aneurysm of the posterior communicating artery must be considered urgently. If pupil is spared, a microvascular infarction is likely the cause, especially in pts with diabetes or hypertension.
- CN IV: Vertical diplopia with cyclotorsion; the affected eye is slightly elevated, and limitation of depression is seen when the eye is held in adduction. The pt may assume a head tilt to the opposite side (e.g., left head tilt in right fourth nerve paresis).
- CN VI: Horizontal diplopia worse on gaze to the side of the lesion; the affected eye cannot abduct.

The development of multiple ocular motor nerve palsies, or diffuse ophthalmoplegia, raises the possibility of myasthenia gravis. In this disease, the pupils are always normal. Systemic weakness may be absent. Multiple ocular motor nerve palsies should be investigated with neuroimaging focusing on the cavernous sinus, superior orbital fissure, and orbital apex where all three nerves are in close proximity. Diplopia that cannot be explained by a single ocular motor nerve palsy may also be caused by carcinomatous or fungal meningitis, Graves' disease, Guillain-Barré syndrome (especially the Miller Fisher variant), or Tolosa-Hunt syndrome (painful granulomatous inflammation of the cavernous sinus).



For a more detailed discussion, see Horton JC: Disorders of the Eye, Chap. 39, p. 195, in HPIM-19.

http://internalmedicinebook.com

53 Weakness and Paralysis

APPROACH TO THE PATIENT: Weakness or Paralysis

Weakness is a reduction of power in one or more muscles. *Paralysis* indicates weakness that is so severe that the muscle cannot be contracted at all, whereas *paresis* refers to less severe weakness. The prefix *hemi-* refers to one half of the body, *para-* to both legs, and *quadri-* to all four limbs. The suffix *-plegia* signifies severe weakness or paralysis.

Increased *fatigability* or limitation in function due to pain or articular stiffness is often confused with weakness by pts. Increased time is sometimes required for full power to be exerted, and this *bradykinesia* may be misinterpreted as weakness. Severe proprioceptive sensory loss may also lead to complaints of weakness because adequate feedback information about the direction and power of movements is lacking. Finally, *apraxia*, a disorder of planning and initiating a skilled or learned movement, is sometimes mistaken for weakness.

The history should focus on the tempo of development of weakness, presence of sensory and other neurologic symptoms, medication history, predisposing medical conditions, and family history.

Weakness or paralysis is typically accompanied by other neurologic abnormalities that help to indicate the site of the responsible lesion (Table 53-1). It is important to distinguish weakness arising from disorders of upper motor neurons (i.e., motor neurons in the cerebral cortex and their axons that descend through the subcortical white matter, internal capsule, brainstem, and spinal cord) from disorders of the motor unit (i.e., lower motor neurons in the ventral horn of the spinal cord and their axons in the spinal roots and peripheral nerves, neuromuscular junction, and skeletal muscle).

Table 53-2 lists common causes of weakness by the primary site of pathology. Table 53-3 summarizes patterns with lesions of different parts of the nervous system.

An algorithm for the initial workup of weakness is shown in Fig. 53-1.

TABLE 53-1 SIGNS THAT DISTINGUISH THE ORIGIN OF WEAKNESS

Sign	Upper Motor Neuron	Lower Motor Neuron	Myopathic	Psychogenic
Atrophy	None	Severe	Mild	None
Fasciculations	None	Common	None	None
Tone	Spastic	Decreased	Normal/ decreased	Variable/ paratonia
Distribution of weakness	Pyramidal/ regional	Distal/ segmental	Proximal	Variable/ inconsistent with daily activities
Muscle stretch reflexes	Hyperactive	Hypoactive/ absent	Normal/ hypoactive	Normal
Babinski sign	Present	Absent	Absent	Absent

http://internalmedicinebook.com

TABLE 53-2 COMMON CAUSES OF WEAKNESS

Upper Motor Neuron
Cortex: Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); extrinsic mass lesion (subdural hematoma); degenerative (amyotrophic lateral sclerosis)
Subcortical white matter/internal capsule: Ischemia; hemorrhage; intrinsic mass lesion (primary or metastatic cancer, abscess); immunologic (multiple sclerosis); infectious (progressive multifocal leukoencephalopathy)
Brainstem: Ischemia, immunologic (multiple sclerosis)
Spinal cord: Extrinsic compression (cervical spondylosis, metastatic cancer, epidural abscess); immunologic (multiple sclerosis, transverse myelitis); infectious (AIDS-associated myelopathy, HTLV-I–associated myelopathy, tabes dorsalis); nutritional deficiency (subacute combined degeneration)
Motor Unit
Spinal motor neuron: Degenerative (amyotrophic lateral sclerosis), infectious (poliomyelitis)
Spinal root: Compressive (degenerative disk disease); immunologic (Guillain-Barré syndrome); infectious (AIDS-associated polyradiculopathy, Lyme disease)
Peripheral nerve: Metabolic (diabetes mellitus, uremia, porphyria); toxic (ethanol, heavy metals, many drugs, diphtheria); nutritional (B_{12} deficiency); inflammatory (polyarteritis nodosa); hereditary (Charcot-Marie-Tooth); immunologic (paraneoplastic, paraproteinemia); infectious (AIDS-associated polyneuropathies and mononeuritis multiplex); compressive (entrapment)
Neuromuscular junction: Immunologic (myasthenia gravis); toxic (botulism, aminoglycosides)
Muscle: Inflammatory (polymyositis, inclusion body myositis); degenerative (muscular dystrophy); toxic (glucocorticoids, ethanol, AZT); infectious (trichinosis); metabolic (hypothyroid, periodic paralyses); congenital (central core disease)

Abbreviation: AZT, azidothymidine.

TABLE 53-3 CLINICAL DIFFERENTIATION OF WEAKNESS ARISING FROM DIFFERENT AREAS OF THE NERVOUS SYSTEM

Location of Lesion	Pattern of Weakness	Associated Signs
Upper motor neuron		
Cerebral cortex	Hemiparesis (face and arm predominantly, or leg predominantly)	Hemisensory loss, seizures, homonymous hemianopia or quadrantanopia, aphasia, apraxias, gaze preference
Internal capsule	Hemiparesis (face, arm, leg may be equally affected)	Hemisensory deficit; homonymous hemianopia or quadrantanopia
Brainstem	Hemiparesis (arm and leg; face may not be involved at all)	Vertigo, nausea and vomiting, ataxia and dysarthria, eye movement abnormalities, cranial nerve dysfunction, altered level of consciousness, Horner's syndrome
Spinal cord	Quadriparesis if midcervical or above Paraparesis if low cervical or thoracic	Sensory level; bowel and bladder dysfunction

(*Continued*)

http://internalmedicinebook.com

TABLE 53-3 CLINICAL DIFFERENTIATION OF WEAKNESS ARISING FROM DIFFERENT AREAS OF THE NERVOUS SYSTEM (*CONTINUED*)

Location of Lesion	Pattern of Weakness	Associated Signs
	Hemiparesis below level of lesion (Brown-Séquard)	Contralateral pain/temperature loss below level of lesion
Motor unit		
Spinal motor neuron	Diffuse weakness, may involve control of speech and swallowing	Muscle fasciculations and atrophy; no sensory loss
Spinal root	Radicular pattern of weakness	Dermatomal sensory loss; radicular pain common with compressive lesions
Peripheral nerve		
Polyneuropathy	Distal weakness, usually feet more than hands; usually symmetric	Distal sensory loss, usually feet more than hands
Mononeuropathy	Weakness in distribution of single nerve	Sensory loss in distribution of single nerve
Neuromuscular junction	Fatigable weakness, usually with ocular involvement producing diplopia and ptosis	No sensory loss; no reflex changes
Muscle	Proximal weakness	No sensory loss; diminished reflexes only when severe; may have muscle tenderness

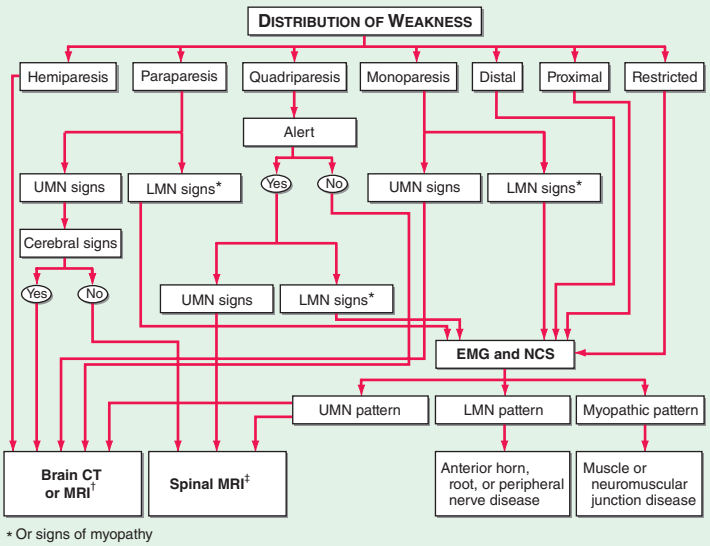


FIGURE 53-1 An algorithm for the initial workup of a pt with weakness. EMG, electromyography; LMN, lower motor neuron; NCS, nerve conduction studies; UMN, upper motor neuron.

http://internalmedicinebook.com

For a more detailed discussion, see Aminoff MJ: Neurologic Causes of Weakness and Paralysis, Chap. 30, p. 154, in HPIM-19.

54 Tremor and Movement Disorders

APPROACH TO THE PATIENT: Movement Disorders

Divided into akinetic rigid forms, with muscle rigidity and slowness of movement, and hyperkinetic forms, with involuntary movements. In both types, preservation of strength is the rule. Most movement disorders arise from disruption of basal ganglia circuits; common causes are degenerative diseases (hereditary and idiopathic), drug induced, organ system failure, CNS infection, and ischemia. Clinical features of the various movement disorders are summarized below.

BRADYKINESIA

Inability to initiate changes in activity or perform ordinary volitional movements rapidly and easily. There is a slowness of movement and a paucity of automatic motions such as eye blinking and arm swinging while walking. Usually due to Parkinson's disease or other causes of parkinsonism (Chap. 182).

TREMOR

Rhythmic oscillation of a part of the body due to intermittent muscle contractions, usually involving the distal limbs and less commonly the head, tongue, or jaw. A coarse tremor at rest, 4–5 beats/s, is usually due to Parkinson's disease. A fine postural tremor of 8–10 beats/s may be an exaggeration of normal physiologic tremor or indicate familial essential tremor (ET). An intention tremor, most pronounced during voluntary movement toward a target, is found with cerebellar pathway disease.

ESSENTIAL TREMOR (ET)

This is the most common movement disorder. The tremor of ET must be distinguished from early Parkinson's disease (Table 54-1). The pathophysiology of ET is unknown. Approximately 50% of cases have a positive family history with autosomal dominant inheritance; linkage studies have implicated several loci, and recently a mutation in the fused in sarcoma (*FUS*) gene, previously implicated in familial ALS, was identified in one ET family. The oligodendrocyte gene *LINGO1* has been suggested in association studies, especially in early onset familial cases. Many pts with ET have mild symptoms and require no treatment.

- When activities of daily living such as eating and writing are impaired, therapy with propranolol (20–120 mg/d) or primidone (12.5–750 mg/d) leads to benefit in 50% of pts.
- Surgical therapies targeting the thalamus may be effective in refractory cases.

http://internalmedicinebook.com

TABLE 54-1 ADVANCED EXAMINATION PEARLS: DIFFERENTIATING ESSENTIAL TREMOR FROM PARKINSONIAN TREMOR

	Essential Tremor	Parkinsonian Tremor
Speed	5–10 Hz	4–6 Hz
Symmetry	Bilateral	Usually asymmetric
Most common component	Postural	Rest
Other parkinsonian symptoms	Absent	Present
Helped with alcohol	Usually	Rarely
Family history	Present often	Usually absent

DYSTONIA

Consists of sustained or repetitive involuntary muscle contractions, frequently causing twisting movements and abnormal posture. May be generalized or focal; >300,000 cases in the United States.

Focal dystonias are common and include blepharospasm of the eyelids; spasmodic dysphonia involving the vocal cords; oromandibular dystonia of the face, lips, tongue, and jaw; cervical dystonia of the neck musculature (torticollis); and limb dystonias that are often task specific such as writer's cramp, playing a musical instrument (musician's cramp), or putting in golf (yips).

More than 16 causative genes have been identified. Idiopathic torsional dystonia is a predominantly childhood-onset form of generalized dystonia with an autosomal dominant pattern of inheritance that mainly affects Ashkenazi Jewish families; most are linked to a mutation in the *DYT1* gene on chromosome 9. Other generalized dystonias occur as a consequence of drugs such as antiemetics, neuroleptics, and treatments for Parkinson's disease.

- Therapy for focal dystonias usually involves botulinum toxin injections into the affected musculature.
- All forms of dystonia may respond to anticholinergic medications (e.g., trihexyphenidyl 20–120 mg/d), baclofen (20–120 mg/d), or tetrabenazine (initial dose 12.5 mg/d, usual maintenance 25–75 mg/d).
- Surgical therapies, including deep brain stimulation (DBS), may be effective in refractory cases.

CHOREOATHETOSIS

A combination of chorea (rapid, graceful, dance-like movements) and athetosis (slow, distal, writhing movements). The two usually exist together, though one may be more prominent. Choreic movements predominate in rheumatic (Sydenham's) chorea and Huntington's disease (HD). Systemic lupus erythematosus is the most common systemic disorder that causes chorea, but it can also be seen with hyperthyroidism, various autoimmune disorders, infections including HIV, metabolic alterations, and with a variety of medications. Hemiballismus is a violent form of chorea that comprises wild, flinging movements on one side of the body; the most common cause is a lesion (often infarct or hemorrhage) of the subthalamic nucleus. Athetosis is prominent in some forms of cerebral palsy. Chronic neuroleptic use may lead to tardive dyskinesia, in which choreoathetotic movements are usually restricted to the buccal, lingual, and mandibular areas.

HUNTINGTON'S DISEASE (HD)

A progressive, fatal, autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction. Onset is typically between 25 and 45 years. Rapid, nonpatterned, semipurposeful, involuntary choreiform movements are the hallmark

http://internalmedicinebook.com

feature; dysarthria, gait disturbance, and oculomotor abnormalities also occur. In late stages, chorea becomes less prominent, and the picture is dominated by dystonia, rigidity, bradykinesia, myoclonus, and spasticity. Eventually, behavioral and cognitive disturbances can be a major source of disability. HD is caused by an expansion in the number of polyglutamine (cytosine-adenine-guanine [CAG]) repeats in coding sequence of the *HTT* gene encoding the protein huntingtin.

- Treatment involves a multidisciplinary approach with medical, neuropsychiatric, social, and genetic counseling for pts and families.
- Dopamine-blocking agents may control the chorea; tetrabenazine may also treat chorea but can cause secondary parkinsonism.
- Depression and anxiety should be treated with appropriate antidepressant and antianxiety drugs.
- Psychosis can be treated with atypical neuroleptic agents.
- No disease-modifying agents currently exist.

TICS

Brief, rapid, recurrent, and seemingly purposeless stereotyped muscle contractions. Gilles de la Tourette syndrome (TS) is a neurobehavioral, multiple tic disorder that may involve motor tics (especially twitches of the face, neck, and shoulders) and phonic tics (grunts, words, coprolalia, echolalia). Pts may experience an irresistible urge to express tics but characteristically can voluntarily suppress them for short periods of time. Onset is usually between 2 and 15 years of age, and tics often lessen or even disappear in adulthood.

- Drug treatment is only indicated when tics are disabling and interfere with quality of life.
- Therapy is generally initiated with clonidine, starting at low dose, or guanfacine (0.5–2 mg/d). If these agents are not effective, neuroleptics may be used.

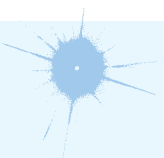
MYOCLONUS

Rapid (<100 ms), brief, shock-like, jerky, movements, usually multifocal. Like asterixis, often occurs in a diffuse encephalopathy. Following cardiac arrest, diffuse cerebral hypoxia may produce multifocal myoclonus. Spinal cord injury can also cause myoclonus. Myoclonus occurs in normal individuals when waking up or falling asleep.

- Treatment, indicated only when function is impaired, consists of treating the underlying condition or removing an offending agent.
- Drug therapies include valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d).

ASTERIXIS

Brief, arrhythmic interruptions of sustained voluntary muscle contraction, usually observed as a brief lapse of posture of wrists in dorsiflexion with arms outstretched, "negative myoclonus." This "liver flap" may be seen in any encephalopathy related to drug intoxication, organ system failure, or CNS infection. Therapy is correction of the underlying disorder.



For a more detailed discussion, see Olanow CW, Schapira AHV, Obeso JA: Parkinson's Disease and Other Movement Disorders, Chap. 449, p. 2609, in HPIM-19.

http://internalmedicinebook.com

55 Aphasia

Aphasias are disturbances in the comprehension or production of spoken or written language. Clinical examination should assess spontaneous speech (fluency), comprehension, repetition, naming, reading, and writing. A classification scheme is presented in Table 55-1. In nearly all right-handed individuals and many left-handed pts, language localization is in the left hemisphere.

CLINICAL FEATURES

Wernicke's Aphasia

Although speech sounds grammatical, melodic, and effortless (fluent), it is virtually incomprehensible due to errors in word usage, structure, and tense and the presence of paraphasic errors and neologisms ("jargon"). Comprehension of written and spoken material is severely impaired, as are reading, writing, and repetition. The pt usually seems unaware of the deficit and is not frustrated. Associated symptoms can include parietal lobe sensory deficits and homonymous hemianopia. Motor disturbances are rare.

Lesion is located in posterior perisylvian region. Most common cause is embolism to the inferior division of dominant middle cerebral artery (MCA); less commonly intracerebral hemorrhage, severe head trauma, or tumor is responsible.

TABLE 55-1 CLINICAL FEATURES OF APHASIAS AND RELATED CONDITIONS COMMONLY SEEN IN CEREBROVASCULAR ACCIDENTS

	Comprehension	Repetition of Spoken Language	Naming	Fluency
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

http://internalmedicinebook.com

Broca's Aphasia

Speech output is sparse (nonfluent), slow, labored, interrupted by many word-finding pauses, and usually dysarthric; output may be reduced to a grunt or single word. Naming and repetition also impaired. Most pts have severe writing impairment. Comprehension of written and spoken language is relatively preserved. The pt is often aware of and visibly frustrated by deficit. With large lesions, a dense hemiparesis may occur, and eyes may deviate toward side of lesion. More commonly, lesser degrees of contralateral face and arm weakness are present. Sensory loss is rarely found, and visual fields are intact.

Lesion involves dominant inferior frontal gyrus (Broca's area), although cortical and subcortical areas along superior sylvian fissure and insula are often involved. Commonly caused by vascular lesions involving the superior division of the MCA; less commonly due to tumor, intracerebral hemorrhage, or abscess.

Global Aphasia

All aspects of speech and language are impaired. Pt cannot read, write, or repeat and has poor auditory comprehension. Speech output is minimal and nonfluent. Hemiplegia, hemisensory loss, and homonymous hemianopia are usually present. Syndrome represents the combined dysfunction of Wernicke's and Broca's areas, usually resulting from proximal occlusion of MCA supplying dominant hemisphere (less commonly hemorrhage, trauma, or tumor).

Conduction Aphasia

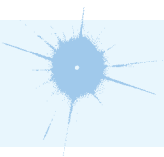
Speech output is fluent but paraphasic, comprehension of spoken language is intact, and repetition is severely impaired, as are naming and writing. Lesion spares, but functionally disconnects, Wernicke's and Broca's areas. Most cases are embolic, involving supramarginal gyrus of dominant parietal lobe, dominant superior temporal lobe, or arcuate fasciculus.

LABORATORY EVALUATION

CT scan or MRI usually identifies the location and nature of the causative lesion.

TREATMENT APHASIA

- Speech therapy may be helpful in treatment of certain types of aphasia; more effective in Broca's aphasia than in Wernicke's.
- When the lesion is caused by a stroke, recovery of language function generally peaks within 2–6 months, after which time further progress is limited.



For a more detailed discussion, see Mesulam M-M: Aphasia, Memory Loss, and Other Focal Cerebral Disorders, Chap. 36, p. 176 in HPIM-19.

http://internalmedicinebook.com

56 Sleep Disorders

Disorders of sleep are among the most common problems seen by clinicians. More than one-half of adults experience at least intermittent sleep disturbances, and 50–70 million Americans suffer from a chronic sleep disturbance which can adversely affect daytime functioning as well as physical and mental health.

APPROACH TO THE PATIENT: Sleep Disorders

Pts may complain of (1) difficulty in initiating and maintaining sleep at night (insomnia); (2) excessive daytime sleepiness or tiredness; (3) unusual behaviors during sleep (parasomnias); or (4) circadian rhythm disorders associated with jet lag, shift work, and delayed sleep phase syndrome. Careful history of sleep habits and reports from the sleep partner (e.g., heavy snoring, falling asleep while driving) are a cornerstone of diagnosis. Pts with excessive sleepiness should be advised to avoid driving until effective therapy achieved. Completion of a day-by-day sleep-work-drug log for 1–2 weeks is often helpful. Work and sleep times (including daytime naps and nocturnal awakenings) as well as drug and alcohol use, including caffeine and hypnotics, should be noted each day. The physical examination may show a small airway, large tonsils, or a neurologic or medical disorder that contributes to the complaint. Objective sleep laboratory recording is necessary to evaluate specific disorders such as sleep apnea, periodic limb movements, and narcolepsy.

INSOMNIA

Insomnia is the complaint of poor sleep and usually presents as difficulty initiating or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel it impairs their ability to function well. Affected individuals often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment. *Chronic insomnia*, lasting >3 months, occurs in about 10% of adults. *Acute or short-term insomnia* affects over 30% of adults and is often precipitated by stressful life events. Most insomnia begins in adulthood, but many patients may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual.

All insomnias can be exacerbated and perpetuated by behaviors that are not conducive to initiating or maintaining sleep. *Inadequate sleep hygiene* is characterized by a behavior pattern prior to sleep, and/or a bedroom environment, that is not conducive to sleep. In preference to hypnotic medications, the pt should attempt to avoid stressful activities before bed, reserve the bedroom environment for sleeping, and maintain regular rising times.

Psychophysiologic Insomnia

These pts are preoccupied with a perceived inability to sleep adequately at night. Rigorous attention should be paid to sleep hygiene and correction of counterproductive, arousing behaviors before bedtime. Behavioral therapies are the treatment of choice.

Drugs and Medications

Caffeine is the most common pharmacologic cause of insomnia although a wide range of psychoactive drugs can interfere with sleep, including alcohol and nicotine.

http://internalmedicinebook.com

Numerous medications, including antidepressants, stimulants, and glucocorticoids, can produce insomnia. Severe rebound insomnia can result from the acute withdrawal of hypnotics, especially following the use of short-acting benzodiazepines.

Movement Disorders

Pts with *restless legs syndrome* (RLS) complain of creeping dysesthesias deep within the calves or feet associated with an irresistible urge to move the affected limbs; symptoms are typically worse at night. Iron deficiency and renal failure can cause secondary RLS. One-third of pts have multiple affected family members. Treatment is with dopaminergic drugs (pramipexole 0.25–0.5 mg daily at 7 PM or ropinirole 0.5–4.0 mg daily at 7 PM). *Periodic limb movements of sleep* (PLMS) consist of stereotyped extensions of the great toe and dorsiflexion of the foot recurring every 20–40 s during non-REM sleep. Treatment options include dopaminergic medications.

Other Neurologic Disorders

A variety of neurologic disorders produce sleep disruption through both indirect, nonspecific mechanisms (e.g., neck or back pain) or by impairment of central neural structures involved in the generation and control of sleep itself. Common disorders to consider include *dementia* from any cause, *epilepsy*, *Parkinson's disease*, and *migraine*.

Psychiatric Disorders

Approximately 80% of pts with mental disorders complain of impaired sleep. The underlying diagnosis may be depression, mania, an anxiety disorder, or schizophrenia.

Medical Disorders

In *asthma*, daily variation in airway resistance results in marked increases in asthmatic symptoms at night, especially during sleep. Treatment of asthma with theophylline-based compounds, adrenergic agonists, or glucocorticoids can independently disrupt sleep. Inhaled glucocorticoids that do not disrupt sleep may provide a useful alternative to oral drugs. *Chronic obstructive pulmonary disease*, pain from rheumatologic disorders or neuropathy, *cystic fibrosis*, *hyperthyroidism*, *menopause*, and *gastroesophageal reflux* are other causes.

TREATMENT INSOMNIA

Primary insomnia is a diagnosis of exclusion.

- Treatment of a medical or psychiatric disease that may be contributing should be addressed first.
- Attention should be paid to improving sleep hygiene and avoiding counterproductive behaviors before bedtime (Table 56-1).
- Cognitive behavioral therapy emphasizes understanding the nature of normal sleep, the circadian rhythm, the use of light therapy, and visual imagery to block unwanted thought intrusions.
- Pharmacotherapy reserved for instances when insomnia persists after treatment of contributing factors. Antihistamines are the primary active ingredient in most over-the-counter sleep aids. Benzodiazepine receptor agonists are effective and well tolerated; options include zaleplon (5–20 mg), zolpidem (5–10 mg), triazolam (0.125–0.25 mg), eszopiclone (1–3 mg), and temazepam (15–30 mg). Heterocyclic antidepressants such as trazodone (25–100 mg) are often used due to their lack of abuse potential and lower cost. Limit use to a short period of time for acute insomnia or intermittent use for chronic insomnia.

http://internalmedicinebook.com

TABLE 56-1 METHODS TO IMPROVE SLEEP HYGIENE IN INSOMNIA PATIENTS

Helpful Behaviors	Behaviors to Avoid
Use the bed only for sleep and sex • If you cannot sleep within 20 min, get out of bed and read or do other relaxing activities in dim light before returning to bed	Avoid behaviors that interfere with sleep physiology, including: • Napping, especially after 3:00 PM • Attempting to sleep too early • Caffeine after lunchtime
Make quality sleep a priority • Go to bed and get up at the same time each day • Ensure a restful environment (comfortable bed, bedroom quiet and dark)	In the 2–3 h before bedtime, avoid: • Heavy eating • Smoking or alcohol • Vigorous exercise
Develop a consistent bedtime routine. For example: • Prepare for sleep with 20–30 min of relaxation (e.g., soft music, meditation, yoga, pleasant reading) • Take a warm bath	When trying to fall asleep, avoid: • Solving problems • Thinking about life issues • Reviewing events of the day

DISORDERS OF EXCESSIVE DAYTIME SLEEPINESS

Differentiation of sleepiness from subjective complaints of fatigue may be difficult. Quantification of daytime sleepiness can be performed in a sleep laboratory using a multiple sleep latency test (MSLT), the repeated daytime measurement of sleep latency under standardized conditions. An approach to the evaluation is summarized in Table 56-2.

Sleep Apnea Syndromes

Respiratory dysfunction during sleep is a common cause of excessive daytime sleepiness and/or disturbed nocturnal sleep, affecting an estimated 24% of middle-aged men and 9% of middle-aged women. Episodes may be due to occlusion of the airway (*obstructive sleep apnea*), absence of respiratory effort (*central sleep apnea*), or a combination of these factors (*mixed sleep apnea*). Obstruction is exacerbated by obesity, supine posture, sedatives (especially alcohol), nasal obstruction, and hypothyroidism. Sleep apnea is particularly prevalent in overweight men and in the elderly and is undiagnosed in most affected individuals. Treatment consists of correction of the above factors, positive airway pressure devices, oral appliances, and sometimes surgery (Chap. 137).

Narcolepsy

A disorder of excessive daytime sleepiness and intrusion of REM-related sleep phenomena into wakefulness (cataplexy, hypnagogic hallucinations, and sleep paralysis). *Cataplexy*, the abrupt loss of muscle tone in arms, legs, or face, is precipitated by emotional stimuli such as laughter or sadness. Symptoms of narcolepsy typically begin in the second decade. The prevalence is 1 in 2000. Narcolepsy has a genetic basis; almost all narcoleptics with cataplexy are positive for HLA DQB1*0602. Hypothalamic neurons containing the neuropeptide hypocretin (orexin) regulate the sleep/wake cycle and loss of these cells, possibly due to autoimmunity, has been implicated in narcolepsy. Diagnosis is made with sleep studies confirming a short daytime sleep latency and a rapid transition to REM sleep.

http://internalmedicinebook.com

TABLE 56-2 EVALUATION OF THE PATIENT WITH EXCESSIVE DAYTIME SLEEPINESS

Findings on History and Physical Examination	Diagnostic Evaluation	Diagnosis	Therapy
Difficulty waking in the morning, rebound sleep on weekends, and vacations with improvement in sleepiness	Sleep log	Insufficient sleep	Sleep education and behavioral modification to increase amount of sleep
Obesity, snoring, hypertension	Polysomnogram	Obstructive sleep apnea (Chap. 137)	Continuous positive airway pressure; upper airway surgery (e.g., uvulopalatopharyngoplasty); dental appliance; weight loss
Cataplexy, hypnogogic hallucinations, sleep paralysis	Polysomnogram and multiple sleep latency test	Narcolepsy	Stimulants (e.g., modafinil, methylphenidate); REM sleep-suppressing antidepressants (e.g., venlafaxine); sodium oxybate
Restless legs, kicking movements during sleep	Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure)	Restless legs syndrome with or without periodic limb movements	Treatment of predisposing condition if possible; dopamine agonists (e.g., pramipexole, ropinirole)
Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson's disease, and other neurodegenerative disorders, hypothyroidism, encephalopathy	Thorough medical history and examination including detailed neurologic examination	Sleepiness due to a drug or medical condition	Change medications, treat underlying condition, consider stimulants

TREATMENT NARCOLEPSY

- Somnolence is treated with modafinil (200–400 mg/d given as a single dose each morning).
- Older stimulants such as methylphenidate (10–20 mg bid) or dextroamphetamine (10 mg bid) are alternatives, particularly in refractory pts.
- Cataplexy, hypnagogic hallucinations, and sleep paralysis respond to the tricyclic antidepressants protriptyline (10–40 mg/d) and clomipramine (25–50 mg/d)

http://internalmedicinebook.com

and to fluoxetine (10–20 mg each morning) and venlafaxine (37.5–150 mg each morning). Alternatively, sodium oxybate given at bedtime, and 3–4 h later, is effective in reducing daytime cataplectic episodes.

- Adequate nocturnal sleep time and the use of short naps are other useful preventative measures.

CIRCADIAN RHYTHM SLEEP DISORDERS

Insomnia or hypersomnia may occur in disorders of sleep timing rather than sleep generation. Such conditions may be (1) organic—due to a defect in the circadian pacemaker or its input from entraining stimuli, or (2) environmental—due to a disruption of exposure to entraining stimuli (light/dark cycle). Examples of the latter include jet-lag disorder and shift work. Shift work sleepiness can be treated with modafinil (200 mg) or armodafinil (150 mg) taken 30–60 min before the start of each night shift as well as properly timed exposure to bright light. Safety programs should promote education about sleep and increase awareness of hazards associated with night work.

Delayed sleep-wake phase syndrome is characterized by late sleep onset and awakening with otherwise normal sleep architecture. Bright-light phototherapy in the morning hours or melatonin therapy during the evening hours may be effective.

Advanced sleep-wake phase syndrome moves sleep onset to the early evening hours with early morning awakening. These pts may benefit from bright-light phototherapy during the evening hours. Some autosomal dominant cases result from mutations in a gene (*PER2*) involved in regulation of the circadian clock.

For a more detailed discussion, see Czeisler CA, Scammell TE, Saper CB: Sleep Disorders, Chap. 38, p. 184, in HPIM-19.

57 Dysuria and Bladder Pain

DYSURIA

Dysuria, or pain that occurs during urination, is commonly perceived as burning or stinging in the urethra and is a symptom of several syndromes that can be distinguished by the presence or absence of other symptoms.

Epidemiology

Approximately 50% of women experience dysuria at some time in their lives; ~20% report having had dysuria within the past year. Dysuria is less common among men.

Clinical manifestations

The underlying syndromes that cause dysuria differ somewhat between men and women.

http://internalmedicinebook.com

- In women, most dysuria syndromes can be categorized as either bacterial cystitis or lower genital tract infections (e.g., vaginitis, urethritis, sexually transmitted infections [STIs]) (see Chaps. 83 and 144). The presence of urinary frequency, urinary urgency, suprapubic pain, and/or hematuria is more typical of bacterial cystitis than of STIs.
- In men, dysuria is often due to STIs or involvement of the prostate (e.g., acute or chronic bacterial prostatitis) (see Chaps. 83 and 144). In addition, dysuria and other symptoms of cystitis can occur in the setting of significant benign prostatic hyperplasia that leads to urinary stasis with an accompanying bacterial infection.
- In both sexes, dysuria can result from noninfectious disorders. Noninfectious causes of acute dysuria include lower urinary tract stones, trauma, and urethral exposure to topical chemicals. Chronic dysuria may be attributable to lower urinary tract cancers, certain medications, Behçet's syndrome, or interstitial cystitis/bladder pain syndrome (see Chap. 144).

Diagnosis

Among women presenting with dysuria, the probability of bacterial cystitis is ~50%. This figure rises to >90% if four criteria are fulfilled: (1) dysuria and (2) frequency without either (3) vaginal discharge or (4) irritation.

- Healthy, nonpregnant women who meet the above criteria can be diagnosed with uncomplicated bacterial cystitis; other women with dysuria should be further evaluated by urine dipstick, urine culture, and a pelvic examination.
- Men should be evaluated with urinalysis, urine culture, and prostate examination.

Treatment

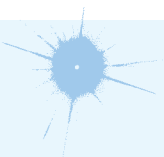
Once the underlying cause of dysuria is identified, it should be treated appropriately, as outlined in other chapters.

BLADDER PAIN

Pts perceive pain as coming from the urinary bladder if it is suprapubic in location, alters with bladder filling or emptying, and/or is associated with urinary symptoms such as urgency and frequency.

- Bladder pain occurring acutely (i.e., lasting ≤2 days) is helpful in distinguishing bacterial cystitis from lower genital tract infections.

Chronic or recurrent bladder pain may accompany lower urinary tract stones, pelvic cancers, urethral diverticulum, cystitis induced by radiation or certain medications, tuberculous cystitis, bladder neck obstruction, neurogenic bladder, urogenital prolapse, or benign prostatic hyperplasia. The diagnosis of interstitial cystitis/bladder pain syndrome should be considered in pts who do not have one of these conditions (see Chap. 144).



For a more detailed discussion, see Warren JW: Dysuria, Bladder Pain, and the Interstitial Cystitis/Bladder Pain Syndrome, Chap. 60e; and Gupta K, Trautner BW: Urinary Tract Infections, Pyelonephritis, and Prostatitis, Chap. 162, p. 861, in HPIM-19.

http://internalmedicinebook.com

58 Sore Throat, Earache, and Upper Respiratory Symptoms

- URIs are among the leading causes of lost time from work or school.
- Distinguishing pts with primary viral URI from those with primary bacterial URI is difficult since the signs and symptoms are the same.
- URIs are often treated with antibiotics even though bacteria cause only 25% of cases. Inappropriate prescribing of antibiotics for URIs is a leading cause of antibiotic resistance in common community-acquired pathogens such as *Streptococcus pneumoniae*.

NONSPECIFIC URIs

- **Definition:** Nonspecific URIs (the "common cold") have no prominent localizing features.
- **Etiology:** A wide variety of viruses (e.g., rhinoviruses, coronaviruses, parainfluenza viruses, influenza viruses, adenoviruses) can cause nonspecific URIs.
- **Clinical manifestations:** an acute, mild, self-limited catarrhal syndrome, typically characterized by rhinorrhea, nasal congestion, cough, and sore throat
  - Hoarseness, malaise, sneezing, and fever are more variable.
  - The median duration of symptoms is ~1 week (range, 2–10 days).
  - Secondary bacterial infections complicate 0.5–2% of colds and are associated with a prolonged course and/or increased severity of illness, often with localization of signs and symptoms. Purulent nasal and throat secretions are poor predictors of bacterial infection.
- **Treatment:** Symptom-based treatment (e.g., with decongestants, NSAIDs) is typically all that is required. Antibiotics are not indicated.

SINUS INFECTIONS

- Rhinosinusitis is an inflammatory condition most commonly involving the maxillary sinus; next, in order of frequency, are the ethmoid, frontal, and sphenoid sinuses.
- Sinusitis accounts for millions of visits to primary care physicians each year and is the fifth most common diagnosis for which antibiotics are prescribed.

ACUTE SINUSITIS

- **Definition:** sinusitis of <4 weeks' duration
- **Etiology:** Infectious and noninfectious causes lead to sinus ostial obstruction and retention of mucus.
  - Infectious causes include viruses (e.g., rhinovirus, parainfluenza virus, influenza virus) and bacteria (e.g., *S. pneumoniae*, nontypable *Haemophilus influenzae*, and [in children] *Moraxella catarrhalis*).
    - In immunocompromised pts, fungi (e.g., *Rhizopus*, *Mucor*, and occasionally *Aspergillus*) can be involved.

http://internalmedicinebook.com

  - Nosocomial cases are often polymicrobial and involve *Staphylococcus aureus* and gram-negative bacilli.
  - Noninfectious causes include allergic rhinitis, barotrauma, and exposure to chemical irritants.
- **Clinical manifestations:** Common manifestations include nasal drainage and congestion, facial pain or pressure, and headache.
  - Tooth pain and halitosis can be associated with bacterial sinusitis.
  - Pain localizes to the involved sinus and is often worse when the pt bends over or is supine.
  - Advanced frontal sinusitis can present as "Pott's puffy tumor": swelling and pitting edema over the frontal bone from a communicating subperiosteal abscess.
  - Life-threatening complications include meningitis, epidural abscess, and brain abscess.
- **Diagnosis:** It is difficult to distinguish viral from bacterial sinusitis clinically, although viral cases greatly outnumber bacterial cases.
  - Only 40–50% of pts with symptoms of >10 days' duration, purulent nasal drainage, nasal obstruction, and facial pain have bacterial sinusitis.
  - If fungal sinusitis is a consideration, involved areas should be biopsied.
  - Except in nosocomial cases, sinus CT or radiography is not recommended for acute sinusitis. Nosocomial sinusitis should be confirmed by sinus CT, with sinus aspirates sent for culture and susceptibility testing (ideally before antimicrobial treatment is initiated).

TREATMENT ACUTE SINUSITIS

- Most pts improve without antibiotic treatment.
- For pts with mild to moderate symptoms, treatment should focus on symptom relief and facilitation of sinus drainage (e.g., oral and topical decongestants, nasal saline lavage).
- Antibiotics should be given to pts with severe disease at presentation and considered for pts without improvement after 10 days.
  - See Table 58-1 for recommended regimens for adults.
  - For pts who do not respond to initial antimicrobial treatment, consultation with an otolaryngologist about possible sinus aspiration and/or lavage should be considered.
- Surgery should be considered for pts with severe disease, intracranial complications, or invasive fungal sinusitis.

CHRONIC SINUSITIS

- **Definition:** sinusitis of >12 weeks' duration
- **Etiology:** commonly associated with bacterial or fungal infection
- **Chronic bacterial sinusitis:** Impaired mucociliary clearance leads to repeated infections as opposed to one persistent infection.
  - Pts have constant nasal congestion and sinus pressure, with periods of increased severity.
  - Sinus CT can define the extent of disease, detect an underlying anatomic defect or obstructing process, and assess response to treatment.
  - Endoscopy-derived tissue samples for histology and culture should be obtained to guide treatment.
  - Repeated antibiotic courses are required, often for 3–4 weeks at a time. Adjunctive measures include intranasal administration of glucocorticoids, sinus irrigation, and surgical evaluation.

http://internalmedicinebook.com

TABLE 58-1 GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE SINUSITIS IN ADULTS

Diagnostic Criteria	Treatment Recommendations[a]
Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d *or* Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain	*Initial therapy:* Amoxicillin, 500 mg PO tid; *or* Amoxicillin/clavulanate, 500/125 mg PO tid or 875/125 mg PO bid[b] *Penicillin allergy:* Doxycycline, 100 mg PO bid; *or* Clindamycin, 300 mg PO tid *Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:* Amoxicillin/clavulanate (extended release), 2000/125 mg PO bid; *or* An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily) *Recent treatment failure:* Amoxicillin/clavulanate (extended release), 2000 mg PO bid; *or* An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)

[a]The duration of therapy is generally 7–10 days (with consideration of a 5-day course), with appropriate follow-up. Severe disease may warrant IV antibiotics and consideration of hospital admission.
[b]Although the evidence is not as strong, amoxicillin/clavulanate may be considered for initial use, particularly if local rates of penicillin resistance or β-lactamase production are high.

- **Chronic fungal sinusitis:** a noninvasive disease in immunocompetent hosts, typically due to *Aspergillus* and dematiaceous molds. Recurrence is common.
  - Mild, indolent disease is usually cured with endoscopic surgery and without antifungal agents.
  - Unilateral disease with a mycetoma (fungus ball) in the sinus is treated with surgery and—if bony erosion has occurred—antifungal agents.
  - Allergic fungal sinusitis, seen in pts with nasal polyps and asthma, presents as pansinusitis and thick, eosinophil-laden mucus with the consistency of peanut butter.

INFECTIONS OF THE EAR AND MASTOID

EXTERNAL EAR INFECTIONS

In the absence of local or regional adenopathy, consider noninfectious causes of inflammation, among which trauma, insect bites, and environmental exposures are more commonly implicated than are autoimmune diseases (e.g., lupus) or vasculitides (e.g., granulomatosis with polyangiitis).

- *Auricular cellulitis*: Tenderness, erythema, swelling, and warmth of the external ear, particularly the lobule, follow minor trauma. Treat with warm compresses and antibiotics active against *S. aureus* and streptococci (e.g., cephalexin, dicloxacillin).

http://internalmedicinebook.com

- *Perichondritis*: Infection of the perichondrium of the auricular cartilage follows local trauma (e.g., ear piercing). The infection may closely resemble auricular cellulitis, although the lobule is less often involved in perichondritis.
  - Treatment requires systemic antibiotics active against the most common etiologic agents, *Pseudomonas aeruginosa* and *S. aureus*, and typically consists of an antipseudomonal penicillin (e.g., piperacillin) or a penicillinase-resistant penicillin (e.g., nafcillin) plus an antipseudomonal quinolone (e.g., ciprofloxacin). Surgical drainage may be needed; resolution can take weeks.
  - If perichondritis fails to respond to adequate treatment, consider noninfectious inflammatory etiologies (e.g., relapsing polychondritis).
- *Otitis externa*: a collection of diseases involving primarily the auditory meatus and resulting from a combination of heat and retained moisture, with desquamation and maceration of the epithelium of the outer ear canal. All forms are predominantly bacterial in origin; *P. aeruginosa* and *S. aureus* are the most common pathogens.
  - *Acute localized otitis externa*: furunculosis in the outer third of the ear canal, usually due to *S. aureus*. Treatment consists of an oral antistaphylococcal penicillin (e.g., dicloxacillin, cephalexin), with surgical drainage in cases of abscess formation.
  - *Acute diffuse otitis externa* (swimmer's ear): infection in macerated, irritated canals that is typically due to *P. aeruginosa* and is characterized by severe pain, erythema, and swelling of the canal and white clumpy discharge from the ear. Treatment includes cleansing of the canal to remove debris and use of topical agents (e.g., hypertonic saline, mixtures of alcohol and acetic acid, antibiotic preparations combining neomycin and polymyxin), with or without glucocorticoids to reduce inflammation.
  - *Chronic otitis externa:* erythematous, scaling, pruritic dermatitis that usually arises from persistent drainage from a chronic middle-ear infection, other causes of repeated irritation, or rare chronic infections such as tuberculosis or leprosy. Treatment consists of identifying and eliminating the offending process; successful resolution is frequently difficult.
  - *Malignant or necrotizing otitis externa*: a slowly progressive infection characterized by purulent otorrhea, an erythematous swollen ear and external canal, and severe otalgia out of proportion to exam findings, with granulation tissue present in the posteroinferior wall of the canal, near the junction of bone and cartilage
    - This potentially life-threatening disease, which occurs primarily in elderly diabetic or immunocompromised pts, can involve the base of the skull, meninges, cranial nerves, and brain.
    - *P. aeruginosa* is the most common etiologic agent, but other gram-negative bacilli, *S. aureus*, *Staphylococcus epidermidis*, *Actinomyces,* and *Aspergillus* have been reported.
    - A biopsy specimen of granulation tissue (or deeper tissues) should be obtained for culture.
    - Treatment involves systemic antibiotics for 6–8 weeks and consists of antipseudomonal agents (e.g., piperacillin, ceftazidime) with an aminoglycoside or a fluoroquinolone; antibiotic drops active against *Pseudomonas*, combined with glucocorticoids, are used as adjunctive treatment.
    - Recurs in up to 20% of cases. Aggressive glycemic control in diabetic pts helps with treatment and prevention of recurrence.

MIDDLE-EAR INFECTIONS

Eustachian tube dysfunction, often in association with URIs, causes inflammation with a sterile transudate. Viral or bacterial superinfection often occurs.

- ***Acute otitis media:*** typically follows a viral URI, which can directly cause viral otitis media or, more commonly, predispose to bacterial otitis media

http://internalmedicinebook.com

- **Etiology:** *S. pneumoniae* is isolated in up to 35% of cases; nontypable *H. influenzae* and *M. catarrhalis* are other common causes of bacterial otitis media. Concern is increasing about community-acquired methicillin-resistant *S. aureus* (MRSA) as an emerging etiologic agent. Viruses (e.g., RSV, influenza virus, rhinovirus, enterovirus) have been recovered either alone or with bacteria in up to 40% of cases.
- **Clinical manifestations:** The tympanic membrane is immobile, erythematous, bulging, or retracted and can perforate spontaneously.
  - Other findings may include otalgia, otorrhea, decreased hearing, and fever.
  - In isolation, erythema of the tympanic membrane is nonspecific as it is common in association with inflammation of the upper respiratory mucosa.
- **Treatment:** Indications for antibiotic treatment and regimens are listed in Table 58-2; antibiotic prophylaxis and surgical interventions offer little benefit in recurrent acute otitis media.

- ***Serous otitis media*:** Also known as otitis media with effusion, this condition can persist for weeks (e.g., acute effusions) or months (e.g., after an episode of acute otitis media) without signs of infection and is associated with significant hearing loss in the affected ear.
  - The majority of cases resolve spontaneously within 3 months without antibiotic treatment.
  - Antibiotic treatment or myringotomy with tympanostomy tubes is reserved for pts with bilateral effusions that have persisted for at least 3 months and are associated with significant bilateral hearing loss.
- ***Chronic otitis media*:** persistent or recurrent purulent otorrhea with tympanic membrane perforation, usually associated with conductive hearing loss
  - Inactive disease, characterized by a central perforation of the tympanic membrane, is treated with repeated courses of topical antibiotic drops during periods of drainage.
  - Active disease involves formation of a cholesteatoma that may enlarge and ultimately lead to erosion of bone, meningitis, and brain abscess; surgical treatment is required.
- ***Mastoiditis*:** accumulation of purulent exudate in the mastoid air cells that erodes surrounding bones and causes abscess-like cavities
  - Pts have pain, erythema, and mastoid process swelling causing displacement of the pinna along with the signs and symptoms of otitis media.
  - Rare complications include subperiosteal abscess, deep neck abscess, and septic thrombosis of the lateral sinus.
  - Broad-spectrum empirical IV antibiotic regimens targeting *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* can be narrowed once culture results are available; mastoidectomy is reserved for complicated cases or pts in whom medical management fails.

INFECTIONS OF THE PHARYNX AND ORAL CAVITY

Sore throat is the most common presenting symptom and one of the most common reasons for ambulatory care visits by adults and children.

ACUTE PHARYNGITIS

- **Etiology:** Respiratory viruses are the most common identifiable cause, although ~30% of cases have no etiology identified.
  - Viruses: Rhinoviruses and coronaviruses cause ~20% and ~5% of cases, respectively; influenza and parainfluenza viruses are seasonal causes; HSV, coxsackievirus, CMV, EBV, and HIV are other important viral causes.
  - Bacteria: Group A *Streptococcus* (GAS) accounts for 5–15% of adult cases. *Fusobacterium necrophorum*, which can cause Lemierre's disease, is increasingly identified as a cause of pharyngitis in adolescents and is isolated nearly as often as

http://internalmedicinebook.com

TABLE 58-2 GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE OTITIS MEDIA

Illness Severity	Diagnostic Criteria	Treatment Recommendations
Mild to moderate	>2 yrs *or* 6 mo to 2 yrs without middle-ear effusion	*Observation alone* (deferring antibiotic therapy for 48–72 h and limiting management to symptom relief)
	<6 mo; *or* 6 mo to 2 yrs with middle-ear effusion (fluid in the middle ear, evidenced by decreased TM mobility, air/fluid level behind TM, bulging TM, purulent otorrhea) *and* acute onset of signs and symptoms of middle-ear inflammation, including fever, otalgia, decreased hearing, tinnitus, vertigo, erythematous TM; *or* >2 yrs with bilateral disease, TM perforation, high fever, immunocompromise, emesis	*Initial therapy*[a] Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); *or* Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses (bid); *or* Cefuroxime, 30 mg/kg qd PO in divided doses (bid); *or* Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b]*:* Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or* Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or* Clindamycin, 30–40 mg/kg qd PO in divided doses (tid)
Severe	As above, with temperature ≥39.0°C (102°F); *or* Moderate to severe otalgia	*Initial therapy*[a] Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); *or* Ceftriaxone, 50 mg/kg IV/IM qd for 3 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b] Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; *or* Clindamycin, 30–40 mg/kg qd PO in divided doses (tid); *or* Consider tympanocentesis with culture

[a]Duration (unless otherwise specified): 10 days for pts <6 years old and pts with severe disease; 5–7 days (with consideration of observation only in previously healthy individuals with mild disease) for pts ≥6 years old.
[b]Failure to improve and/or clinical worsening after 48–72 h of observation or treatment.
Abbreviation: TM, tympanic membrane.
Source: American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media, 2004.

http://internalmedicinebook.com

GAS. Rare bacterial causes that should be considered in appropriate exposure groups include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Yersinia enterocolitica*, and *Treponema pallidum*.

- **Clinical manifestations:** Specific signs and symptoms sometimes suggest that one etiology is more likely than another.
  - Respiratory viruses: Symptoms usually are not severe and are associated with coryza without fever, tender cervical lymphadenopathy, or pharyngeal exudates.
  - Influenza virus and adenovirus: evidenced by severe exudative pharyngitis with fever, myalgias, and—for adenovirus—conjunctivitis
  - HSV: presents as pharyngeal inflammation and exudates with vesicles and ulcers on the palate
  - Coxsackievirus (herpangina): characterized by small vesicles on the soft palate and uvula that rupture to form shallow white ulcers
  - EBV and CMV: present as exudative pharyngitis in association with other signs of infectious mononucleosis
  - HIV: associated with fever, acute pharyngitis, myalgias, malaise, and sometimes a maculopapular rash
  - Streptococci: Presentation ranges from mild disease to profound pharyngeal pain, fever, chills, abdominal pain, and a hyperemic pharyngeal membrane with tonsillar hypertrophy and exudates; coryzal symptoms are absent.
  - Other bacteria: often present as exudative pharyngitis without other specific findings
- **Diagnosis:** The primary goal of diagnostic testing is to identify cases of GAS pharyngitis.
  - Rapid antigen-detection tests for GAS offer good specificity (>90%) but variable sensitivity (65–90%); throat cultures are recommended for children, but not adults, in the setting of negative rapid testing.
  - Samples for specific cultures for other bacterial and viral causes should be obtained if these diagnoses are suspected.
  - If HIV is being considered, testing for HIV RNA should be performed.
- **Treatment:** Antibiotic treatment for GAS infection (penicillin VK, 500 mg PO tid × 10 days; or benzathine penicillin G, 1.2 million units IM × 1 dose) is recommended for pts with a positive rapid antigen detection test or throat swab culture; treatment modestly reduces symptom duration and prevents the development of rheumatic fever.
  - Long-term penicillin prophylaxis (benzathine penicillin G, 1.2 million units IM every 3–4 weeks; or penicillin VK, 250 mg PO bid) is indicated for pts at risk of recurrent rheumatic fever.
  - Symptom-based treatment of viral pharyngitis is generally sufficient.
  - Specific antiviral treatment (e.g., oseltamivir, acyclovir) may be helpful in selected cases of influenza and HSV infection.

ORAL INFECTIONS

Oral-labial herpesvirus infections and oropharyngeal candidiasis are discussed in Chaps. 99 and 106, respectively.

INFECTIONS OF THE LARYNX AND EPIGLOTTIS

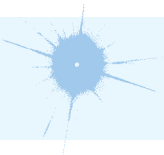
- *Laryngitis*: Acute laryngitis is a common syndrome caused by nearly all the major respiratory viruses and by some bacteria (e.g., GAS, *C. diphtheriae*, and *M. catarrhalis*). Chronic cases of infectious laryngitis are much less common in developed countries than in low-income countries and are caused by *Mycobacterium tuberculosis*, endemic fungi (e.g., *Histoplasma*, *Blastomyces*, *Coccidioides*), and *Cryptococcus*.
  - Pts are hoarse, exhibit reduced vocal pitch or aphonia, and have coryzal symptoms.

http://internalmedicinebook.com

  - Treatment of acute laryngitis consists of humidification, voice rest, and—if GAS is cultured—antibiotic administration. Treatment of chronic laryngitis depends on the pathogen, whose identification usually requires biopsy with culture.
- *Epiglottitis*: acute, rapidly progressive cellulitis of the epiglottis and adjacent structures that can result in complete—and sometimes fatal—airway obstruction
  - Epiglottitis is caused by GAS, *S. pneumoniae*, *Haemophilus parainfluenzae*, and *S. aureus*; pediatric cases due to *H. influenzae* type b are now rare because of vaccination.
  - Symptoms include fever, severe sore throat, and systemic toxicity, and pts often drool while sitting forward. Examination may reveal respiratory distress, inspiratory stridor, and chest wall retractions.
  - Direct visualization in the examination room (i.e., with a tongue blade) should not be performed, given the risk of complete airway obstruction. Direct fiberoptic laryngoscopy in a controlled environment (e.g., an operating room) may be performed for diagnosis, procurement of specimens for culture, and placement of an endotracheal tube.
  - Treatment focuses on airway protection. After blood and epiglottis samples are obtained for cultures, IV antibiotics active against *H. influenzae* (e.g., ampicillin/sulbactam or a second- or third-generation cephalosporin) should be given for 7–10 days.

INFECTIONS OF DEEP NECK STRUCTURES

These infections, which include Ludwig's angina, Lemierre's syndrome, and retropharyngeal abscess, are discussed in Chap. 92.



For a more detailed discussion, see Rubin MA, Ford LC, Gonzales R: Sore Throat, Earache, and Upper Respiratory Symptoms, Chap. 44, p. 225, in HPIM-19.

http://internalmedicinebook.com

59 General Examination of the Skin

As dermatologic evaluation relies heavily on the objective cutaneous appearance, physical examination is often performed prior to taking a complete history in pts presenting with a skin problem. A differential diagnosis can usually be generated on the basis of a thorough examination with precise descriptions of the skin lesion(s) and narrowed with pertinent facts from the history. Laboratory or diagnostic procedures are then used, when appropriate, to clarify the diagnosis.

PHYSICAL EXAMINATION

Examination of skin should take place in a well-illuminated room with pt completely disrobed. Helpful ancillary equipment includes a hand lens and a pocket flashlight to provide peripheral illumination of lesions. An ideal examination includes evaluation of the skin, hair, nails, and mucous membranes. The examination often begins with an assessment of the entire skin viewed at a distance, which is then narrowed down to focus on the individual lesions.

DISTRIBUTION

As illustrated in Fig. 59-1, the distribution of skin lesions can provide valuable clues to the identification of the disorder: generalized (systemic diseases); sun-exposed (SLE, photoallergic, phototoxic, polymorphous light eruption, porphyria cutanea tarda); dermatomal (herpes zoster); extensor surfaces (elbows and knees in psoriasis); flexural surfaces (antecubital and popliteal fossae in atopic dermatitis).

ARRANGEMENT AND SHAPE

Can describe individual or multiple lesions: *Linear* (contact dermatitis such as poison ivy); *annular*—"ring-shaped" lesion (erythema chronicum migrans, erythema annulare centrificum, tinea corporis); *iris* or *target lesion*—two or three concentric circles of differing hue (erythema multiforme); *nummular*—"coin-shaped" (nummular eczema); *morbilliform*—"measles-like" with small confluent papules coalescing into unusual shapes (measles, drug eruption); *herpetiform*—grouped vesicles, papules, or erosions (herpes simplex).

PRIMARY LESIONS

Cutaneous changes caused directly by disease process (Table 59-1).

SECONDARY LESIONS

Changes in area of primary pathology often due to secondary events, e.g., scratching, secondary infection, bleeding (Table 59-2).

OTHER DESCRIPTIVE TERMS

Color, e.g., violaceous, erythematous; physical characteristics, e.g., warm, tender; sharpness of edge, surface contour—flat-topped, pedunculated (on a stalk), verrucous (wartlike), umbilicated (containing a central depression).

http://internalmedicinebook.com

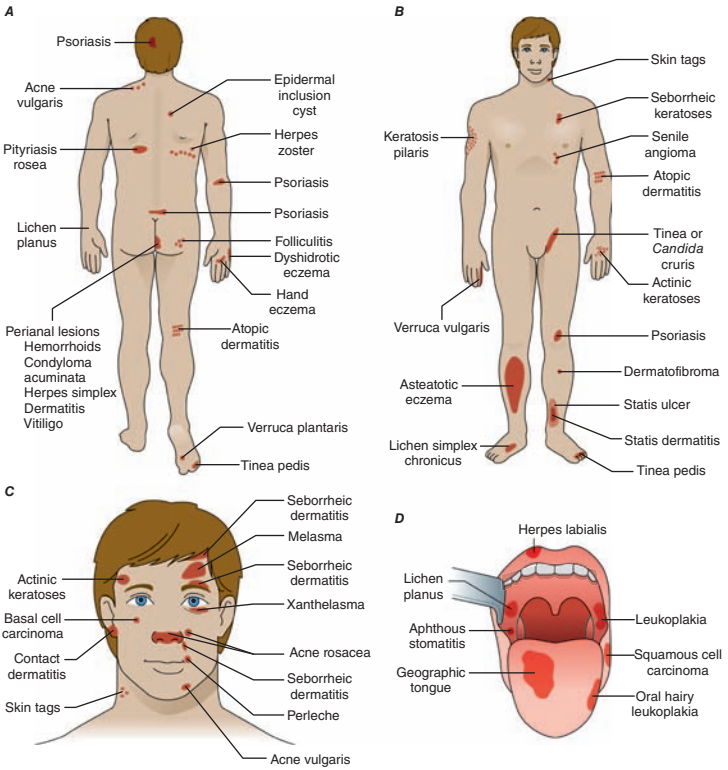


FIGURE 59-1 The distribution of some common dermatologic diseases and lesions.

HISTORY

A complete history should be obtained, with special attention being paid to the following points:

1. Evolution of the lesion—site of onset, manner in which eruption progressed or spread, duration, periods of resolution or improvement in chronic eruptions
2. Symptoms associated with the eruption—itching, burning, pain, numbness; what has relieved symptoms; time of day when symptoms are most severe
3. Current or recent medications—both prescription and over-the-counter
4. Associated systemic symptoms (e.g., malaise, fatigue, arthralgias)
5. Ongoing or previous illnesses
6. History of allergies
7. Presence of photosensitivity
8. Review of systems
9. Family history
10. Social, sexual, or travel history

ADDITIONAL DIAGNOSTIC PROCEDURES

SKIN BIOPSY

Minor surgical procedure. Choice of site very important.

http://internalmedicinebook.com

TABLE 59-1 DESCRIPTION OF PRIMARY SKIN LESIONS

Macule: A flat, colored lesion, <2 cm in diameter, not raised above the surface of the surrounding skin. A "freckle," or ephelid, is a prototype pigmented macule.

Patch: A large (>2 cm) flat lesion with a color different from the surrounding skin. This differs from a macule only in size.

Papule: A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and hence palpable (e.g., a closed comedone, or whitehead, in acne).

Nodule: A larger (0.5–5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a dermal nevomelanocytic nevus).

Tumor: A solid, raised growth >5 cm in diameter.

Plaque: A large (>1 cm), flat-topped, raised lesion; edges may either be distinct (e.g., in psoriasis) or gradually blend with surrounding skin (e.g., in eczematous dermatitis).

Vesicle: A small, fluid-filled lesion, <0.5 cm in diameter, raised above the plane of surrounding skin. Fluid is often visible, and the lesions are translucent [e.g., vesicles in allergic contact dermatitis caused by *Toxicodendron* (poison ivy)].

Pustule: A vesicle filled with leukocytes. ***Note:*** The presence of pustules does not necessarily signify the existence of an infection.

Bulla: A fluid-filled, raised, often translucent lesion >0.5 cm in diameter.

Wheal: A raised, erythematous, edematous papule or plaque, usually representing short-lived vasodilatation and vasopermeability.

Telangiectasia: A dilated, superficial blood vessel.

POTASSIUM HYDROXIDE PREPARATION

Useful for detection of dermatophyte or yeast. Scale is collected from advancing edge of a scaling lesion by gently scraping with side of a microscope slide or a scalpel blade. Nail lesions are best sampled by trimming back nail and scraping subungual debris. A drop of 10–20% potassium hydroxide is added to slide, and coverslip is applied. The slide may be gently heated and examined under microscope.

TABLE 59-2 DESCRIPTION OF SECONDARY SKIN LESIONS

Lichenification: A distinctive thickening of the skin that is characterized by accentuated skin-fold markings.

Scale: Excessive accumulation of stratum corneum.

Crust: Dried exudate of body fluids that may be either yellow (i.e., serous crust) or red (i.e., hemorrhagic crust).

Erosion: Loss of epidermis without an associated loss of dermis.

Ulcer: Loss of epidermis and at least a portion of the underlying dermis.

Excoriation: Linear, angular erosions that may be covered by crust and are caused by scratching.

Atrophy: An acquired loss of substance. In the skin, this may appear as a depression with intact epidermis (i.e., loss of dermal or subcutaneous tissue) or as sites of shiny, delicate, wrinkled lesions (i.e., epidermal atrophy).

Scar: A change in the skin secondary to trauma or inflammation. Sites may be erythematous, hypopigmented, or hyperpigmented depending on their age or character. Sites on hair-bearing areas may be characterized by destruction of hair follicles.

http://internalmedicinebook.com

This technique can be utilized to identify hyphae in dermatophyte infections, pseudohyphae and budding yeast in *Candida* infections, and "spaghetti and meatballs" yeast forms in tinea versicolor.

TZANCK PREPARATION

Useful for determining presence of herpes viruses (herpes simplex virus or herpes zoster virus). Optimal lesion to sample is an early vesicle. Lesion is gently unroofed with no. 15 scalpel blade, and base of vesicle is gently scraped with belly of blade (keep blade perpendicular to skin surface to prevent laceration). Scrapings are transferred to slide and stained with Wright's or Giemsa stain. A positive preparation has multinucleated giant cells. Culture or immunofluorescence testing must be performed to identify the specific virus.

DIASCOPY

Assesses whether a lesion blanches with pressure. Done by pressing a magnifying lens or microscope slide on lesion and observing changes in vascularity. For example, hemangiomas will usually blanch; purpuric lesions will not.

WOOD'S LIGHT EXAMINATION

Useful for detecting bacterial or fungal infection or accentuating features of some skin lesions.

PATCH TESTS

To document cutaneous sensitivity to specific antigen.

For a more detailed discussion, see Lawley TJ, Yancey KB: Approach to the Patient with a Skin Disorder, Chap. 70, p. 339, in HPIM-19.

60 Common Skin Conditions

PAPULOSQUAMOUS DISORDERS

Disorders exhibiting papules and scale.

PSORIASIS

A chronic, recurrent disorder. Classic lesion is a well-marginated, erythematous plaque with silvery-white surface scale. Distribution includes extensor surfaces (i.e., knees, elbows, and buttocks); may also involve palms and scalp (particularly anterior scalp margin). Associated findings include psoriatic arthritis (**Chap. 161**) and nail changes (onycholysis, pitting or thickening of nail plate with accumulation of subungual debris).

http://internalmedicinebook.com

TREATMENT PSORIASIS

Maintain cutaneous hydration; topical glucocorticoids; topical vitamin D analogue (calcipotriol) and retinoid (tazarotene); UV light (PUVA, when UV used in combination with psoralens); for severe disease methotrexate or cyclosporine; acitretin can also be used but is teratogenic. Ustekinumab (human monoclonal antibody that blocks IL-12 and IL-23) or apremilast (phosphodiesterase 4 inhibitor) can be considered for chronic, moderate to severe plaque psoriasis. Etanercept (dimeric fusion protein: TNF receptor/Fc human IgG1), infliximab, and adalimumab (monoclonal antibodies directed against TNF) are approved for psoriasis and psoriatic arthritis.

PITYRIASIS ROSEA

A self-limited condition lasting 3–8 weeks. Initially, there is a single 2- to 6-cm annular salmon-colored patch (herald patch) with a peripheral rim of scale, followed in days to weeks by a generalized eruption involving the trunk and proximal extremities. Individual lesions are similar to but smaller than the herald patch and are arranged in symmetric fashion with long axis of each individual lesion along skin lines of cleavage. Appearance may be similar to that of secondary syphilis.

TREATMENT PITYRIASIS ROSEA

Disorder is self-limited, so treatment is directed at symptoms; oral antihistamines for pruritus; topical glucocorticoids; UV-B phototherapy in some cases.

LICHEN PLANUS

Disorder of unknown cause; can follow administration of certain drugs, chronic graft-versus-host disease, hepatitis C; lesions are pruritic, polygonal, flat-topped, and violaceous. Course is variable, but most pts have spontaneous remissions 6–24 months after onset of disease.

TREATMENT LICHEN PLANUS

Topical glucocorticoids.

ECZEMATOUS DISORDERS

ECZEMA

Eczema, or dermatitis, is a reaction pattern that presents with variable clinical and histologic findings; it is the final common expression for a number of disorders.

ATOPIC DERMATITIS

One aspect of atopic triad of hayfever, asthma, and eczema. Usually an intermittent, chronic, severely pruritic, eczematous dermatitis with scaly erythematous patches, vesiculation, crusting, and fissuring. Lesions are most commonly on flexures, with prominent involvement of antecubital and popliteal fossae; generalized erythroderma in severe cases.

TREATMENT ECZEMA AND ATOPIC DERMATITIS

Avoidance of irritants; cutaneous hydration; topical glucocorticoids; treatment of infected lesions [often with *Staphylococcus aureus* (SA)—consider

http://internalmedicinebook.com

community-acquired methicillin-resistant strains (CA-MRSA)]. Systemic glucocorticoids only for severe exacerbations unresponsive to topical conservative therapy. Topical calcineurin inhibitors have been used for severe disease but may carry toxicity.

ALLERGIC CONTACT DERMATITIS

A delayed hypersensitivity reaction that occurs after cutaneous exposure to an antigenic substance. Lesions occur at site of contact and are vesicular, weeping, crusting; linear arrangement of vesicles is common. Most frequent allergens are resin from plants of the genus *Toxicodendron* (poison ivy, oak, sumac), nickel, rubber, and cosmetics.

TREATMENT ALLERGIC CONTACT DERMATITIS

Avoidance of sensitizing agent; topical glucocorticoids; consideration of systemic glucocorticoids over 2–3 weeks for widespread disease.

IRRITANT CONTACT DERMATITIS

Inflammation of the skin due to direct injury by an exogenous agent. The most common area of involvement is the hands, where dermatitis is initiated or aggravated by chronic exposure to water and detergents. Features may include skin dryness, cracking, erythema, and edema.

TREATMENT IRRITANT CONTACT DERMATITIS

Avoidance of irritants; barriers (use of protective gloves); topical glucocorticoids; treatment of secondary bacterial or dermatophyte infection.

SEBORRHEIC DERMATITIS

A chronic noninfectious process characterized by erythematous patches with greasy yellowish scale. Lesions are generally on scalp, eyebrows, nasolabial folds, axillae, central chest, and posterior auricular area.

TREATMENT SEBORRHEIC DERMATITIS

Nonfluorinated topical glucocorticoids; shampoos containing coal tar, salicylic acid, or selenium sulfide.

INFECTIONS

IMPETIGO

A superficial infection of skin secondary to either *S. aureus* or group A β-hemolytic streptococci. The primary lesion is a superficial pustule that ruptures and forms a "honey-colored" crust. Tense bullae are associated with *S. aureus* infections (bullous impetigo). Lesions may occur anywhere but commonly involve the face. Impetigo and *furunculosis* (painful erythematous nodule, or boil) have gained prominence because of increasing incidence of CA-MRSA.

http://internalmedicinebook.com

TREATMENT IMPETIGO

Gentle debridement of adherent crusts with soaks and topical antibiotics; appropriate oral antibiotics depending on organism.

ERYSIPELAS

Superficial cellulitis, most commonly on face, characterized by a bright red, sharply demarcated, intensely painful, warm plaque. Because of superficial location of infection and associated edema, surface of plaque may exhibit a *peau d'orange* (orange peel) appearance. Most commonly due to infection with group A β-hemolytic streptococci, occurring at sites of trauma or other breaks in skin.

TREATMENT ERYSIPELAS

Appropriate antibiotics depending on organism.

HERPES SIMPLEX (SEE ALSO CHAP. 99)

Recurrent eruption characterized by grouped vesicles on an erythematous base that progress to erosions; often secondarily infected with staphylococci or streptococci. Infections frequently involve mucocutaneous surfaces around the oral cavity, genitals, or anus. Can also cause severe visceral disease including esophagitis, pneumonitis, encephalitis, and disseminated herpes simplex virus infection. Tzanck preparation of an unroofed early vesicle reveals multinucleated giant cells. Confirmed by detection of virus, viral antigen, or viral DNA in scrapings from lesions.

TREATMENT HERPES SIMPLEX

Will differ based on disease manifestations and level of immune competence (Chap. 99); appropriate antibiotics for secondary infections, depending on organism.

HERPES ZOSTER (SEE ALSO CHAP. 99)

Eruption of grouped vesicles on an erythematous base usually limited to a single dermatome ("shingles"); disseminated lesions can also occur, especially in immunocompromised pts. Tzanck preparation reveals multinucleated giant cells; indistinguishable from herpes simplex except by culture. Detection of varicella zoster virus DNA by PCR is confirmatory but of limited availability. Postherpetic neuralgia, lasting months to years, may occur, especially in the elderly.

TREATMENT HERPES ZOSTER

Will differ based on disease manifestations and level of immune competence (Chap. 99).

DERMATOPHYTE INFECTION

Skin fungus, may involve any area of body; due to infection of stratum corneum, nail plate, or hair. Appearance may vary from mild scaliness to florid inflammatory dermatitis. Common sites of infection include the foot (tinea pedis), nails (tinea unguium), groin (tinea cruris), or scalp (tinea capitis). Classic lesion of tinea corporis ("ringworm") is an erythematous papulosquamous patch, often with central clearing

http://internalmedicinebook.com

and scale along peripheral advancing border. Hyphae are often seen on KOH preparation, although tinea capitis and tinea corporis may require culture or biopsy.

TREATMENT DERMATOPHYTE INFECTION

Depends on affected site and type of infection. Topical imidazoles, triazoles, and allylamines may be effective. Haloprogin, undecylenic acid, ciclopirox olamine, and tolnaftate are also effective, but nystatin is not active against dermatophytes. Griseofulvin, 500 mg/d, if systemic therapy required. Itraconazole or terbinafine may be effective for nail infections.

CANDIDIASIS

Fungal infection caused by a related group of yeasts. Manifestations may be localized to the skin or rarely systemic and life-threatening. Predisposing factors include diabetes mellitus, cellular immune deficiencies, and HIV (Chap. 105). Frequent sites include the oral cavity, chronically wet macerated areas, around nails, intertriginous areas. Diagnosed by clinical pattern and demonstration of yeast on KOH preparation or culture.

TREATMENT CANDIDIASIS

(See also Chap. 106) Removal of predisposing factors; topical nystatin or azoles; systemic therapy reserved for immunosuppressed pts, unresponsive chronic or recurrent disease; vulvovaginal candidiasis may respond to a single dose of fluconazole, 150 mg.

WARTS

Cutaneous neoplasms caused by human papilloma viruses (HPVs). Typically dome-shaped lesions with irregular, filamentous surface. Propensity for the face, arms, and legs; often spread by shaving. HPVs are also associated with genital or perianal lesions and play a role in the development of cancer of the uterine cervix and anogenital skin (Chap. 83).

TREATMENT WARTS

Cryotherapy with liquid nitrogen, keratinolytic agents (salicylic acid). For genital warts, application of podophyllin solution is effective but can be associated with marked local reactions; topical imiquimod also has been used. HPV vaccine reduces the incidence of anogenital and cervical carcinoma.

ACNE

ACNE VULGARIS

Usually a self-limited disorder of teenagers and young adults. Comedones (small cysts formed in hair follicles) are clinical hallmark; often accompanied by inflammatory lesions of papules, pustules, or nodules; may scar in severe cases.

TREATMENT ACNE VULGARIS

Careful cleaning and removal of oils; oral tetracycline or erythromycin; topical antibacterials (e.g., benzoyl peroxide), topical retinoic acid. Systemic isotretinoin

http://internalmedicinebook.com

only for unresponsive severe nodulocystic acne (risk of severe adverse events including teratogenicity and possible association with depression).

ACNE ROSACEA

Inflammatory disorder affecting predominantly the central face, rarely affecting pts <30 years of age. Tendency toward exaggerated flushing, with eventual superimposition of papules, pustules, and telangiectasias; may lead to rhinophyma and ocular problems.

TREATMENT ACNE ROSACEA

Oral tetracycline, 250–500 mg bid; doxycycline 100 mg bid, minocycline 50-100 mg bid, topical metronidazole and topical nonfluorinated glucocorticoids may be useful.

VASCULAR DISORDERS

ERYTHEMA NODOSUM

Septal panniculitis characterized by erythematous, warm, tender subcutaneous nodular lesions typically over anterior tibia. Lesions are usually flush with skin surface but are indurated and have appearance of an erythematous/violaceous bruise. Lesions usually resolve spontaneously in 3–6 weeks without scarring. Commonly seen in sarcoidosis, administration of certain drugs (esp. sulfonamides, oral contraceptives, and estrogens), and a wide range of infections including streptococcal and tubercular; may be idiopathic.

TREATMENT ERYTHEMA NODOSUM

Identification and treatment/removal of underlying cause. NSAIDs for severe or recurrent lesions; systemic glucocorticoids are effective but dangerous if underlying infection is not appreciated.

ERYTHEMA MULTIFORME

A reaction pattern of skin consisting of a variety of lesions but most commonly erythematous papules and bullae. "Target" or "iris" lesion is characteristic and consists of concentric circles of erythema and normal flesh-colored skin, often with a central vesicle or bulla.

Distribution of lesions classically acral, esp. palms and soles. Three most common causes are drug reaction (particularly penicillins and sulfonamides) or concurrent herpetic or *Mycoplasma* infection. Can rarely affect mucosal surfaces and internal organs (erythema multiforme major or Stevens-Johnson syndrome).

TREATMENT ERYTHEMA MULTIFORME

Provocative agent should be sought and eliminated if drug-related. In mild cases limited to skin, only symptomatic treatment is needed (antihistamines, NSAID). For Stevens-Johnson syndrome, systemic glucocorticoids have been used but are controversial; prevention of secondary infection and maintenance of nutrition and fluid/electrolyte balance are critical.

http://internalmedicinebook.com

URTICARIA

A common disorder, either acute or chronic, characterized by evanescent (individual lesions lasting <24 h), pruritic, edematous, pink to erythematous plaques with a whitish halo around margin of individual lesions. Lesions range in size from papules to giant coalescent lesions (10–20 cm in diameter). Often due to drugs, systemic infection, or foods (esp. shellfish). If individual lesions last >24 h, consider diagnosis of urticarial vasculitis.

TREATMENT URTICARIA

See Chap. 156.

VASCULITIS

Palpable purpura (nonblanching, elevated lesions) is the cutaneous hallmark of vasculitis. Other lesions include petechiae (esp. early lesions), necrosis with ulceration, bullae, and urticarial lesions (urticarial vasculitis). Lesions usually most prominent on lower extremities. Associations include infections, autoimmune diseases, primary systemic vasculitides, malignancy, hepatitis B and C, drugs (esp. thiazides), and inflammatory bowel disease. May occur as an idiopathic, predominantly cutaneous vasculitis.

TREATMENT VASCULITIS

Will differ based on cause. Pursue identification and treatment/elimination of an exogenous cause or underlying disease. If part of a systemic vasculitis, treat based on major organ-threatening features (Chap. 159). Immunosuppressive therapy should be avoided in idiopathic, predominantly cutaneous vasculitis as disease frequently does not respond and rarely causes irreversible organ system dysfunction.

CUTANEOUS DRUG REACTIONS

Cutaneous reactions are among the most frequent medication toxicities. These can have a wide range of severity and manifestations including urticaria, photosensitivity, erythema multiforme, fixed drug reactions, erythema nodosum, vasculitis, lichenoid reactions, bullous drug reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). Diagnosis is usually made by appearance and careful medication history.

TREATMENT CUTANEOUS DRUG REACTIONS

Withdrawal of the medication. Treatment based on nature and severity of cutaneous pathology.



For a more detailed discussion, see Lawley LP, McCall CO, Lawley TJ: Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders, Chap. 71, p. 344; Shinkai K, Stern RS, Wintroub BU: Cutaneous Drug Reactions, Chap. 74, p. 377; and Bolognia JL, Braverman IM: Skin Manifestations of Internal Disease, Chap. 72, p. 353, in HPIM-19.

http://internalmedicinebook.com

61 Examination of Blood Smears and Bone Marrow

BLOOD SMEARS

ERYTHROCYTE (RBC) MORPHOLOGY

- Normal: 7.5 μm diameter. Roughly the size of the nucleus of a small lymphocyte.
- *Reticulocytes* (Wright's stain): large, grayish-blue, admixed with pink (polychromasia).
- *Anisocytosis*: variation in RBC size; large cells imply delay in erythroid precursor DNA synthesis caused by folate or B_{12} deficiency or drug effect; small cells imply a defect in hemoglobin synthesis caused by iron deficiency or abnormal hemoglobin genes. The automated red cell distribution width (RDW) is a measure of anisocytosis.
- *Poikilocytosis*: abnormal RBC shapes; the following are examples:
  1. *Acanthocytes* (spur cells): irregularly spiculated; abetalipoproteinemia, severe liver disease, rarely anorexia nervosa.
  2. *Echinocytes* (burr cells): regularly shaped, uniformly distributed spiny projections; uremia, RBC volume loss.
  3. *Elliptocytes*: elliptical; hereditary elliptocytosis.
  4. *Schistocytes* (schizocytes): fragmented cells of varying sizes and shapes; microangiopathic or macroangiopathic hemolytic anemia.
  5. *Sickled cells*: elongated, crescentic; sickle cell anemias.
  6. *Spherocytes*: small hyperchromic cells lacking normal central pallor; hereditary spherocytosis, extravascular hemolysis as in autoimmune hemolytic anemia, G6PD deficiency.
  7. *Target cells*: central and outer rim staining with intervening ring of pallor; liver disease, thalassemia, hemoglobin C, and sickle C diseases.
  8. *Teardrop cells*: myelofibrosis, other infiltrative processes of marrow (e.g., carcinoma).
  9. *Rouleaux formation*: alignment of RBCs in stacks; may be artifactual or due to paraproteinemia (e.g., multiple myeloma, macroglobulinemia).

RBC INCLUSIONS

- *Howell-Jolly bodies*: 1-μm-diameter basophilic cytoplasmic inclusion that represents a residual nuclear fragment, usually single; asplenic pts.
- *Basophilic stippling*: multiple, punctate basophilic cytoplasmic inclusions composed of precipitated mitochondria and ribosomes; lead poisoning, thalassemia, myelofibrosis.
- *Pappenheimer (iron) bodies*: iron-containing granules usually composed of mitochondria and ribosomes resemble basophilic stippling but also stain with Prussian blue; lead poisoning, other sideroblastic anemias.
- *Heinz bodies*: spherical inclusions of precipitated hemoglobin seen only with supravital stains, such as crystal violet; G6PD deficiency (after oxidant stress such as infection, certain drugs), unstable hemoglobin variants.
- *Parasites*: characteristic intracytoplasmic inclusions; malaria, babesiosis.

http://internalmedicinebook.com

LEUKOCYTE INCLUSIONS AND NUCLEAR CONTOUR ABNORMALITIES

- *Toxic granulations*: dark cytoplasmic granules; bacterial infection.
- *Döhle bodies*: 1- to 2-μm blue, oval cytoplasmic inclusions; bacterial infection, Chédiak-Higashi anomaly.
- *Auer rods*: eosinophilic, rodlike cytoplasmic inclusions; acute myeloid leukemia (some cases).
- *Hypersegmentation*: neutrophil nuclei contain more than the usual 2–4 lobes; usually >5% have ≥5 lobes or a single cell with 7 lobes is adequate to make the diagnosis; folate or B_{12} deficiency, drug effects.
- *Hyposegmentation*: neutrophil nuclei contain fewer lobes than normal, either one or two: Pelger-Hüet anomaly, pseudo–Pelger-Hüet or acquired Pelger-Hüet anomaly in acute leukemia.

PLATELET ABNORMALITIES

- *Platelet clumping*: an in vitro artifact—is often readily detectable on smear; can lead to falsely low platelet count by automated cell counters.
- *Giant platelets*: can be a sign of a very young platelet or increased platelet production or abnormal karyocyte maturation; if the platelets are >5–6 μm in diameter, they may not be counted as platelets by electronic counters.

BONE MARROW

Aspiration assesses cell morphology. *Biopsy* assesses overall marrow architecture, including degree of cellularity. Biopsy should precede aspiration to avoid aspiration artifact (mainly hemorrhage) in the specimen.

INDICATIONS

Aspiration

Hypoproliferative or unexplained anemia, leukopenia, or thrombocytopenia, suspected leukemia or myeloma or marrow defect, evaluation of iron stores, workup of some cases of fever of unknown origin.

Special Tests

Histochemical staining (leukemias), cytogenetic studies (leukemias, lymphomas), microbiology (bacterial, mycobacterial, fungal cultures), Prussian blue (iron) stain (assessment of iron stores, diagnosis of sideroblastic anemias).

Biopsy

Performed in addition to aspiration for pancytopenia (aplastic anemia), metastatic tumor, granulomatous infection (e.g., mycobacteria, brucellosis, histoplasmosis), myelofibrosis, lipid storage disease (e.g., Gaucher's, Niemann-Pick), any case with "dry tap" on aspiration; evaluation of marrow cellularity. When biopsy and aspirate are both planned, the biopsy should be performed first because of the risk of bleeding artifact from biopsy of an aspiration site.

Special Tests

Histochemical staining (e.g., acid phosphatase for metastatic prostate carcinoma), immunoperoxidase staining (e.g., immunoglobulin or cell surface marker detection in multiple myeloma, leukemia, or lymphoma; lysozyme detection in monocytic leukemia), reticulin staining (increased in myelofibrosis), microbiologic staining (e.g., acid-fast staining for mycobacteria).

http://internalmedicinebook.com

INTERPRETATION

Cellularity

Defined as percentage of space occupied by hematopoietic cells. The space that is not hematopoietic tissue is usually fat. Cellularity decreases with age after age 65 years from about 50% to 25–30% with a corresponding increase in fat.

Erythroid:Granulocytic (E:G) Ratio

Normally about 1:2, the E:G ratio is decreased in acute and chronic infection, leukemoid reactions (e.g., chronic inflammation, metastatic tumor), acute and chronic myeloid leukemia, myelodysplastic disorders ("preleukemia"), and pure red cell aplasia; increased in agranulocytosis, anemias with erythroid hyperplasia (megaloblastic, iron-deficiency, thalassemia, hemorrhage, hemolysis, sideroblastic), and erythrocytosis (excessive RBC production); normal in aplastic anemia (though marrow hypocellular), myelofibrosis (marrow hypocellular), multiple myeloma, lymphoma, anemia of chronic disease. Some centers use the term M:E (myeloid to erythroid) ratio; normal value is 2:1 and increases with diseases that promote myeloid activity or inhibit erythroid activity and decreases with diseases that inhibit myeloid activity or promote erythroid activity.



For a more detailed discussion, see Adamson JW, Longo DL: Anemia and Polycythemia, Chap. 77, p. 392; Holland SM, Gallin JI: Disorders of Granulocytes and Monocytes, Chap. 80, p. 413; and Longo DL: Atlas of Hematology and Analysis of Peripheral Blood Smears, Chap. 81e in HPIM-19.

62 Red Blood Cell Disorders

Anemia is a common clinical problem in medicine. A physiologic approach (outlined in Chap. 45) provides the most efficient path to diagnosis and management. Anemias arise either because red blood cell (RBC) production is inadequate or because RBC lifespan (normally 120 days) is shortened through loss from the circulation or destruction.

HYPOPROLIFERATIVE ANEMIAS

These are the most common anemias. Usually the RBC morphology is normal and the reticulocyte index (RI) is low. Marrow damage, early iron deficiency, and decreased erythropoietin production or action may produce anemia of this type.

Marrow damage may be caused by infiltration of the marrow with tumor or fibrosis that crowds out normal erythroid precursors or by the absence of erythroid precursors (aplastic anemia) as a consequence of exposure to drugs, radiation, chemicals, viruses (e.g., hepatitis), autoimmune mechanisms, or genetic factors,

http://internalmedicinebook.com

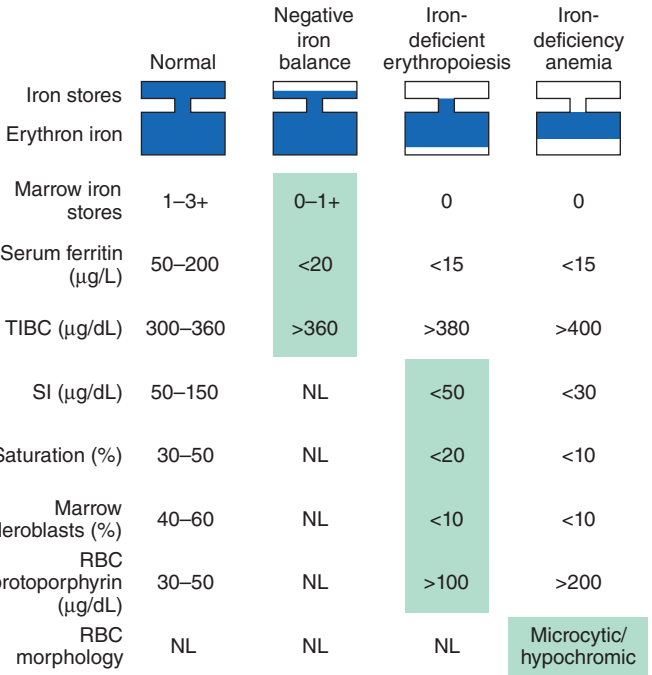


FIGURE 62-1 Measurements of marrow iron stores, serum ferritin, and total iron-binding capacity (TIBC) are sensitive to early iron-store depletion. Iron-deficient erythropoiesis is recognized from additional abnormalities in the serum iron (SI), percent transferrin saturation, the pattern of marrow sideroblasts, and the red cell protoporphyrin level. Pts with iron-deficiency anemia demonstrate all the same abnormalities plus hypochromic microcytic anemia. (*From RS Hillman, CA Finch: Red Cell Manual, 7th. ed, Philadelphia, Davis, 1996, with permission.*)

either hereditary (e.g., Fanconi's anemia) or acquired (e.g., paroxysmal nocturnal hemoglobinuria). Most cases of aplasia are idiopathic. The tumor or fibrosis that infiltrates the marrow may originate in the marrow (as in leukemia or myelofibrosis) or be secondary to processes originating outside the marrow (as in metastatic cancer or myelophthisis).

Early iron-deficiency anemia (or iron-deficient erythropoiesis) is associated with a decrease in serum ferritin levels (<15 μg/L), moderately elevated total iron-binding capacity (TIBC) (>380 μg/dL), serum iron (SI) level <50 μg/dL, and an iron saturation of <30% but >10% (Fig. 62-1). RBC morphology is generally normal until iron deficiency is severe (see below).

Decreased stimulation of erythropoiesis can be a consequence of inadequate erythropoietin production [e.g., renal disease destroying the renal tubular cells that produce it or hypometabolic states (endocrine deficiency or protein starvation)] in which insufficient erythropoietin is produced or of inadequate erythropoietin action. In older people, erythropoietin levels normally increase to maintain normal hemoglobin levels. If this increase does not happen, anemia may develop. About 11% of community-dwelling adults over age 65 and up to 45% of nursing home residents have this aging-related anemia. It is a relative erythropoietin deficiency without renal disease. The anemia of chronic disease is a common entity. It is multifactorial in pathogenesis: inhibition of erythropoietin production, inhibition of iron

http://internalmedicinebook.com

reutilization (which blocks the response to erythropoietin), and inhibition of erythroid colony proliferation by inflammatory cytokines (e.g., tumor necrosis factor, interferon γ). Hepcidin, a small iron-binding molecule produced by the liver during an acute-phase inflammatory response, may bind iron and prevent its reutilization in hemoglobin synthesis. The laboratory tests shown in Table 62-1 may assist in the differential diagnosis of hypoproliferative anemias. Measurement of hepcidin in the urine is not yet practical or widely available.

MATURATION DISORDERS

These result from either defective hemoglobin synthesis, leading to cytoplasmic maturation defects and small relatively empty red cells, or abnormally slow DNA replication, leading to nuclear maturation defects and large full red cells. Defects in hemoglobin synthesis usually result from insufficient iron supply (iron deficiency) or decreased globin production (thalassemia) or are idiopathic (sideroblastic anemia). Defects in DNA synthesis are usually due to nutritional problems (vitamin B_{12} and folate deficiency), toxic (methotrexate or other cancer chemotherapeutic agent) exposure, or intrinsic marrow maturation defects (refractory anemia, myelodysplasia).

Laboratory tests useful in the differential diagnosis of the microcytic anemias are shown in Table 62-2. Mean corpuscular volume (MCV) is generally 60–80 fL. Increased lactate dehydrogenase (LDH) and indirect bilirubin levels suggest an increase in RBC destruction and favor a cause other than iron deficiency. Iron status is best assessed by measuring SI, TIBC, and ferritin levels. Macrocytic MCVs are >94 fL. Folate status is best assessed by measuring red blood cell folate levels. Vitamin B_{12} status is best assessed by measuring serum B_{12}, homocysteine, and methylmalonic acid levels. Homocysteine and methylmalonic acid levels are elevated in the setting of B_{12} deficiency.

ANEMIA DUE TO RBC DESTRUCTION OR ACUTE BLOOD LOSS

BLOOD LOSS

Trauma, GI hemorrhage (may be occult) are common causes; less common are genitourinary sources (menorrhagia, gross hematuria), internal bleeding such as intraperitoneal from spleen or organ rupture, retroperitoneal, iliopsoas hemorrhage (e.g., in hip fractures). Acute bleeding is associated with manifestations of hypovolemia, reticulocytosis, macrocytosis; chronic bleeding is associated with iron deficiency, hypochromia, microcytosis.

HEMOLYSIS

Causes are listed in Table 62-3.

1. *Intracellular RBC abnormalities*: most are inherited enzyme defects [glucose-6-phosphate dehydrogenase (G6PD) deficiency > pyruvate kinase deficiency], hemoglobinopathies, sickle cell anemia and variants, thalassemia, unstable hemoglobin variants.
2. *G6PD deficiency*: leads to episodes of hemolysis precipitated by ingestion of drugs that induce oxidant stress on RBCs. These include antimalarials (chloroquine), sulfonamides, analgesics (phenacetin), and other miscellaneous drugs (Table 62-4).
3. *Sickle cell anemia*: characterized by a single-amino-acid change in β globin (valine for glutamic acid in the 6th residue) that produces a molecule of decreased solubility, especially in the absence of O_2. Although anemia and chronic hemolysis are present, the major disease manifestations relate to vasoocclusion from misshapen sickled RBCs. Infarcts in lung, bone, spleen, retina, brain, and other organs lead to symptoms and dysfunction (Fig. 62-2).

http://internalmedicinebook.com

TABLE 62-1 DIAGNOSIS OF HYPOPROLIFERATIVE ANEMIAS

Tests	Iron Deficiency	Inflammation	Renal Disease	Hypometabolic States	Anemia of Aging
Anemia	Mild to severe	Mild	Mild to severe	Mild	Mild
MCV (fL)	60–90	80–90	90	90	80–90
Morphology	Normomicrocytic	Normocytic	Normocytic	Normocytic	Normocytic
SI	<30	<50	Normal	Normal	Normal
TIBC	>360	<300	Normal	Normal	Normal
Saturation (%)	<10	10–20	Normal	Normal	Normal
Serum ferritin (μg/L)	<15	30–200	115–150	Normal	Normal
Iron stores	0	2–4+	1–4+	Normal	Normal
Erythropoietin levels	High	Normal or High	Low	Normal or Low	Normal

Abbreviations: MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron-binding capacity.

http://internalmedicinebook.com

TABLE 62-2 DIAGNOSIS OF MICROCYTIC ANEMIA

Tests	Iron Deficiency	Inflammation	Thalassemia	Sideroblastic Anemia
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
SI	<30	<50	Normal to high	Normal to high
TIBC	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (μg/L)	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with β thalassemia; can be normal with α thalassemia	Normal

Abbreviations: SI, serum iron; TIBC, total iron-binding capacity.

4. *Membrane abnormalities* (rare): spur cell anemia (cirrhosis, anorexia nervosa), paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis (increased RBC osmotic fragility, spherocytes), hereditary elliptocytosis (causes mild hemolytic anemia).
5. *Immunohemolytic anemia* (positive Coombs' test, spherocytes). Two types: (a) *warm antibody* (usually IgG): idiopathic, lymphoma, chronic lymphocytic leukemia, systemic lupus erythematosus, drugs (e.g., methyldopa, penicillins, quinine, quinidine, isoniazid, sulfonamides); and (b) *cold antibody*—cold agglutinin disease (IgM) due to *Mycoplasma* infection, infectious mononucleosis, lymphoma, idiopathic; paroxysmal cold hemoglobinuria (IgG) due to syphilis, viral infections.

TABLE 62-3 CLASSIFICATION OF HEMOLYTIC ANEMIAS[a]

	Intracorpuscular Defects	Extracorpuscular Factors
Hereditary	Hemoglobinopathies	Familial (atypical) hemolytic uremic syndrome
	Enzymopathies	
	Membrane-cytoskeletal defects	
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic)
		Toxic agents
		Drugs
		Infectious
		Autoimmune

[a]Hereditary causes correlate with intracorpuscular defects because these defects are due to inherited mutations. The one exception is PNH because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorpuscular factors because mostly these factors are exogenous. The one exception is familial hemolytic uremic syndrome (HUS; often referred to as atypical HUS) because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells.

http://internalmedicinebook.com

TABLE 62-4 DRUGS THAT CARRY RISK OF CLINICAL HEMOLYSIS IN PERSONS WITH G6PD DEFICIENCY

	Definite Risk	Possible Risk	Doubtful Risk
Antimalarials	Primaquine Dapsone/ chlorproguanil[a]	Chloroquine	Quinine
Sulphonamides/ sulphones	Sulfamethoxazole Others Dapsone	Sulfasalazine Sulfadimidine	Sulfisoxazole Sulfadiazine
Antibacterial/ antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin	Chloramphenicol *p*-Aminosalicylic acid
Antipyretic/ analgesics	Acetanilide Phenazopyridine	Acetylsalicylic acid high dose (>3 g/d)	Acetylsalicylic acid (<3 g/d) Acetaminophen Phenacetin
Other	Naphthalene Methylene blue	Vitamin K analogues Ascorbic acid >1 g Rasburicase	Doxorubicin Probenecid

[a]Marketed as Lapdap from 2003 to 2008.

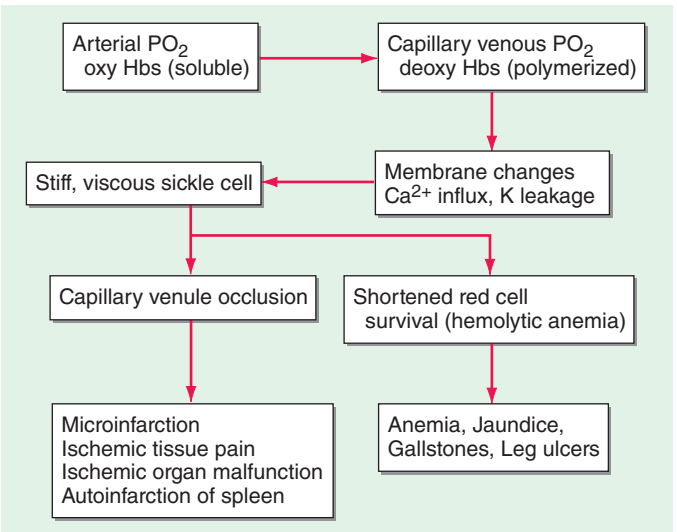


FIGURE 62-2 Pathophysiology of sickle cell crisis.

http://internalmedicinebook.com

6. *Mechanical trauma* (macro- and microangiopathic hemolytic anemias; schistocytes): prosthetic heart valves, vasculitis, malignant hypertension, eclampsia, renal graft rejection, giant hemangioma, scleroderma, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, march hemoglobinuria (e.g., marathon runners, bongo drummers).
7. *Direct toxic effect*: infections (e.g., malaria, *Clostridium perfringens* toxin, toxoplasmosis).
8. *Hypersplenism* (pancytopenia may be present).

LABORATORY ABNORMALITIES

Elevated RI, polychromasia and nucleated RBCs on smear; also spherocytes, elliptocytes, schistocytes, or target, spur, or sickle cells may be present depending on disorder; elevated unconjugated serum bilirubin and LDH, elevated plasma hemoglobin, low or absent haptoglobin; urine hemosiderin present in intravascular but not extravascular hemolysis, Coombs' test (immunohemolytic anemias), osmotic fragility test (hereditary spherocytosis), hemoglobin electrophoresis (sickle cell anemia, thalassemia), G6PD assay (best performed after resolution of hemolytic episode to prevent false-negative result).

TREATMENT ANEMIA

GENERAL APPROACHES The acuteness and severity of the anemia determine whether transfusion therapy with packed RBCs is indicated. Rapid occurrence of severe anemia (e.g., after acute GI hemorrhage resulting in Hct <25%, following volume repletion) or development of angina or other symptoms is an indication for transfusion. Hct should increase 3–4% [Hb by 10 g/L (1 g/dL)] with each unit of packed RBCs, assuming no ongoing losses. Chronic anemia (e.g., vitamin B_{12} deficiency), even when severe, may not require transfusion therapy if the pt is compensated and specific therapy (e.g., vitamin B_{12}) is instituted.

SPECIFIC DISORDERS

1. *Iron deficiency*: find and treat cause of blood loss, oral iron (e.g., $FeSO_4$ 300 mg tid).
2. *Folate deficiency*: common in malnourished, alcoholics; less common now than before folate food supplementation; folic acid 1 mg PO qd (5 mg qd for pts with malabsorption).
3. *Vitamin B_{12} deficiency*: can be managed either with parenteral vitamin B_{12} 100 µg IM qd for 7 d, then 100–1000 µg IM per month or with 2 mg oral crystalline vitamin B_{12} per day. An inhaled formulation is also available.
4. *Anemia of chronic disease*: treat underlying disease; in uremia use recombinant human erythropoietin, 50–150 U/kg three times a week; role of erythropoietin in other forms of anemia of chronic disease is less clear; response more likely if serum erythropoietin levels are low. Target Hb 9–10 g/dL. Iron administration is not useful.
5. *Sickle cell anemia*: hydroxyurea 10–30 mg/kg per day PO increases level of Hemoglobin F (HbF) and prevents sickling, treat infections early, supplemental folic acid; painful crises treated with oxygen, analgesics (opioids), hydration, and hypertransfusion; consider allogeneic bone marrow transplantation in pts with increasing frequency of crises.
6. *Thalassemia*: transfusion to maintain Hb >90 g/L (>9 g/dL), folic acid, prevention of Fe overload with deferoxamine (parenteral) or deferasirox (oral) chelation; consider splenectomy and allogeneic bone marrow transplantation.

http://internalmedicinebook.com

7. *Aplastic anemia*: antithymocyte globulin and cyclosporine leads to improvement in 70%, bone marrow transplantation in young pts with a matched donor.
8. *Autoimmune hemolysis*: glucocorticoids, sometimes immunosuppressive agents, danazol, plasmapheresis, rituximab.
9. *G6PD deficiency*: avoid agents known to precipitate hemolysis.

For a more detailed discussion, see Adamson JW: Iron Deficiency and Other Hypoproliferative Anemias, Chap. 126, p. 625; Benz EJ: Disorders of Hemoglobin, Chap. 127, p. 631; Hoffbrand AV: Megaloblastic Anemias, Chap. 128, p. 640; Luzzato L: Hemolytic Anemias and Anemia Due to Acute Blood Loss, Chap. 129, p. 649; and Young NS: Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia, Chap. 130; p. 662 in HPIM-19.

63 Leukocytosis and Leukopenia

LEUKOCYTOSIS

APPROACH TO THE PATIENT: Leukocytosis

Review smear (are abnormal cells present?) and obtain differential count. The normal values for concentration of blood leukocytes are shown in Table 63-1.

NEUTROPHILIA

Absolute neutrophil count (polys and bands) >10,000/μL. The pathophysiology of neutrophilia involves increased production, increased marrow mobilization, or decreased margination (adherence to vessel walls).

Causes

(1) *Exercise*, *stress*; (2) *infections*—esp. bacterial; smear shows increased numbers of immature neutrophils ("left shift"), toxic granulations, Döhle bodies; (3) *burns*;

TABLE 63-1 NORMAL VALUES FOR LEUKOCYTE CONCENTRATION IN BLOOD

Cell Type	Mean, cells/μL	95% Confidence Intervals, cells/μL	Total WBC, %
Neutrophil	3650	1830–7250	30–60%
Lymphocyte	2500	1500–4000	20–50%
Monocyte	430	200–950	2–10%
Eosinophil	150	0–700	0.3–5%
Basophil	30	0–150	0.6–1.8%

http://internalmedicinebook.com

(4) *tissue necrosis* (e.g., myocardial, pulmonary, renal infarction); (5) *chronic inflammatory disorders* (e.g., gout, vasculitis); (6) *drugs* (e.g., glucocorticoids, epinephrine, lithium); (7) *cytokines* [e.g., granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)]; (8) *myeloproliferative disorders* (Chap. 65); (9) *metabolic* (e.g., ketoacidosis, uremia); (10) *other*—malignant neoplasms, acute hemorrhage or hemolysis, after splenectomy.

LEUKEMOID REACTION

Extreme elevation of leukocyte count (>50,000/μL) composed of mature and/or immature neutrophils.

Causes

(1) *Infection* (severe, chronic, e.g., tuberculosis), esp. in children; (2) *hemolysis* (severe); (3) *malignant neoplasms* (esp. carcinoma of the breast, lung, kidney); (4) *cytokines* (e.g., G-CSF, GM-CSF). May be distinguished from chronic myeloid leukemia (CML) by measurement of the leukocyte alkaline phosphatase (LAP) level: elevated in leukemoid reactions, depressed in CML.

LEUKOERYTHROBLASTIC REACTION

Similar to leukemoid reaction with addition of nucleated red blood cells (RBCs) and schistocytes on blood smear.

Causes

(1) *Myelophthisis*—invasion of the bone marrow by tumor, fibrosis, granulomatous processes; smear shows "teardrop" RBCs; (2) *myelofibrosis*—same pathophysiology as myelophthisis, but the fibrosis is a primary marrow disorder; (3) *hemorrhage* or *hemolysis* (rarely, in severe cases).

LYMPHOCYTOSIS

Absolute lymphocyte count >5000/μL.

Causes

(1) *Infection*—infectious mononucleosis, hepatitis, cytomegalovirus, rubella, pertussis, tuberculosis, brucellosis, syphilis; (2) *endocrine disorders*—thyrotoxicosis, adrenal insufficiency; (3) *neoplasms*—chronic lymphocytic leukemia (CLL), most common cause of lymphocyte count >10,000/μL.

MONOCYTOSIS

Absolute monocyte count >800/μL.

Causes

(1) *Infection*—subacute bacterial endocarditis, tuberculosis, brucellosis, rickettsial diseases (e.g., Rocky Mountain spotted fever), malaria, leishmaniasis; (2) *granulomatous diseases*—sarcoidosis, Crohn's disease; (3) *collagen vascular diseases*—rheumatoid arthritis, systemic lupus erythematosus (SLE), polyarteritis nodosa, polymyositis, temporal arteritis; (4) *hematologic diseases*—leukemias, lymphoma, myeloproliferative and myelodysplastic syndromes, hemolytic anemia, chronic idiopathic neutropenia; (5) *malignant neoplasms*.

EOSINOPHILIA

Absolute eosinophil count >500/μL.

Causes

(1) *Drugs*, (2) *parasitic infections*, (3) *allergic diseases*, (4) *collagen vascular diseases*, (5) *malignant neoplasms*, (6) *hypereosinophilic syndromes*.

http://internalmedicinebook.com

BASOPHILIA

Absolute basophil count >100/μL.

Causes

(1) *Allergic diseases*, (2) *myeloproliferative disorders* (esp. CML), (3) *chronic inflammatory disorders* (rarely).

LEUKOPENIA

Total leukocyte count <4300/μL.

NEUTROPENIA

Absolute neutrophil count <2000/μL (increased risk of bacterial infection with count <1000/μL). The pathophysiology of neutropenia involves decreased production or increased peripheral destruction.

Causes

(1) *Drugs*—cancer chemotherapeutic agents are most common cause, also phenytoin, carbamazepine, indomethacin, chloramphenicol, penicillins, sulfonamides, cephalosporins, propylthiouracil, phenothiazines, captopril, methyldopa, procainamide, chlorpropamide, thiazides, cimetidine, allopurinol, colchicine, ethanol, penicillamine, and immunosuppressive agents; (2) *infections*—viral (e.g., influenza, hepatitis, infectious mononucleosis, HIV), bacterial (e.g., typhoid fever, miliary tuberculosis, fulminant sepsis), malaria; (3) *nutritional*—B_{12}, folate deficiencies; (4) *benign*—benign ethnic neutropenia (BEN) seen in up to 25% of blacks, no associated risk of infection; (5) *hematologic diseases*—cyclic neutropenia (q21d, with recurrent infections common), leukemia, myelodysplasia (preleukemia), aplastic anemia, bone marrow infiltration (uncommon cause), Chédiak-Higashi syndrome; (6) *hypersplenism*—e.g., Felty's syndrome, congestive splenomegaly, Gaucher's disease; (7) *autoimmune diseases*—idiopathic, SLE, lymphoma (may see positive antineutrophil antibodies); (8) *genetics*—inheritance of an allele of the Duffy antigen receptor for cytokines (DARC) can be associated with constitutive neutropenia that is not associated with predilection to infection; more common in African Americans.

TREATMENT THROMBOTIC DISORDERS

In addition to usual sources of infection, consider paranasal sinuses, oral cavity (including teeth and gums), anorectal region; empirical therapy with broad-spectrum antibiotics (e.g., ceftazidime) is indicated after blood and other appropriate cultures are obtained. Prolonged febrile neutropenia (>7 days) leads to increased risk of disseminated fungal infections; requires addition of antifungal chemotherapy (e.g., amphotericin B). The duration of chemotherapy-induced neutropenia may be shortened by a few days by treatment with the cytokines GM-CSF or G-CSF.

LYMPHOPENIA

Absolute lymphocyte count <1000/μL.

Causes

(1) *Acute stressful illness*—e.g., myocardial infarction, pneumonia, sepsis; (2) *glucocorticoid therapy*; (3) *lymphoma* (esp. Hodgkin's lymphoma); (4) *immunodeficiency syndromes*—ataxia telangiectasia and Wiskott-Aldrich and DiGeorge syndromes; (5) *immunosuppressive therapy*—e.g., antilymphocyte globulin, cyclophosphamide; (6) *large-field radiation therapy* (esp. for lymphoma); (7) *intestinal lymphangiectasia*

http://internalmedicinebook.com

(increased lymphocyte loss); (8) *chronic illness*—e.g., congestive heart failure, uremia, SLE, disseminated malignancies; (9) *bone marrow failure/replacement*—e.g., aplastic anemia, miliary tuberculosis.

MONOCYTOPENIA

Absolute monocyte count <100/μL.

Causes

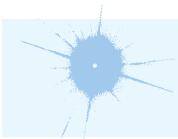
(1) *Acute stressful illness*, (2) *glucocorticoid therapy*, (3) *aplastic anemia*, (4) *leukemia* (certain types, e.g., hairy cell leukemia), (5) *chemotherapeutic and immunosuppressive agents*.

EOSINOPENIA

Absolute eosinophil count <50/μL.

Causes

(1) *Acute stressful illness*, (2) *glucocorticoid therapy*.



For a more detailed discussion, see Holland SM, Gallin JI: Disorders of Granulocytes and Monocytes, Chap. 80, p. 413; in HPIM-19.

64 Bleeding and Thrombotic Disorders

BLEEDING DISORDERS

Bleeding may result from abnormalities of (1) platelets, (2) blood vessel walls, or (3) coagulation. Platelet disorders characteristically produce petechial and purpuric skin lesions and bleeding from mucosal surfaces. Defective coagulation results in ecchymoses, hematomas, and mucosal and, in some disorders, recurrent joint bleeding (hemarthroses).

PLATELET DISORDERS

Thrombocytopenia

Normal platelet count is 150,000–350,000/μL. Thrombocytopenia is defined as a platelet count <100,000/μL. Bleeding time, a measurement of platelet function, is abnormally increased if platelet count <100,000/μL; injury or surgery may provoke excess bleeding. Spontaneous bleeding is unusual unless count <20,000/μL; platelet count <10,000/μL is often associated with serious hemorrhage. Bone marrow examination shows increased number of megakaryocytes in disorders associated with accelerated platelet destruction; decreased number in disorders of platelet production. Evaluation of thrombocytopenia is shown in Fig. 64-1.

Causes

(1) Production defects such as marrow injury (e.g., drugs, irradiation), marrow failure (e.g., aplastic anemia), marrow invasion (e.g., carcinoma, leukemia, fibrosis); (2) sequestration due to splenomegaly; (3) accelerated destruction—causes include:

http://internalmedicinebook.com

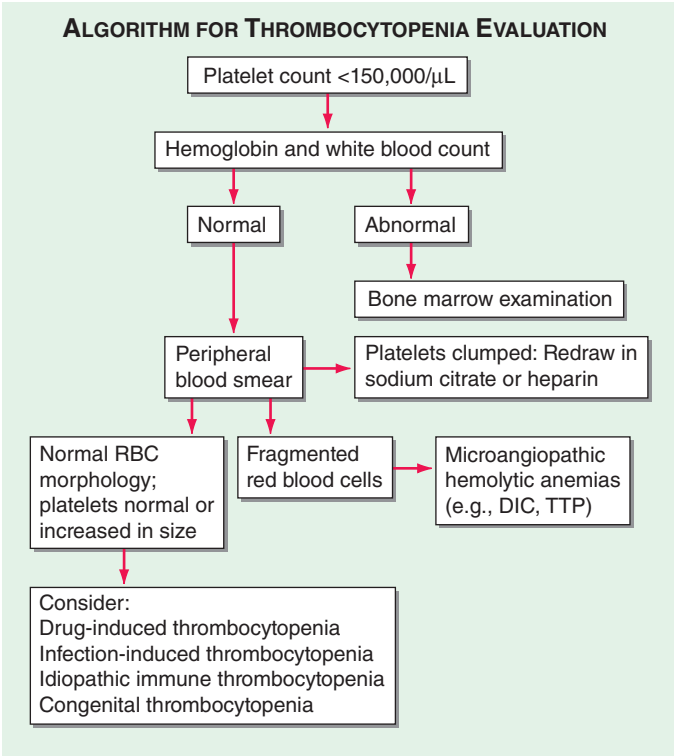


FIGURE 64-1 Algorithm for evaluating the thrombocytopenic pt. DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura.

- *Drugs* such as chemotherapeutic agents, thiazides, ethanol, estrogens, sulfonamides, quinidine, quinine, methyldopa.
- *Heparin-induced thrombocytopenia* (HIT) is seen in 5% of pts receiving >5 days of therapy and is due to in vivo platelet aggregation often from anti–platelet factor 4 antibodies. Arterial and occasionally venous thromboses may result. Despite the low platelets, HIT is a hypercoagulable state.
- *Autoimmune destruction* by an antibody mechanism; may be idiopathic or associated with systemic lupus erythematosus (SLE), lymphoma, HIV.
- *Idiopathic thrombocytopenic purpura* (ITP) has two forms: an acute, self-limited disorder of childhood requiring no specific therapy, and a chronic disorder of adults (esp. women 20–40 years). Chronic ITP may be due to autoantibodies to glycoprotein IIb/IIIa or glycoprotein Ib-IX complexes.
- *Disseminated intravascular coagulation* (DIC): platelet consumption with coagulation factor depletion [prolonged prothrombin time (PT), partial thromboplastin time (PTT)] and stimulation of fibrinolysis [generation of fibrin split products (FSPs)]. Blood smear shows microangiopathic hemolysis (schistocytes). Causes include infection (esp. meningococcal, pneumococcal, gram-negative bacteremias), extensive burns, trauma, or thrombosis; giant hemangioma, retained dead fetus, heat stroke, mismatched blood transfusion, metastatic carcinoma, acute promyelocytic leukemia.

http://internalmedicinebook.com

- *Thrombotic thrombocytopenic purpura* (TTP): rare disorder characterized by microangiopathic hemolytic anemia, fever, thrombocytopenia, renal dysfunction (and/or hematuria), and neurologic dysfunction caused by failure to cleave von Willebrand factor (vWF) normally.
- *Hemorrhage with extensive transfusion*.

Pseudothrombocytopenia

Platelet clumping usually secondary to collection of blood in EDTA (0.3% of pts). Examination of blood smear establishes diagnosis.

Thrombocytosis

Platelet count >350,000/μL. Either primary (essential thrombocytosis; Chap. 65) or secondary (reactive); latter secondary to severe hemorrhage, iron deficiency, surgery, after splenectomy (transient), malignant neoplasms (esp. Hodgkin's lymphoma, polycythemia vera), chronic inflammatory diseases (e.g., inflammatory bowel disease), recovery from acute infection, vitamin B_{12} deficiency, drugs (e.g., vincristine, epinephrine). Rebound thrombocytosis may occur after marrow recovery from cytotoxic agents, alcohol, vitamin B_{12} replenishment. Primary thrombocytosis may be complicated by bleeding and/or thrombosis; secondary rarely causes hemostatic problems.

Disorders of Platelet Function

Suggested by the finding of prolonged bleeding time with normal platelet count. Defect is in platelet adhesion, aggregation, or granule release. Causes include (1) drugs—aspirin, other nonsteroidal anti-inflammatory drugs, dipyridamole, clopidogrel or prasugrel, heparin, penicillins, esp. carbenicillin, ticarcillin; (2) uremia; (3) cirrhosis; (4) dysproteinemias; (5) myeloproliferative and myelodysplastic disorders; (6) von Willebrand disease (vWD; see below); (7) cardiopulmonary bypass.

HEMOSTATIC DISORDERS DUE TO BLOOD VESSEL WALL DEFECTS

Causes include (1) aging; (2) drugs—e.g., glucocorticoids (chronic therapy), penicillins, sulfonamides; (3) vitamin C deficiency; (4) TTP; (5) hemolytic uremic syndrome; (6) Henoch-Schönlein purpura; (7) paraproteinemias; (8) hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).

DISORDERS OF BLOOD COAGULATION

Congenital Disorders

1. *Hemophilia A*: incidence 1:5000; sex-linked recessive deficiency of factor VIII (low plasma factor VIII coagulant activity, but normal amount of factor VIII–related antigen—vWF). Laboratory features: elevated PTT, normal PT.
2. *Hemophilia B* (Christmas disease): incidence 1:30,000, sex-linked recessive, due to factor IX deficiency. Clinical and laboratory features similar to hemophilia A.
3. *von Willebrand disease:* most common inherited coagulation disorder (1:800–1000), usually autosomal dominant; primary defect is reduced synthesis or chemically abnormal factor VIII–related antigen produced by platelets and endothelium, resulting in abnormal platelet function.

Acquired Disorders

1. *Vitamin K deficiency*: impairs production of factors II (prothrombin), VII, IX, and X; vitamin K is a cofactor in the carboxylation of glutamate residues on prothrombin complex proteins; major source of vitamin K is dietary (esp. green vegetables), with minor production by gut bacteria. Laboratory features: elevated PT and PTT.
2. *Liver disease*: results in deficiencies of all clotting factors except VIII. Laboratory features: elevated PT, normal or elevated PTT.

http://internalmedicinebook.com

3. *Other disorders*: DIC, fibrinogen deficiency (liver disease, L-asparaginase therapy, rattlesnake bites), other factor deficiencies, circulating anticoagulants (lymphoma, SLE, idiopathic), massive transfusion (dilutional coagulopathy).

TREATMENT BLEEDING DISORDERS

THROMBOCYTOPENIA CAUSED BY DRUGS

Discontinue use of possible offending agents; expect recovery in 7–10 days. Platelet transfusions may be needed if platelet count <10,000/μL.

HIT

Discontinue heparin promptly. A direct thrombin inhibitor such as lepirudin (0.4-mg/kg bolus, 0.15-mg/kg per hour infusion; PTT target 1.5–2.5 × baseline) or argatroban (2-μg/kg per min infusion; PTT target 1.5–3 × baseline) should be used for treatment of thromboses. Do not use low-molecular-weight heparin (LMWH), as antibodies often cross-react. Fondaparinux is also effective.

CHRONIC ITP

Prednisone, initially 1–2 mg/kg per day, then slow taper to keep the platelet count >60,000/μL. Dexamethasone 40 mg/d for 4 days, q2–4 weeks may be even more effective. intravenous immunoglobulin (IVIg) (2 g/kg in divided doses over 2–5 days) to block phagocytic destruction may be useful. Rituximab is effective in pts refractory to glucocorticoids. Eltrombopag (50 mg PO qd) boosts platelet production and allows delay or avoidance of splenectomy. Splenectomy, danazol (androgen), or other agents (e.g., vincristine, cyclophosphamide, fludarabine) are indicated for refractory pts or those requiring >5–10 mg prednisone daily.

DIC

Control of underlying disease most important; platelets, fresh-frozen plasma (FFP) to correct clotting parameters. Heparin may be beneficial in pts with acute promyelocytic leukemia.

TTP

Plasmapheresis and FFP infusions (plasma exchange), possibly IV IgG; recovery in two-thirds of cases. Plasmapheresis removes inhibitors of the vWF cleavage enzyme (ADAMTS13), and FFP replaces the enzyme.

DISORDERS OF PLATELET FUNCTION

Remove or reverse underlying cause. Dialysis and/or cryoprecipitate infusions (10 bags/24 h) may be helpful for platelet dysfunction associated with uremia.

HEMOSTATIC DISORDERS

Withdraw offending drugs, replace vitamin C, plasmapheresis, and plasma infusion for TTP.

HEMOPHILIA A

Factor VIII replacement for bleeding or before surgical procedure; degree and duration of replacement depends on severity of bleeding. Give factor VIII (e.g., Recombinate) to obtain a 15% (for mild bleeding) to 50% (for severe bleeding) factor VIII level. The duration should range from a single dose of factor VIII to therapy bid for up to 2 weeks. Dose is calculated as follows:

$$\text{Factor VIII dose} = (\text{Target level} - \text{baseline level}) \times \text{weight (kg)} \times 0.5 \text{ unit/kg}$$

http://internalmedicinebook.com

Up to 30% of pts may develop anti–factor VIII antibodies; activated factor VII or factor eight inhibitor bypass agent (FEIBA) may stop or prevent bleeding in these pts.

HEMOPHILIA B

Recombinant factor IX (e.g., Benefix), FFP or factor IX concentrates (e.g., Proplex, Konyne). Because of the longer half-life, once-daily treatment is sufficient. Dose is calculated as follows:

$$\text{Factor IX dose} = (\text{Target level} - \text{baseline level}) \times \text{weight (kg)} \times 1 \text{ unit/kg}$$

VON WILLEBRAND DISEASE

Desmopressin (1-deamino-8-D-arginine vasopressin) increases release of vWF from endothelial stores in type 1 vWD. It is given IV (0.3 μg/kg) or by nasal spray (2 squirts of 1.5-mg/mL fluid in each nostril). For types 2A, 2M, and 3, cryoprecipitate (plasma product rich in factor VIII) or factor VIII concentrate (Humate-P, Koate HS) is used: up to 10 bags bid for 48–72 h, depending on the severity of bleeding.

VITAMIN K DEFICIENCY

Vitamin K, 10 mg SC or slow IV.

LIVER DISEASE

Fresh-frozen plasma.

THROMBOTIC DISORDERS

HYPERCOAGULABLE STATE

Consider in pts with recurrent episodes of venous thrombosis [i.e., deep-vein thrombosis (DVT), pulmonary embolism (PE)]. Causes include (1) venous stasis (e.g., pregnancy, immobilization); (2) vasculitis; (3) cancer and myeloproliferative disorders; (4) oral contraceptives; (5) lupus anticoagulant—antibody to platelet phospholipid, stimulates coagulation; (6) HIT; (7) deficiencies of endogenous anticoagulant factors—antithrombin III, protein C, protein S; (8) factor V Leiden—mutation in factor V (Arg → Glu at position 506) confers resistance to inactivation by protein C, accounts for 25% of cases of recurrent thrombosis; (9) prothrombin gene mutation—Glu → Arg at position 20210 results in increased prothrombin levels; accounts for about 6% of thromboses; (10) other—paroxysmal nocturnal hemoglobinuria, dysfibrinogenemias (abnormal fibrinogen).

The approach to the diagnosis of the pt with DVT and/or PE is discussed in Chap. 133.

TREATMENT THROMBOTIC DISORDERS

Correct underlying disorder whenever possible; long-term warfarin therapy is otherwise indicated.

ANTICOAGULANT AGENTS

1. *Heparin:* enhances activity of antithrombin III; parenteral agent of choice. LMWH is the preparation of choice (enoxaparin or dalteparin). It can be administered SC, monitoring of the PTT is unnecessary, and it is less likely to induce antibodies and thrombocytopenia. The usual dose is 100 U/kg SC bid. Unfractionated heparin should be given only if LMWH is unavailable. In adults, the dose of unfractionated heparin is 25,000–40,000 U continuous IV infusion over 24 h following initial IV bolus of 5000 U; monitor by following PTT; should be maintained between 1.5 and 2 times upper normal limit. Prophylactic

http://internalmedicinebook.com

anticoagulation to lower risk of venous thrombosis recommended in some pts (e.g., postoperative, immobilized). Prophylactic doses of unfractionated heparin are 5000 U SC bid or tid. Major complication of unfractionated heparin therapy is hemorrhage—manage by discontinuing heparin; for severe bleeding, administer protamine (1 mg/100 U heparin); results in rapid neutralization.

2. *Warfarin* (Coumadin): vitamin K antagonist, decreases levels of factors II, VII, IX, X, and anticoagulant proteins C and S. Administered over 2–3 days; initial load of 5–10 mg PO qd followed by titration of daily dose to keep PT 1.5–2 times control PT or 2–3 times if the International Normalized Ratio (INR) method is used. Complications include hemorrhage, warfarin-induced skin necrosis (rare, occurs in persons deficient in protein C), teratogenic effects. Warfarin effect reversed by administration of vitamin K; FFP infused if urgent reversal necessary. Numerous drugs potentiate or antagonize warfarin effect. Potentiating agents include chlorpromazine, chloral hydrate, sulfonamides, chloramphenicol, other broad-spectrum antibiotics, allopurinol, cimetidine, tricyclic antidepressants, disulfiram, laxatives, high-dose salicylates, thyroxine, clofibrate. Some pts who are sensitive to warfarin effects have genetic defects metabolizing the drug. Antagonizing agents include vitamin K, barbiturates, rifampin, cholestyramine, oral contraceptives, thiazides.
3. *Fondaparinux:* a pentapeptide that directly inhibits factor Xa. It is given at a dose of 2.5 mg SC daily for prophylaxis and 7.5 mg SC daily for treatment of thrombosis and does not require monitoring. Unlike the heparins, it does not bind to platelet factor 4 and does not elicit the antibodies that produce HIT. *Apixaban* and *rivaroxaban* are oral factor Xa inhibitors. Apixaban (5 mg PO bid) as effective as warfarin in DVT and more effective in stroke prevention in atrial fibrillation (AF).
4. *Argatroban and lepirudin:* direct thrombin inhibitors. These agents are being compared to LMWH and are commonly used in pts with HIT. Both are monitored with the activated PTT. *Dabigatran* (150 mg PO bid) is an oral thrombin inhibitor and is non-inferior to warfarin in both DVT and stroke prevention in AF.

In-hospital anticoagulation is usually initiated with heparin for 4–10 days, with subsequent maintenance on warfarin after an overlap of 3 days. Duration of therapy depends on underlying condition; calf DVT with clear precipitating cause, 3 months; proximal or idiopathic DVT or PE, 6–12 months; recurrent idiopathic DVT, 12 months minimum; embolic disease with ongoing risk factor, long term, indefinite. The new oral Xa and thrombin inhibitors are easier to use than warfarin but much more expensive. They are at least comparably effective, have lower bleeding rates, and do not require laboratory monitoring. Reversal agents are in development.

FIBRINOLYTIC AGENTS

Tissue plasminogen activators (tPAs) mediate clot lysis by activating plasmin, which degrades fibrin. Currently available versions include streptokinase, urokinase, anistreplase (acylated plasminogen streptokinase activator complex), and three modestly distinct forms of recombinant tPA: alteplase, tenecteplase, and reteplase. Indications include treatment of DVT, with lower incidence of postphlebitic syndrome (chronic venous stasis, skin ulceration) than with heparin therapy; massive PE, arterial embolic occlusion of an extremity, treatment of acute myocardial infarction (MI), unstable angina pectoris. Dosages for fibrinolytic agents: (1) tPA—for acute MI and massive PE (adult >65 kg), 10-mg IV bolus over 1–2 min, then 50 mg IV over 1 h, and 40 mg IV over next 2 h (total dose = 100 mg). tPA is slightly more effective but more expensive than streptokinase for treatment of acute MI. (2) Streptokinase—for acute MI, 1.5 million IU IV over 60 min; or 20,000 IU as a bolus intracoronary (IC) infusion, followed by 2000 IU/min for 60 min IC. For PE or arterial or DVT, 250,000 IU over 30 min, then 100,000 IU/h for 24 h (PE) or

http://internalmedicinebook.com

72 h (arterial or DVT). (3) Urokinase—for PE, 4400 IU/kg IV over 10 min, then 4400 (IU/kg)/h IV for 12 h.

Fibrinolytic therapy is usually followed by a period of anticoagulant therapy with heparin. Fibrinolytic agents are contraindicated in pts with (1) active internal bleeding; (2) recent (<2–3 months) cerebrovascular accident; (3) intracranial neoplasm, aneurysm, or recent head trauma.

ANTIPLATELET AGENTS

Aspirin inhibits platelet function by blocking the ability of cyclooxygenase (COX-1) to synthesize thromboxane A2. The thienopyridines (ticlopidine and clopidogrel) inhibit ADP-induced platelet aggregation by blocking its receptor ($P2Y_{12}$). Dipyridamole acts by inhibiting phosphodiesterase, which permits cAMP levels to increase and block activation. Glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists block the integrin receptors on the platelet and prevent platelet aggregation. Three such agents are now in use: abciximab, an Fab antibody fragment that binds to the activated form of GPIIb/IIIa; eptifibatide, a cyclic heptapeptide that includes the KGD tripeptide motif that the GPIIb/IIIa receptor recognizes; and tirofiban, a tyrosine derivative that mimics the KGD motif.

Aspirin (160–325 mg/d) plus clopidogrel (400-mg loading dose then 75 mg/d) may be beneficial in lowering incidence of arterial thrombotic events (stroke, MI) in high-risk pts. Antiplatelet agents are useful in preventing strokes, complications from percutaneous coronary interventions, and progression of unstable angina.

For a more detailed discussion, see Konkle BA: Bleeding and Thrombosis, Chap. 78, p. 400; Konkle BA: Disorders of Platelets and Vessel Wall, Chap. 140, p. 725; Arruda VR, High KA: Coagulation Disorders, Chap. 141, p. 732; Freedman JE, Loscalzo J: Arterial and Venous Thrombosis, Chap. 142, p. 740; and Weitz JI: Antiplatelet, Anticoagulant, and Fibrinolytic Drugs, Chap. 143, p. 745, in HPIM-19.

65 Myeloid Leukemias, Myelodysplasia, and Myeloproliferative Syndromes

ACUTE MYELOID LEUKEMIA (AML)

AML is a clonal malignancy of myeloid bone marrow precursors in which poorly differentiated cells accumulate in the bone marrow and circulation.

Signs and symptoms occur because of the absence of mature cells normally produced by the bone marrow, including granulocytes (susceptibility to infection) and platelets (susceptibility to bleeding). In addition, if large numbers of immature malignant myeloblasts circulate, they may invade organs and rarely produce dysfunction. There are distinct morphologic subtypes (Table 65-1) that have largely

http://internalmedicinebook.com

TABLE 65-1 AML CLASSIFICATION SYSTEMS

World Health Organization Classification[a]
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*[b]
AML with inv(16)(p13.1;1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*[b]
Acute promyelocytic leukemia with t(15;17)(q22;q12); *PML-RARA*[b]
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemia of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11,20); *BCR-ABL11*
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B/myeloid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS
Provisional entity: Natural killer (NK)-cell lymphoblastic leukemia/lymphoma
French-American-British (FAB) Classification[c]
MO: Minimally differentiated leukemia
Ml: Myeloblastic leukemia without maturation
M2: Myeloblastic leukemia with maturation
M3: Hypergranular promyelocytic leukemia
M4: Myelomonocytic leukemia
M4Eo: Variant: Increase in abnormal marrow eosinophils
M5: Monocytic leukemia
M6: Erythroleukemia (DiGuglielmo's disease)
M7: Megakaryoblastic leukemia

[a]From SH Swerdlow et al (eds): *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon, IARC Press, 2008.
[b]Diagnosis is AML regardless of blast count.
[c]From JM Bennett et al: *Ann Intern Med* 103:620, 1985.
Abbreviation: AML, acute myeloid leukemia.

http://internalmedicinebook.com

overlapping clinical features. Of note is the propensity of pts with acute promyelocytic leukemia (APL) (FAB M3) to develop bleeding and disseminated intravascular coagulation, especially during induction chemotherapy, because of the release of procoagulants from their cytoplasmic granules.

Incidence and Etiology

In the United States about 20,830 cases occurred in 2015. AML accounts for about 80% of acute leukemias in adults. Etiology is unknown for the vast majority. As we age, mutations may occur in normal stem cells that convey a proliferative advantage and establish so-called clonal hematopoiesis. In the setting of clonal hematopoiesis, the relative risk for developing acute leukemia increases but the absolute risk is still very small. Three environmental exposures increase the risk: chronic benzene exposure, radiation exposure, and prior treatment with alkylating agents (especially in addition to radiation therapy) and topoisomerase II inhibitors (e.g., doxorubicin and etoposide). Chronic myeloid leukemia (CML), myelodysplasia, and myeloproliferative syndromes may all evolve into AML. Certain genetic abnormalities are associated with particular morphologic variants: t(15;17) with APL, inv(16) with eosinophilic leukemia; others occur in a number of types. Chromosome 11q23 abnormalities are often seen in leukemias developing after exposure to topoisomerase II inhibitors. Chromosome 5 or 7 deletions are seen in leukemias following radiation plus chemotherapy. The particular genetic abnormality has a strong influence on treatment outcome. Expression of MDR1 (multidrug resistance efflux pump) is common in older pts and adversely affects prognosis.

Clinical and Laboratory Features

Initial symptoms of acute leukemia have usually been present for <3 months; a preleukemic syndrome may be present in some 25% of pts with AML. Signs of anemia, pallor, fatigue, weakness, palpitations, and dyspnea on exertion are most common. White blood cell count (WBC) may be low, normal, or markedly elevated; circulating blast cells may or may not be present; with WBC $>100 \times 10^9$ blasts per liter, leukostasis in lungs and brain may occur. Minor pyogenic infections of the skin are common. Thrombocytopenia leads to spontaneous bleeding, epistaxis, petechiae, conjunctival hemorrhage, gingival bleeding, and bruising, especially with platelet count <20,000/μL. Anorexia and weight loss are common; fever may be present.

Bacterial and fungal infection are common; risk is heightened with total neutrophil count <5000/μL, and breakdown of mucosal and cutaneous barriers aggravates susceptibility; infections may be clinically occult in presence of severe leukopenia, and prompt recognition requires a high degree of clinical suspicion.

Hepatosplenomegaly occurs in about one-third of pts; leukemic meningitis may present with headache, nausea, seizures, papilledema, cranial nerve palsies.

Metabolic abnormalities may include hyponatremia, hypokalemia, elevated serum lactate dehydrogenase (LDH), hyperuricemia, and (rarely) lactic acidosis. With very high blast cell count in the blood, spurious hyperkalemia and hypoglycemia may occur (potassium released from and glucose consumed by tumor cells after the blood was drawn).

TREATMENT ACUTE MYELOID LEUKEMIA

Leukemic cell mass at time of presentation may be 10^{11}–10^{12} cells; when total leukemic cell numbers fall below ~10^9, they are no longer detectable in blood or bone marrow and pt appears to be in complete remission (CR). Thus, aggressive therapy must continue past the point when initial cell bulk is reduced if leukemia is to be eradicated. Typical phases of chemotherapy include remission induction and postremission therapy, with treatment lasting about 1 year. Figure 65-1 outlines a treatment algorithm.

http://internalmedicinebook.com

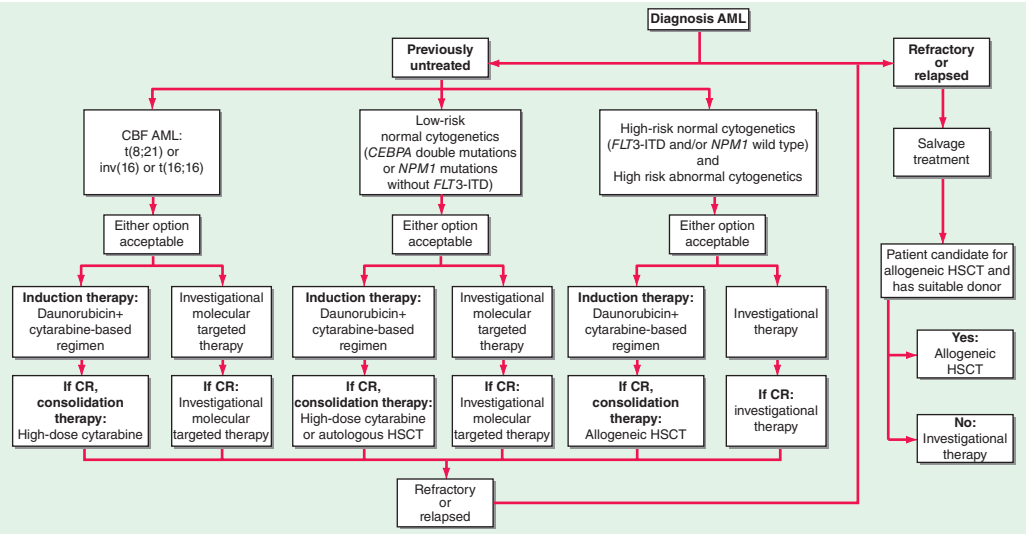


FIGURE 65-1 Flow chart for the therapy of newly diagnosed acute myeloid leukemia (AML). For all forms of AML except acute promyelocytic leukemia (APL), standard therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m2 per day) and a 3-day course of daunorubicin (60–90 mg/m2 per day) with or without additional drugs. Idarubicin (12–13 mg/m2 per day) could be used in place of daunorubicin (not shown). Patients who achieve complete remission (CR) undergo postremission consolidation therapy, including sequential courses of high-dose cytarabine, autologous hematopoietic stem cell transplantation (HSCT), allogeneic HSCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Patients with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. CBF, core binding factor; ITD, internal tandem duplication.

http://internalmedicinebook.com

Supportive care with transfusions of red cells and platelets [from cytomegalovirus (CMV)-seronegative donors, if pt is a candidate for bone marrow transplantation] is very important, as are aggressive prevention, diagnosis, and treatment of infections. Colony-stimulating factors offer little or no benefit; some recommend their use in older pts and those with active infections. Febrile neutropenia should be treated with broad-spectrum antibiotics (e.g., ceftazidime 1 g q8h); if febrile neutropenia persists beyond 7 days, amphotericin B should be added.

About 60–80% of pts will achieve initial remission when treated with cytarabine 100–200 (mg/m^2)/d by continuous infusion for 7 days, and daunorubicin [45 (mg/m^2)/d] or idarubicin [12–13 (mg/m^2)/d] for 3 days. Addition of etoposide may improve CR duration. Half of treated pts enter CR with the first cycle of therapy, and another 25% require two cycles. About 10–30% of pts achieve 5-year disease-free survival and probable cure. Pts achieving a CR who have low risk of relapse [cells contain t(8;21) or inv(16)] receive 3–4 cycles of cytarabine. Those at high risk of relapse may be considered for allogeneic bone marrow transplantation.

Response to treatment after relapse is short, and prognosis for pts who have relapsed is poor. In APL, arsenic trioxide plus *trans*-retinoic acid (tretinoin) induces differentiation of the leukemic cells and molecular complete remissions. A fraction of patients may develop pulmonary symptoms from the sludging of differentiated neoplastic granulocytes in the lung. Glucocorticoids may speed recovery from this syndrome.

Bone marrow transplantation from identical twin or human leukocyte antigen (HLA)-identical sibling is effective treatment for AML. Typical protocol uses high-dose chemotherapy ± total-body irradiation to ablate host marrow, followed by infusion of marrow from donor. Risks are substantial (unless marrow is from identical twin). Complications include graft-versus-host disease, interstitial pneumonitis, opportunistic infections (especially CMV). Comparison between transplantation and high-dose cytarabine as postremission therapy has not produced a clear advantage for either approach. Up to 30% of otherwise end-stage pts with refractory leukemia achieve probable cure from transplantation; results are better when transplant is performed during remission. Results are best for children and young adults.

CHRONIC MYELOID LEUKEMIA (CML)

CML is a clonal malignancy usually characterized by splenomegaly and production of increased numbers of granulocytes; course is initially indolent but eventuates in leukemic phase (blast crisis) that has a poorer prognosis than de novo AML; rate of progression to blast crisis is variable; overall survival averages 4 years from diagnosis.

Incidence and Etiology

In the United States about 14,620 cases have occurred in 2015. More than 90% of cases have a reciprocal translocation between chromosomes 9 and 22, creating the Philadelphia (Ph) chromosome and a fusion gene product called *BCR-ABL*. (BCR is from 9, ABL from 22.) The chromosome abnormality appears in all bone marrow–derived cells except T cells. The protein made by the chimeric gene is 210 kDa in chronic phase and 190 kDa in acute blast transformation. In some pts, the chronic phase is clinically silent and pts present with acute leukemia with the Ph chromosome.

Clinical and Laboratory Features

Symptoms develop gradually; easy fatigability, malaise, anorexia, abdominal discomfort and early satiety from the large spleen, excessive sweating. Occasional pts are found incidentally based on elevated leukocyte count. WBC is usually >25,000/μL

http://internalmedicinebook.com

with the increase accounted for by granulocytes and their precursors back to the myelocyte stage; bands and mature forms predominate. Basophils may account for 10–15% of the cells in the blood. Platelet count is normal or increased. Anemia is often present. Neutrophil alkaline phosphatase score is low. Marrow is hypercellular with granulocytic hyperplasia. Marrow blast cell count is normal or slightly elevated. Serum levels of vitamin B_{12}, B_{12}-binding proteins, and LDH are elevated in proportion to the WBC. With high blood counts, spurious hyperkalemia and hypoglycemia may be seen.

Natural History

Chronic phase lasts for 2–4 years. Accelerated phase is marked by anemia disproportionate to the disease activity or treatment. Platelet counts fall. Additional cytogenetic abnormalities appear. Blast cell counts increase. Usually within 6–8 months, overt blast crisis develops in which maturation ceases and blasts predominate. The clinical picture is that of acute leukemia. Half of the cases become AML, one-third have morphologic features of acute lymphoid leukemia, 10% are erythroleukemia, and the rest are undifferentiated. Survival in blast crisis is often <4 months.

TREATMENT CHRONIC MYELOID LEUKEMIA

Criteria for response are provided in Table 65-2. Allogeneic bone marrow transplantation has the potential to cure the disease in chronic phase. However, the first treatment is imatinib, a molecule that inhibits the chimeric gene product's tyrosine kinase activity. A daily oral dose of 400 mg produces complete hematologic remission of >90% and cytogenetic remission in 76%. If a matched donor is available, it is best to transplant pts in complete remission. Several mechanisms of resistance to imatinib have emerged, and it is unlikely that it leads to permanent remissions when used alone; however, follow-up is not sufficient to draw firm conclusions.

Pts who no longer respond to imatinib may respond to other tyrosine kinase inhibitors such as dasatinib (100 mg PO qd) or nilotinib (400 mg PO bid). The T315I mutation in the *BCR/ABL* gene conveys resistance to all three kinase inhibitors.

TABLE 65-2 RESPONSE CRITERIA IN CHRONIC MYELOID LEUKEMIA

Hematologic	
Complete response[a]	White blood cell count <10,000/μL, normalmorphology Normal hemoglobin and platelet counts
Incomplete response	White blood cell count ≥10,000/μl
Cytogenetic	Percentage of bone marrow metaphases with t(9;22)
Complete response	0
Partial response	≤35
Minor response	36–85[b]
No response	85–100
Molecular	Presence of *BCR/ABL* transcript by RT-PCR
Complete response	None (<0.1%)
Incomplete response	Any

[a]Complete hematologic response requires the disappearance of splenomegaly.
[b]Up to 15% normal metaphases are occasionally seen at diagnosis (when 30 metaphases are analyzed).
Abbreviation: RT-PCR, reverse transcriptase polymerase chain reaction.

http://internalmedicinebook.com

Ponatinib (45 mg/d) is effective in patients with the T315I mutation, but concerns have been raised about vascular toxicity. Allopurinol, 300 mg/d, prevents urate nephropathy. The only curative therapy for the disease is HLA-matched allogeneic bone marrow transplantation. The optimal timing of transplantation is unclear, but transplantation in chronic phase is more effective than transplantation in accelerated phase or blast crisis. Transplantation appears most effective in pts treated within a year of diagnosis. Long-term disease-free survival may be obtained in 50–60% of transplanted pts. Infusion of donor lymphocytes can restore remission in relapsing pts. In pts without a matched donor, autologous transplantation may be helpful using peripheral blood stem cells. Treatment of pts in blast crisis with imatinib can obtain responses, but they are not durable.

MYELODYSPLASTIC SYNDROMES (MDS)

These are clonal abnormalities of marrow cells characterized by varying degrees of cytopenias affecting one or more cell lines. The World Health Organization (WHO) classification of myelodysplastic syndromes is shown in Table 65-3. Other terms that have been used to describe one or more of the entities include *preleukemia* and *oligoblastic leukemia*.

Incidence and Etiology

About 3000 cases occur each year, mainly in persons >50 years old (median age, 68). As in AML, exposure to benzene, radiation, and chemotherapeutic agents may lead to MDS. Chromosome abnormalities occur in up to 80% of cases, including deletion of part or all of chromosomes 5, 7, and 9 (20 or 21 less commonly) and addition of part or all of chromosome 8. Mutations in genes involved in RNA splicing such as *SF3B1* have a more favorable outcome; mutations in genes often involve in AML such as *RUNX* and *ASXL1* have poorer prognosis.

Clinical and Laboratory Features

Symptoms depend on the affected lineages, 85% of pts are anemic, 50% have neutropenia, and about one-third have thrombocytopenia. The pathologic features of MDS are a cellular marrow with varying degrees of cytologic atypia including delayed nuclear maturation, abnormal cytoplasmic maturation, accumulation of ringed sideroblasts (iron-laden mitochondria surrounding the nucleus), uni- or bilobed megakaryocytes, micromegakaryocytes, and increased myeloblasts. Table 65-3 lists features used to identify distinct entities. Prognosis is defined by marrow blast %, karyotype, and lineages affected. The International Prognostic Scoring System is shown in Table 65-4.

TREATMENT MYELODYSPLASTIC SYNDROMES

Allogeneic bone marrow transplantation is the only curative therapy and may cure 60% of those so treated. However, the majority of pts with MDS are too old to receive transplantation. 5-Azacytidine (75 mg/m^2 daily × 7, q 4 weeks) can delay transformation to AML by 8–10 months. Decitabine (15 mg/m^2 by continuous IV infusion, q8h daily × 3, q 6 weeks) may induce responses lasting a median of 1 year in 20% of pts. Lenalidomide (10 mg/d), a thalidomide analogue with fewer central nervous system effects, causes a substantial fraction of pts with the 5q– syndrome to become transfusion-independent. Pts with low erythropoietin levels may respond to erythropoietin, and a minority of pts with neutropenia respond to granulocyte colony-stimulating factor. Supportive care is the cornerstone of treatment.

http://internalmedicinebook.com

TABLE 65-3 WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES/NEOPLASMS

Name	WHO Estimated Proportion of Patients with MDS	Peripheral Blood: Key Features	Bone Marrow: Key Features
Refractory cytopenias with unilineage dysplasia (RCUD):			
Refractory anemia (RA)	10–20%	Anemia <1% of blasts	Unilineage erythroid dysplasia (in ≥10% of cells) <5% blasts
Refractory neutropenia (RN)	<1%	Neutropenia <1% blasts	Unilineage granulocytic dysplasia <5% blasts
Refractory thrombocytopenia (RT)	<1%	Thrombocytopenia <1% blasts	Unilineage megakaryocytic dysplasia <5% blasts
Refractory anemia with ring sideroblasts (RARS)	3–11%	Anemia	Unilineage erythroid dysplasia ≥15% of erythroid precursors are ring sideroblasts <5% blasts
		No blasts	
Refractory cytopenias with multilineage dysplasia (RCMD)	30%	Cytopenia(s) <1% blasts	Multilineage dysplasia ± ring sideroblasts <5% blasts
		No Auer rods	No Auer rods
Refractory anemia with excess blasts, type 1 (RAEB-1)	40%	Cytopenia(s) <5% blasts	Unilineage or multilineage dysplasia
		No Auer rods	
Refractory anemia with excess blasts, type 2 (RAEB-2)		Cytopenia(s) 5–19% blasts	Unilineage or multilineage dysplasia 10–19% blasts
		± Auer rods	± Auer rods
MDS associated with isolated del(5q)	Uncommon	Anemia	Isolated 5q31 chromosome deletion
		Normal or high platelet count	Anemia; hypolobated megakaryocytes
		<1% blasts	<5% blasts

http://internalmedicinebook.com

Childhood MDS, including refractory cytopenia of childhood (*provisional*) (RCC)	1 %	Pancytopenia	<5% marrow blasts for RCC Marrow usually hypocellular
MDS, unclassifiable (MDS-U)	?	Cytopenia ≤1% blasts	Does not fit other categories Dysplasia <5% blasts If no dysplasia, MDS-associated karyotype

Note: If peripheral blood blasts are 2–4%, the diagnosis is RAEB-1 even if marrow blasts are <5%. If Auer rods are present, the WHO considers the diagnosis RAEB-2 if the blast proportion is <20% (even if <10%), AML if at least 20% blasts. For all subtypes, peripheral blood monocytes are $<1 \times 10^9$/L. Bicytopenia may be observed in RCUD subtypes, but pancytopenia with unilineage marrow dysplasia should be classified as MDS-U. Therapy-related MDS (t-MDS), whether due to alkylating agents, topoisomerase II (t-MDS/t-AML) in the WHO classification of AML and precursor lesions. The listing in this table excludes MDS/myeloproliferative neoplasm overlap categories, such as chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, and the provisional entity RARS with thrombocytosis.

Abbreviation: MDS, myelodysplastic syndrome.

http://internalmedicinebook.com

TABLE 65-4 INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)

	Score Value				
Prognostic Variable	**0**	**0.5**	**1**	**1.5**	**2**
Bone marrow blasts (%)	<5%	5–10%		11–20%	21–30%
Karyotype[a]	Good	Intermediate	Poor		
Cytopenia[b] (lineages affected)	0 or 1	2 or 3			
Risk Group Scores	**Score**				
Low	0				
Intermediate-1	0.5–1				
Intermediate-2	1.5–2				
High	≥2.5				

[a]Good, normal, -Y, del(5q), del(20q); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, all other abnormalities.
[b]Cytopenias defined as Hb <100 g/L, platelet count <100,000/μL, absolute neutrophil count <1500/μL.

MYELOPROLIFERATIVE SYNDROMES

The three major myeloproliferative syndromes are polycythemia vera, idiopathic myelofibrosis, and essential thrombocytosis. All are clonal disorders of hematopoietic stem cells and all are associated with a mutation in the *JAK2* kinase (V617F) that results in activation of the kinase. The mutation is seen in 90% of pts with polycythemia vera and ~45% of pts with idiopathic myelofibrosis and essential thrombocytosis.

POLYCYTHEMIA VERA

The most common myeloproliferative syndrome, this is characterized by an increase in red blood cell (RBC) mass, massive splenomegaly, and clinical manifestations related to increased blood viscosity, including neurologic symptoms (vertigo, tinnitus, headache, visual disturbances) and thromboses (myocardial infarction, stroke, peripheral vascular disease; uncommonly, mesenteric and hepatic). It must be distinguished from other causes of increased RBC mass (Chap. 45). This is most readily done by assaying serum erythropoietin levels. Polycythemia vera is associated with very low erythropoietin levels; in other causes of erythrocytosis, erythropoietin levels are high. Assays for the *JAK2*(V617F) mutation are now widely available. Pts are effectively managed with phlebotomy. Some pts require splenectomy to control symptoms, and those with severe pruritus may benefit from psoralens and UV light. 20% develop myelofibrosis, <5% acute leukemia. An inhibitor of JAK1 and *JAK2*, ruxolitinib, is being tested.

IDIOPATHIC MYELOFIBROSIS

This rare entity is characterized by marrow fibrosis, myeloid metaplasia with extramedullary hematopoiesis, and splenomegaly. Evaluation of a blood smear reveals teardrop-shaped RBC, nucleated RBC, and some early granulocytic forms, including promyelocytes. However, many entities may lead to marrow fibrosis and extramedullary hematopoiesis, and the diagnosis of primary idiopathic myelofibrosis is made only when the many other potential causes are ruled out. The following diseases are in the differential diagnosis: CML, polycythemia vera, Hodgkin's disease, cancer metastatic to the marrow (especially from breast and prostate), infection (particularly granulomatous infections), and hairy cell leukemia. Supportive therapy

http://internalmedicinebook.com

is generally used; novel inhibitors of *JAK2* and telomerase have shown activity in reducing splenomegaly and marrow fibrosis in some cases; however, no study has yet shown a particular drug therapy to improve survival. Cases that do not have *JAK2* mutations often have mutations in *CALR*.

ESSENTIAL THROMBOCYTOSIS

This is usually noted incidentally upon routine platelet count done in an asymptomatic person. Like myelofibrosis, many conditions can produce elevated platelet counts; thus, the diagnosis is one of exclusion. Platelet count must be >500,000/μL, and known causes of thrombocytosis must be ruled out including CML, iron deficiency, splenectomy, malignancy, infection, hemorrhage, polycythemia vera, myelodysplasia, and recovery from vitamin B_{12} deficiency. Although usually asymptomatic, pts should be treated if they develop migraine headache, transient ischemic attack, or other bleeding or thrombotic disease manifestations. Interferon α is effective therapy, as are anagrelide and hydroxyurea. Treatment should not be given just because the absolute platelet count is high in the absence of other symptoms. *JAK2* and *CALR* mutations account for about 80% of cases; *MPL* mutations, about 10%.

For a more detailed discussion, see Young NS: Aplastic Anemia, Myelodysplasia, and Related Bone Marrow Failure Syndromes, Chap. 130, p. 662; Spivak JL: Polycythemia Vera and Other Myeloproliferative Diseases, Chap. 131, p. 672; and Marcucci G, Bloomfield CD: Acute Myeloid Leukemia, Chap. 132, p. 678; Kantarjian H, Cortes J: Chronic Myeloid Leukemia, Chap. 133, p. 687, in HPIM-19.

66 Lymphoid Malignancies

DEFINITION

Neoplasms of lymphocytes usually represent malignant counterparts of cells at discrete stages of normal lymphocyte differentiation. When bone marrow and peripheral blood involvement dominate the clinical picture, the disease is classified as a *lymphoid leukemia*. When lymph nodes and/or other extranodal sites of disease are the dominant site(s) of involvement, the tumor is called a *lymphoma*. The distinction between lymphoma and leukemia is sometimes blurred; e.g., small lymphocytic lymphoma and chronic lymphoid leukemia are tumors of the same cell type and are distinguished arbitrarily on the basis of the absolute number of peripheral blood lymphocytes (>5 × 10^9/L defines leukemia).

CLASSIFICATION

Historically, lymphoid tumors have had separate pathologic classifications based on the clinical syndrome—lymphomas according to the Rappaport, Kiel, or Working Formulation systems; acute leukemias according to the French-American-British (FAB) system; Hodgkin's disease (HD) according to the Rye classification. Myelomas

http://internalmedicinebook.com

have generally not been subclassified by pathologic features of the neoplastic cells. The World Health Organization (WHO) has proposed a unifying classification system that brings together all lymphoid neoplasms into a single framework. Although the new system bases the definitions of disease entities on histology, genetic abnormalities, immunophenotype, and clinical features, its organization is based on cell of origin (B cell vs. T cell) and maturation stage (precursor vs. mature) of the tumor, features that are of limited value to the clinician. Table 66-1 lists the disease entities according to a more clinically useful schema based on the clinical manifestations and natural history of the diseases.

INCIDENCE

Lymphoid tumors are increasing in incidence. Nearly 127,000 cases were diagnosed in 2015 in the United States (Fig. 66-1).

ETIOLOGY

The cause(s) for the vast majority of lymphoid neoplasms is unknown. The malignant cells are monoclonal and often contain numerous genetic abnormalities. Some genetic alterations are characteristic of particular histologic entities: t(8;14) in Burkitt's lymphoma, t(14;18) in follicular lymphoma, t(11;14) in mantle cell lymphoma, t(2;5) in anaplastic large cell lymphoma, translocations or mutations involving *bcl*-6 on 3q27 in diffuse large cell lymphoma, and others. In most cases, translocations involve insertion of a distant chromosome segment into the antigen receptor genes (either immunoglobulin or T cell receptor) during the rearrangement of the gene segments that form the receptors.

Three viruses—Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8) (both herpes family viruses), and human T-lymphotropic virus type I (HTLV-I, a retrovirus)—may cause some lymphoid tumors. EBV has been strongly associated with African Burkitt's lymphoma and the lymphomas that complicate immunodeficiencies (disease-related or iatrogenic). EBV has an uncertain relationship to mixed cellularity HD and angiocentric lymphoma. HHV-8 causes a rare entity, body cavity lymphoma, mainly in pts with AIDS. HTLV-I is associated with adult T cell leukemia/lymphoma (ATL). Both the virus and the disease are endemic to southwestern Japan and the Caribbean.

Gastric *Helicobacter pylori* infection is associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma and perhaps gastric large-cell lymphoma. Eradication of the infection produces durable remissions in about half of pts with gastric MALT lymphoma. MALT lymphomas of other sites are associated with either infection (ocular adnexae, *Chlamydia psittaci*; small intestine, *Campylobacter jejuni*; skin, *Borrelia*) or autoimmunity (salivary gland, Sjögren's syndrome; thyroid gland, Hashimoto's thyroiditis).

Inherited or acquired immunodeficiencies and autoimmune disorders predispose individuals to lymphoma. Lymphoma is 17 times more common in HIV-infected than in HIV-noninfected people. Lymphoma occurs with increased incidence in farmers and meat workers; HD is increased in wood workers.

DIAGNOSIS AND STAGING

Excisional biopsy is the standard diagnostic procedure; adequate tissue must be obtained. Tissue undergoes three kinds of studies: (1) light microscopy to discern the pattern of growth and the morphologic features of the malignant cells, (2) flow cytometry for assessment of immunophenotype, and (3) genetic studies (cytogenetics, DNA sequencing). Needle aspirates of nodal or extranodal masses are not adequate diagnostic procedures. Leukemia diagnosis and lymphoma staging include generous bilateral iliac crest bone marrow biopsies. Differential diagnosis of adenopathy is reviewed in Chap. 44.

http://internalmedicinebook.com

TABLE 66-1 CLINICAL SCHEMA OF LYMPHOID NEOPLASMS

Chronic lymphoid leukemias/lymphomas
Chronic lymphocytic leukemia/small lymphocytic lymphoma (99% B cell, 1% T cell)
Prolymphocytic leukemia (90% B cell, 10% T cell)
Large granular lymphocyte leukemia (80% NK cell, 20% T cell)
Hairy cell leukemia (99–100% B cell)
Indolent lymphoma
Follicular center cell lymphoma, grades I and II (100% B cell)
Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (100% B cell)
Marginal zone lymphoma (100% B cell)
Extranodal (MALT lymphoma)
Nodal (monocytoid B cell lymphoma)
Splenic marginal zone lymphoma
Cutaneous T cell lymphoma (mycosis fungoides) (100% T cell)
Aggressive lymphoma
Diffuse large cell lymphoma (85% B cell, 15% T cell) includes immunoblastic
Follicular center cell lymphoma, grade III (100% B cell)
Mantle cell lymphoma (100% B cell)
Primary mediastinal (thymic) large B cell lymphoma (100% B cell)
Burkitt-like lymphoma (100% B cell)
Peripheral T cell lymphoma (100% T cell)
Angioimmunoblastic lymphoma (100% T cell)
Angiocentric lymphoma (80% T cell, 20% NK cell)
Intestinal T cell lymphoma (100% T cell)
Anaplastic large cell lymphoma (70% T cell, 30% null cell)
Acute lymphoid leukemias/lymphomas
Precursor lymphoblastic leukemia/lymphoma (80% T cell, 20% B cell)
Burkitt's leukemia/lymphoma (100% B cell)
Adult T cell leukemia/lymphoma (100% T cell)
Plasma cell disorders (100% B cell)
Monoclonal gammopathy of uncertain significance
Solitary plasmacytoma
Extramedullary plasmacytoma
Multiple myeloma
Plasma cell leukemia
Hodgkin's lymphoma (cell of origin mainly B cell)
Lymphocyte predominant
Nodular sclerosis
Mixed cellularity
Lymphocyte depleted

Abbreviations: MALT, mucosa-associated lymphatic tissue; NK, natural killer.

http://internalmedicinebook.com

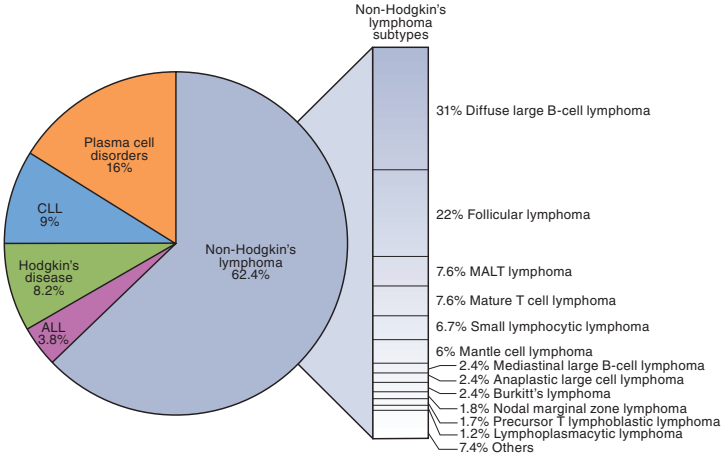


FIGURE 66-1 Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

Staging varies with the diagnosis. In acute leukemia, peripheral blood blast counts are most significant in assessing prognosis. In chronic leukemia, peripheral blood red blood cell (RBC) and platelet counts are most significant in assessing prognosis. Non-Hodgkin's lymphomas have five clinical prognostic factors; indolent and aggressive lymphomas share three of these, advanced stage, high lactate dehydrogenase (LDH) levels, and age >60 years. In follicular lymphoma, the last two factors are Hb <120 g/L (<12 g/dL) and more than four nodal sites of involvement. In aggressive lymphoma, more than one extranodal site and performance status predict outcome. In myeloma, serum levels of paraprotein, creatinine, and β_2-microglobulin levels predict survival.

CHRONIC LYMPHOID LEUKEMIAS/LYMPHOMAS

Most of these entities have a natural history measured in years. (Prolymphocytic leukemia is very rare and can be very aggressive.) Chronic lymphocytic leukemia (CLL) is the most common entity in this group (~15,000 cases/year in the United States) and the most common leukemia in the Western world.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Usually presents as asymptomatic lymphocytosis in pts >60 years. The malignant cell is a CD5+ B cell that looks like a normal small lymphocyte. Trisomy 12 is the most common genetic abnormality. Prognosis is related to stage; stage is determined mainly by the degree to which the tumor cells crowd out normal hematopoietic elements from the marrow (Table 66-2). Cells may infiltrate nodes and spleen as well as marrow. Nodal involvement may be related to the expression of an adhesion molecule that allows the cells to remain in the node rather than recirculate. Pts often have hypogammaglobulinemia. Up to 20% have autoimmune antibodies that may produce autoimmune hemolytic anemia, thrombocytopenia, or red cell aplasia. Death is from infection, marrow failure, or intercurrent illnesses. In 5%, the disease evolves to aggressive lymphoma (Richter's syndrome) that is refractory to treatment.

Subsets of CLL may exist based on whether the immunoglobulin expressed by the tumor cell contains mutations (more indolent course, good prognosis) or retains the

http://internalmedicinebook.com

TABLE 66-2 STAGING OF B-CELL CLL AND RELATION TO SURVIVAL

Stage	Clinical Features	Median Survival, Years
RAI		
0	Lymphocytosis	12
I	Lymphocytosis + adenopathy	9
II	Lymphocytosis + splenomegaly	7
III	Anemia	1–2
IV	Thrombocytopenia	1–2
BINET		
A	No anemia/thrombocytopenia, <3 involved sites	>10
B	No anemia/thrombocytopenia, >3 involved sites	5
C	Anemia and/or thrombocytopenia	2

germ-line sequence (more aggressive course, poor response to therapy). Methods to distinguish the two subsets clinically are not well defined; CD38+ tumors may have poorer prognosis. The expression of ZAP-70, an intracellular tyrosine kinase normally present in T cells and aberrantly expressed in about 45% of CLL cases, may be a better way to define prognostic subsets. ZAP-70-positive cases usually need treatment within about 3–4 years from diagnosis; ZAP-70-negative cases usually don't require treatment for 8–11 years.

TREATMENT CHRONIC LYMPHOCYTIC LEUKEMIA

Supportive care is generally given until anemia or thrombocytopenia develops. At that time, tests are indicated to assess the cause of the anemia or thrombocytopenia. Decreased RBC and/or platelet counts related to peripheral destruction may be treated with splenectomy or glucocorticoids without cytotoxic therapy in many cases. If marrow replacement is the mechanism, therapy is indicated. Fludarabine, 25 (mg/m^2)/d IV × 5 days every 4 weeks, induces responses in about 75% of pts, complete responses in half. Rituximab (375–500 mg/m^2 day 1), fludarabine (25 mg/m^2 days 2–4 on cycle 1 and 1–3 in subsequent cycles), plus cyclophosphamide (250 mg/m^2 with fludarabine) induce complete responses in nearly 70% of pts but the regimen is associated with significant myelotoxicity. Glucocorticoids increase the risk of infection without adding a substantial antitumor benefit. Monthly IV immunoglobulin (IVIg) significantly reduces risk of serious infection but is expensive and usually reserved for pts who have had a serious infection. Alkylating agents are also active against the tumor. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, is highly active in CLL and some use it as primary therapy. Therapeutic intent is palliative in most pts. Young pts may be candidates for high-dose therapy and autologous or allogeneic hematopoietic cell transplantation; long-term disease-free survival has been noted. Minitransplant, in which the preparative regimen is immunosuppressive but not myeloablative, may be less toxic and as active or more active in disease treatment than high-dose therapy. Monoclonal antibodies alemtuzumab (anti-CD52) and rituximab, obinutuzumab, and ofatumumab (all anti-CD20s) also are active as single agents or combined with chlorambucil.

See Chaps. 134 and 135e in HPIM-19 for discussion of the rarer entities.

http://internalmedicinebook.com

INDOLENT LYMPHOMAS

These entities have a natural history measured in years. Median survival is about 14 years. Follicular lymphoma is the most common indolent lymphoma, accounting for about one-third of all lymphoid malignancies.

FOLLICULAR LYMPHOMA

Usually presents with painless peripheral lymphadenopathy, often involving several nodal regions. "B symptoms" (fever, sweats, weight loss) occur in 10%, less common than with Hodgkin's lymphoma. In about 25%, nodes wax and wane before the pt seeks medical attention. Median age is 55 years. Disease is widespread at diagnosis in 85%. Liver and bone marrow are commonly involved extranodal sites.

The tumor has a follicular or nodular growth pattern reflecting the follicular center origin of the malignant cell. The t(14;18) is present in 85% of cases, resulting in the overexpression of bcl-2, a protein involved in prevention of programmed cell death. The normal follicular center B cell is undergoing active mutation of the immunoglobulin variable regions in an effort to generate antibody of higher affinity for the selecting antigen. Follicular lymphoma cells also have a high rate of mutation that leads to the accumulation of genetic damage. Over time, follicular lymphomas acquire sufficient genetic damage (e.g., mutated p53) to accelerate their growth and evolve into diffuse large B-cell lymphomas that are often refractory to treatment. The majority of pts dying from follicular lymphoma have undergone histologic transformation. This transformation occurs at a rate of about 7% per year and is an attribute of the disease, not the treatment. The rate of histologic progression has decreased as treatment has improved.

TREATMENT FOLLICULAR LYMPHOMA

Only 15% of pts have localized disease, but the majority of these pts are curable with radiation therapy. Although many forms of treatment induce tumor regression in advanced-stage pts, disease cure has been elusive. No therapy, single-agent alkylators, nucleoside analogues (fludarabine, cladribine), combination chemotherapy, radiation therapy, and biologic agents [interferon (IFN) α, monoclonal antibodies such as rituximab (anti-CD20)] are all considered appropriate. More than 90% of pts are responsive to treatment; complete responses are seen in about 50–75% of pts treated aggressively. The median duration of remission of pts treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) + rituximab exceeds 6 years. Bendamustine + rituximab is an active combination. Younger pts are being treated experimentally with high-dose therapy and autologous hematopoietic stem cells or minitransplant. It is not yet clear whether this is curative. Radioimmunotherapy with isotopes guided by anti-CD20 antibody (ibritumomab tiuxetan, In-111; tositumomab, I-131) may produce durable responses. Combination chemotherapy with or without IFN maintenance may prolong survival and delay or prevent histologic progression, especially in pts with poor prognostic features. Remissions appear to last longer with chemotherapy plus rituximab; some data suggest that the longer remissions are leading to improved survival.

See Chaps. 134 and 135e in HPIM-19 for discussion of the other indolent lymphomas.

AGGRESSIVE LYMPHOMAS

A large number of pathologic entities share an aggressive natural history; median survival untreated is 6 months, and nearly all untreated pts are dead within 1 year. Pts may present with asymptomatic adenopathy or symptoms referable to involvement

http://internalmedicinebook.com

of practically any nodal or extranodal site: Mediastinal involvement may produce superior vena cava syndrome or pericardial tamponade; retroperitoneal nodes may obstruct ureters; abdominal masses may produce pain, ascites, or GI obstruction or perforation; CNS involvement may produce confusion, cranial nerve signs, headache, seizures, and/or spinal cord compression; bone involvement may produce pain or pathologic fracture. About 45% of pts have B symptoms.

Diffuse large B-cell lymphoma is the most common histologic diagnosis among the aggressive lymphomas, accounting for 35–45% of all lymphomas. Aggressive lymphomas together account for ~60% of all lymphoid tumors. About 85% of aggressive lymphomas are of mature B-cell origin; 15% are derived from peripheral (postthymic) T cells.

APPROACH TO THE PATIENT: **Aggressive Lymphoma**

Early diagnostic biopsy is critical. Pt workup is directed by symptoms and known patterns of disease. Pts with Waldeyer's ring involvement should undergo careful evaluation of the GI tract. Pts with bone or bone marrow involvement should have a lumbar puncture to evaluate meningeal CNS involvement.

TREATMENT AGGRESSIVE LYMPHOMAS

Localized aggressive lymphomas are usually treated with four cycles of CHOP combination chemotherapy ± involved-field radiation therapy. About 85% of these pts are cured. CHOP + rituximab appears to be even more effective than CHOP + radiation therapy. The specific therapy used for pts with more advanced disease is controversial. Six cycles of CHOP + rituximab is the treatment of choice for advanced-stage disease. Outcome is influenced by tumor bulk (usually measured by LDH levels, stage, and number of extranodal sites) and physiologic reserve (usually measured by age and Karnofsky status) (Table 66-3). CHOP + rituximab cures about two-thirds of pts. The use of a sequential high-dose chemotherapy regimen in pts with high-intermediate and high-risk disease has yielded long-term survival in about 75% of pts in some institutions. Other studies fail to confirm a role for high-dose therapy.

About 30–45% of pts not cured with initial standard combination chemotherapy may be salvaged with high-dose therapy and autologous hematopoietic stem cell transplantation.

Specialized approaches are required for lymphomas involving certain sites (e.g., CNS, stomach) or under certain complicating clinical circumstances (e.g., concurrent illness, AIDS). Lymphomas occurring in iatrogenically immunosuppressed pts may regress when immunosuppressive medication is withheld. Lymphomas occurring post–allogeneic marrow transplant may regress with infusions of donor leukocytes.

Pts with rapidly growing bulky aggressive lymphoma may experience tumor lysis syndrome when treated (Chap. 25); prophylactic measures (hydration, urine alkalinization, allopurinol, rasburicase) may be lifesaving.

ACUTE LYMPHOID LEUKEMIAS/LYMPHOMAS

ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

These are more common in children than adults (~6000 total cases/year). The majority of cases have tumor cells that appear to be of thymic origin, and pts may have mediastinal masses. Pts usually present with recent onset of signs of marrow failure

http://internalmedicinebook.com

TABLE 66-3 INTERNATIONAL PROGNOSTIC INDEX FOR NHL

Five clinical risk factors:	
Age ≥60 years	
Serum lactate dehydrogenase levels elevated	
Performance status ≥2 (ECOG) or ≤70 (Karnofsky)	
Ann Arbor stage III or IV	
>1 site of extranodal involvement	
Pts are assigned a number for each risk factor they have.	
Pts are grouped differently based on the type of lymphoma.	
For diffuse large B-cell lymphoma:	
0, 1 factor = low risk:	35% of cases; 5-year survival, 73%
2 factors = low-intermediate risk:	27% of cases; 5-year survival, 51%
3 factors = high-intermediate risk:	22% of cases; 5-year survival, 43%
4, 5 factors = high risk:	16% of cases; 5-year survival, 26%
For diffuse large B-cell lymphoma treated with R-CHOP:	
0 factor = very good:	10% of cases; 5-year survival, 94%
1, 2 factors = good:	45% of cases; 5-year survival, 79%
3, 4, 5 factors = poor:	45% of cases; 5-year survival, 55%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NHL, non-Hodgkin's lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

(pallor, fatigue, bleeding, fever, infection). Hepatosplenomegaly and adenopathy are common. Males may have testicular enlargement reflecting leukemic involvement. Meningeal involvement may be present at diagnosis or develop later. Elevated LDH, hyponatremia, and hypokalemia may be present, in addition to anemia, thrombocytopenia, and high peripheral blood blast counts. The leukemic cells are more often FAB type L2 in adults than in children, where L1 predominates. Leukemia diagnosis requires at least 20% lymphoblasts in the marrow. Prognosis is adversely affected by high presenting white count, age >35 years, and the presence of t(9;22), t(1;19), and t(4;11) translocations. HOX11 expression identifies a more favorable subset of T cell acute lymphoblastic leukemia.

TREATMENT ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

Successful treatment requires intensive induction phase, CNS prophylaxis, and maintenance chemotherapy that extend for about 2 years. Vincristine, L-asparaginase, cytarabine, daunorubicin, and prednisone are particularly effective agents. Intrathecal or high-dose systemic methotrexate is effective CNS prophylaxis. Long-term survival of 60–65% of pts may be achieved. The role and timing of bone marrow transplantation in primary therapy are debated, but up to 30% of relapsed pts may be cured with salvage transplantation.

BURKITT'S LYMPHOMA/LEUKEMIA

This is also more common in children. It is associated with translocations involving the c-*myc* gene on chromosome 8 rearranging with immunoglobulin heavy or light chain genes. Pts often have disseminated disease with large abdominal masses, hepatomegaly, and adenopathy. If a leukemic picture predominates, it is classified as FAB L3.

http://internalmedicinebook.com

TREATMENT **BURKITT'S LYMPHOMA/LEUKEMIA**

Resection of large abdominal masses improves treatment outcome. Aggressive leukemia regimens that include vincristine, cyclophosphamide, 6-mercaptopurine, doxorubicin, and prednisone are active. CODOX-M and the BFM regimen are the most effective regimens. Cure may be achieved in 50–60%. The need for maintenance therapy is unclear. Prophylaxis against tumor lysis syndrome is important (Chap. 25).

ADULT T CELL LEUKEMIA/LYMPHOMA (ATL)

This is very rare; only a small fraction (~2%) of persons infected with HTLV-I go on to develop the disease. Some HTLV-I-infected pts develop spastic paraplegia from spinal cord involvement without developing cancer. The characteristic clinical syndrome of ATL includes high white count without severe anemia or thrombocytopenia, skin infiltration, hepatomegaly, pulmonary infiltrates, meningeal involvement, and opportunistic infections. The tumor cells are CD4+ T cells with cloven hoof- or flower-shaped nuclei. Hypercalcemia occurs in nearly all pts and is related to cytokines produced by the tumor cells.

TREATMENT **ADULT T CELL LEUKEMIA/LYMPHOMA**

Aggressive therapy is associated with serious toxicity related to the underlying immunodeficiency. Glucocorticoids relieve hypercalcemia. The tumor is responsive to therapy, but responses are generally short lived. Zidovudine and IFN may be palliative in some pts.

PLASMA CELL DISORDERS

The hallmark of plasma cell disorders is the production of immunoglobulin molecules or fragments from abnormal plasma cells. The intact immunoglobulin molecule, or the heavy chain or light chain produced by the abnormal plasma cell clone, is detectable in the serum and/or urine and is called the M (for monoclonal) component. The amount of the M component in any given pt reflects the tumor burden in that pt. In some, the presence of a clonal light chain in the urine (Bence Jones protein) is the only tumor product that is detectable. M components may be seen in pts with other lymphoid tumors, nonlymphoid cancers, and noncancerous conditions such as cirrhosis, sarcoidosis, parasitic infestations, and autoimmune diseases.

MULTIPLE MYELOMA

A malignant proliferation of plasma cells in the bone marrow (notably not in lymph nodes). Nearly 27,000 new cases are diagnosed each year. Disease manifestations result from tumor expansion, local and remote actions of tumor products, and the host response to the tumor. About 70% of pts have bone pain, usually involving the back and ribs, precipitated by movement. Bone lesions are multiple, lytic, and rarely accompanied by an osteoblastic response. Thus, bone scans are less useful than radiographs. The production of osteoclast-activating cytokines by tumor cells leads to substantial calcium mobilization, hypercalcemia, and symptoms related to it. Decreased synthesis and increased catabolism of normal immunoglobulins lead to hypogammaglobulinemia, and a poorly defined tumor product inhibits granulocyte migration. These changes create a susceptibility to bacterial infections, especially the pneumococcus, *Klebsiella pneumoniae*, and *Staphylococcus aureus* affecting the lung and *Escherichia coli* and other gram-negative pathogens affecting the urinary tract. Infections affect at least 75% of pts at some time in their course. Renal failure may affect 25% of pts; its pathogenesis is multifactorial—hypercalcemia, infection, toxic

http://internalmedicinebook.com

effects of light chains, urate nephropathy, and dehydration. Neurologic symptoms may result from hyperviscosity, cryoglobulins, and rarely amyloid deposition in nerves. Anemia occurs in 80% related to myelophthisis and inhibition of erythropoiesis by tumor products. Clotting abnormalities may produce bleeding.

Diagnosis

Marrow plasmacytosis >10%, lytic bone lesions, and a serum and/or urine M component are the classic triad. Monoclonal gammopathy of uncertain significance (MGUS) is much more common than myeloma, affecting about 6% of people over age 70 years; in general, MGUS is associated with a level of M component <20 g/L, low serum β_2-microglobulin, <10% marrow plasma cells, and no bone lesions. Lifetime risk of progression of MGUS to myeloma is about 25%.

Staging

Disease stage influences survival (Table 66-4).

TREATMENT MULTIPLE MYELOMA

About 10% of pts have very slowly progressive disease (the so-called smoldering myeloma) and do not require treatment until the paraprotein levels rise above 50 g/L or progressive bone disease occurs. Pts with solitary plasmacytoma and extramedullary plasmacytoma are usually cured with localized radiation therapy. Supportive care includes early treatment of infections; control of hypercalcemia with glucocorticoids, hydration, and natriuresis; chronic administration of bisphosphonates to antagonize skeletal destruction; and prophylaxis against urate nephropathy and dehydration. Therapy aimed at the tumor is usually palliative. Initial therapy is usually one of several approaches, based on whether the pt is a candidate for high-dose therapy and autologous stem cell transplant. Transplant eligible (avoid alkylating agents): thalidomide, 400 mg/d PO or 200 mg qhs, plus dexamethasone, 40 mg/d on days 1–4 each month, with or without bortezomib, or chemotherapy such as liposomal doxorubicin. Transplant ineligible: melphalan, 8 mg/m^2 orally for 4–7 days every 4–6 weeks, plus prednisone. About 60% of pts have significant symptomatic improvement plus a 75% decline in the M component. Bortezomib also appears to improve response rates to melphalan. Experimental approaches using sequential high-dose pulses of melphalan plus two successive autologous stem cell transplants have produced complete responses in about 50% of pts <65 years. Long-term follow-up is required to see whether survival is enhanced. Palliatively treated pts generally follow a chronic course for 2–5 years, followed by an acceleration characterized by organ infiltration with myeloma cells and marrow failure. More aggressive treatment may produce median survival of 6 years. New approaches to salvage treatment include bortezomib, 1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks, often used with dexamethasone, vincristine, and/or liposomal doxorubicin. Lenalidomide is also active and increasingly used as maintenance therapy.

HODGKIN'S LYMPHOMA

About 9000 new cases are diagnosed each year. HD is a tumor of Reed-Sternberg cells, aneuploid cells that usually express CD30 and CD15 but may also express other B or T cell markers. Most tumors are derived from B cells in that immunoglobulin genes are rearranged but not expressed. Most of the cells in an enlarged node are normal lymphoid, plasma cells, monocytes, and eosinophils. The etiology is unknown, but the incidence in both identical twins is 99-fold increased over the expected concordance, suggesting a genetic susceptibility. Distribution of histologic subtypes is 75% nodular sclerosis, 20% mixed cellularity, with lymphocyte predominant and lymphocyte depleted representing about 5%.

http://internalmedicinebook.com

TABLE 66-4 MYELOMA STAGING SYSTEMS

Durie-Salmon Staging System

Stage	Criteria	Estimated tumor burden × 10^{12} cells/m^2
I	All of the following: 1. Hemoglobin >100 g/L (>10 g/dL) 2. Serum calcium <3 mmol/L (<12 mg/dL) 3. Normal bone x-ray or solitary lesion 4. Low M-component production a. IgG level <50 g/L (<5 g/dL) b. IgA level <30 g/L (<3 g/dL) c. Urine light chain <4 g/24 h	<0.6 (low)
II	Fitting neither I nor III	0.6–1.20 (intermediate)
III	One or more of the following: 1. Hemoglobin <85 g/L (<8.5 g/dL) 2. Serum calcium >3 mmol/L (>12 mg/dL) 3. Advanced lytic bone lesions 4. High M-component production a. IgG level >70 g/L (>7 g/dL) b. IgA level >50 g/L (>5 g/dL) c. Urine light chains >12 g/24 h	>1.20 (high)

Level	Stage	Median Survival, Months
Subclassification based on serum creatinine levels		
A <177 µmol/L (<2 mg/dL)	IA	61
B >177 µmol/L (>2 mg/dL)	IIA, B	55
	IIIA	30
	IIIB	15
International Staging System		
β_2M <3.5, alb ≥3.5	I (28%)	62
β_2M <3.5, alb <3.5 *or* β_2M = 3.5–5.5	II (39%)	44
β_2M >5.5	III (33%)	29

Note: β_2M, serum β_2-microglobulin in mg/L; alb, serum albumin in g/dL; (#), % pts presenting at each stage.

http://internalmedicinebook.com

Clinical Manifestations

Usually presents with asymptomatic lymph node enlargement or with adenopathy associated with fever, night sweats, weight loss, and sometimes pruritus. Mediastinal adenopathy (common in nodular sclerosing HD) may produce cough. Spread of disease tends to be to contiguous lymph node groups. Superior vena cava obstruction or spinal cord compression may be presenting manifestation. Involvement of bone marrow and liver is rare.

Differential Diagnosis

- Infection: mononucleosis, viral syndromes, *Toxoplasma*, *Histoplasma*, primary tuberculosis
- Other malignancies: especially head and neck cancers
- Sarcoidosis: mediastinal and hilar adenopathy

Immunologic and Hematologic Abnormalities

- Defects in cell-mediated immunity (remains even after successful treatment of lymphoma), cutaneous anergy, diminished antibody production to capsular antigens of *Haemophilus* and pneumococcus
- Anemia; elevated erythrocyte sedimentation rate, leukemoid reaction, eosinophilia, lymphocytopenia, fibrosis and granulomas in marrow

Staging

The Ann Arbor staging classification is shown in Table 66-5. Disease is staged by performing physical examination, chest x-ray, thoracoabdominal CT, bone marrow biopsy, ultrasound examinations, and lymphangiogram. Staging laparotomy should be used, especially to evaluate the spleen, if pt has early-stage disease on clinical grounds and radiation therapy is being contemplated. Pathologic staging is unnecessary if the pt is treated with chemotherapy.

TREATMENT HODGKIN'S DISEASE

About 85% of pts are curable. Therapy should be performed by experienced clinicians in centers with appropriate facilities. Most pts are clinically staged and treated with chemotherapy alone or combined-modality therapy. Those with stage II disease often receive either two or four cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) with or without involved-field radiation therapy or Stanford V, a combined-modality program using lower doses of chemotherapy. Those with stage III or IV disease receive six cycles of combination chemotherapy, usually ABVD. Pts with any stage disease accompanied by a large mediastinal mass (greater than one-third the greatest chest diameter) should receive combined-modality therapy with MOPP/ABVD or mechlorethamine, vincristine, procarbazine, prednisone (MOPP)-ABV hybrid followed by mantle field radiation therapy. (Radiation plus ABVD is too toxic to the lung.) A persistently positive midtreatment positron emission tomography scan may be an index of risk of relapse and need for additional therapy. About one-half of pts (or more) not cured by their initial chemotherapy regimen may be rescued by high-dose therapy and autologous stem cell transplant. Brentuximab vedotin, an anti-CD30 drug conjugate, has activity in pts relapsing after transplant.

With long-term follow-up, it has become clear that more pts are dying of late fatal toxicities related to radiation therapy (myocardial infarction, stroke, second cancers) than from HD. It may be possible to avoid radiation exposure by using combination chemotherapy alone in early-stage disease as well as in advanced-stage disease.

http://internalmedicinebook.com

TABLE 66-5 THE ANN ARBOR STAGING SYSTEM FOR HODGKIN'S LYMPHOMA

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E"
	More than one extranodal deposit at any location
	Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation
	Unexplained, persistent, or recurrent fever with temperatures >38°C (100.5°F) during the previous month
	Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow



For a more detailed discussion, see Longo DL: Malignancies of Lymphoid Cells, Chap. 134, p. 695; Tefferi A, Longo DL: Less Common Hematologic Malignancies, Chap. 135e; Munshi NC, Longo DL, Anderson KC: Plasma Cell Disorders, Chap. 136, p. 710 in HPIM-19.

67 Skin Cancer

MALIGNANT MELANOMA

Most dangerous cutaneous malignancy, high metastatic potential, poor prognosis with metastatic spread.

Incidence

Melanoma has been diagnosed in 73,870 people in the United States in 2015 and caused 9940 deaths.

http://internalmedicinebook.com

TABLE 67-1 FACTORS ASSOCIATED WITH INCREASED RISK OF MELANOMA

Total body nevi (higher number = higher risk)
Family or personal history
Dysplastic nevi
Light skin/hair/eye color
Poor tanning ability
Freckling
UV exposure/sunburns/tanning booths
CDKN2A mutation
MC1R variants

Predisposing Factors (Table 67-1)

Fair complexion, sun exposure, family history of melanoma, dysplastic nevus syndrome (autosomal dominant disorder with multiple nevi of distinctive appearance and cutaneous melanoma may be associated with 9p deletion), and presence of a giant congenital nevus. Blacks have a low incidence.

Prevention

Sun avoidance lowers risk. Sunscreens are not proven effective.

Types

1. *Superficial spreading melanoma:* Most common; begins with initial radial growth phase before invasion.
2. *Lentigo maligna melanoma:* Very long radial growth phase before invasion, lentigo maligna (Hutchinson's melanotic freckle) is precursor lesion, most common in elderly and in sun-exposed areas (esp. face).
3. *Acral lentiginous:* Most common form in darkly pigmented pts; occurs on palms and soles, mucosal surfaces, in nail beds and mucocutaneous junctions; similar to lentigo maligna melanoma but with more aggressive biologic behavior.
4. *Nodular:* Generally poor prognosis because of invasive growth from onset.

Biology

About half of melanomas carry an activating somatic mutation in the *BRAF* gene, often a valine to glutamate substitution at amino acid 600 (V600E). *N-ras* is mutated in about 20% and rare pts have activating mutations in *c-kit*. These mutations have been targeted by therapeutic agents that have antitumor activity.

Clinical Appearance

Generally pigmented (rarely amelanotic); color of lesions varies, but red, white, and/or blue are common, in addition to brown and/or black. Suspicion should be raised by a pigmented skin lesion that is >6 mm in diameter, asymmetric, has an irregular surface or border, or has variation in color.

Prognosis

Best with thin lesions without evidence of metastatic spread; with increasing thickness or evidence of spread, prognosis worsens. Stages I and II (primary tumor without spread) have 85% 5-year survival. Stage III (palpable regional nodes with tumor) has a 50% 5-year survival when only one node is involved and 15–20% when four or more are involved. Stage IV (disseminated disease) has <5% 5-year survival.

http://internalmedicinebook.com

TREATMENT MALIGNANT MELANOMA

Early recognition and local excision for localized disease is best; 1- to 2-cm margins are as effective as 4- to 5-cm margins and do not usually require skin grafting. Elective lymph node dissection offers no advantage in overall survival compared with deferral of surgery until clinical recurrence. Pts with stage II disease may have improved disease-free survival with adjuvant interferon (IFN)-α 3 million units three times weekly for 12–18 months. In one study, pts with stage III disease had improved survival with adjuvant IFN, 20 million units IV daily × 5 for 4 weeks, then 10 million units SC three times weekly for 11 months. This result was not confirmed in a second study. Metastatic disease may be treated with chemotherapy or immunotherapy. Vemurafenib 960 mg PO bid or dabrafenib 150 mg PO bid induces responses in about 50% of pts with *BRAF* mutations. Median survival is about 16 months. Addition of a MET inhibitor (trametinib 2 mg/d) improved response rate to 64% and median overall survival to >20 months. The anti-CTLA4 antibody ipilimumab prolongs survival by about 4 months. The combination of ipilimumab and the PD-1 blocker nivolumab induced responses in both BRAF mutant and BRAF wild-type tumors. Response rate 58% with responses lasting about 12 months. Dacarbazine (250 mg/m^2 IV daily × 5 q3w) plus tamoxifen (20 mg/m^2 PO daily) may induce partial responses in one-quarter of pts. IFN and interleukin 2 (IL-2) at maximum tolerated doses induce partial responses in 15% of pts. Rare long remissions occur with IL-2. Temozolomide is an oral agent that has some activity. It can enter the central nervous system (CNS) and is being evaluated with radiation therapy for CNS metastases. No therapy for metastatic disease is curative. Vaccines and adoptive cellular therapies are being tested.

BASAL CELL CARCINOMA (BCC)

Most common form of skin cancer; most frequently on sun-exposed skin, esp. face.

Predisposing Factors

Fair complexion, chronic UV exposure, exposure to inorganic arsenic (i.e., Fowler's solution or insecticides such as Paris green), or exposure to ionizing radiation.

Prevention

Avoidance of sun exposure and use of sunscreens lower risk.

Types

Five general types: noduloulcerative (most common), superficial (mimics eczema), pigmented (may be mistaken for melanoma), morpheaform (plaquelike lesion with telangiectasia—with keratotic is most aggressive), keratotic (basosquamous carcinoma).

Clinical Appearance

Classically a pearly, translucent, smooth papule with rolled edges and surface telangiectasia.

TREATMENT BASAL CELL CARCINOMA

Local removal with electrodesiccation and curettage, excision, cryosurgery, or radiation therapy; metastases are rare but may spread locally. Exceedingly unusual for BCC to cause death. Locally advanced or metastatic disease may respond to vismodegib, an inhibitor of the hedgehog pathway often activated in this disease.

http://internalmedicinebook.com

SQUAMOUS CELL CARCINOMA (SCC)

Less common than basal cell but more likely to metastasize.

Predisposing Factors

Fair complexion, chronic UV exposure, previous burn, or other scar (i.e., scar carcinoma), exposure to inorganic arsenic or ionizing radiation. Actinic keratosis is a premalignant lesion.

Types

Most commonly occurs as an ulcerated nodule or a superficial erosion on the skin. Variants include:

1. *Bowen's disease:* Erythematous patch or plaque, often with scale; noninvasive; involvement limited to epidermis and epidermal appendages (i.e., SCC in situ).
2. *Scar carcinoma:* Suggested by sudden change in previously stable scar, esp. if ulceration or nodules appear.
3. *Verrucous carcinoma:* Most commonly on plantar aspect of foot; low-grade malignancy but may be mistaken for a common wart.

Clinical Appearance

Hyperkeratotic papule or nodule or erosion; nodule may be ulcerated.

TREATMENT SQUAMOUS CELL CARCINOMA

Local excision and Mohs micrographic surgery are most common; radiation therapy in selected cases. Metastatic disease may be treated with radiation therapy or with combination biologic therapy; 13-*cis*-retinoic acid 1 mg/d PO plus IFN 3 million units/d SC.

Prognosis

Favorable if secondary to UV exposure; less favorable if in sun-protected areas or associated with ionizing radiation.

SKIN CANCER PREVENTION

Most skin cancer is related to sun exposure. Encourage pts to avoid the sun and use sunscreen.



For a more detailed discussion, see Urba WJ, Curti BD: Cancer of the Skin, Chap. 105, p. 493, in HPIM-19.

68 Head and Neck Cancer

Epithelial cancers may arise from the mucosal surfaces of the head and neck including the sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. These tumors are usually squamous cell cancers. Thyroid cancer is discussed in Chap. 170.

http://internalmedicinebook.com

INCIDENCE AND EPIDEMIOLOGY

About 58,000 cases are diagnosed each year and 12,000 people die from the disease. Oral cavity, oropharynx, and larynx are the most frequent sites of primary lesions in the United States; nasopharyngeal primaries are more common in the Far East and Mediterranean countries. Alcohol and tobacco (including smokeless) abuse are risk factors. Human papillomavirus (usually types 16 and 18) is associated with about half of oropharynx cancers in Western countries.

PATHOLOGY

Nasopharyngeal cancer in the Far East has a distinct histology, nonkeratinizing undifferentiated carcinoma with infiltrating lymphocytes called *lymphoepithelioma*, and a distinct etiology, Epstein-Barr virus. Squamous cell head and neck cancer may develop from premalignant lesions (erythroplakia, leukoplakia), and the histologic grade affects prognosis. Pts who have survived head and neck cancer commonly develop a second cancer of the head and neck, lung, or esophagus, presumably reflecting the exposure of the upper aerodigestive mucosa to similar carcinogenic stimuli.

GENETIC ALTERATIONS

Chromosomal deletions and mutations have been found in chromosomes 3p, 9p, 17p, and 13q; mutations in p53 have been reported. Cyclin D1 may be overexpressed. Epidermal growth factor receptor is commonly overexpressed.

CLINICAL PRESENTATION

Most occur in persons >50 years. Symptoms vary with the primary site. Nasopharynx lesions do not usually cause symptoms until late in the course and then cause unilateral serous otitis media or nasal obstruction or epistaxis. Oral cavity cancers present as nonhealing ulcers, sometimes painful. Oropharyngeal lesions also present late with sore throat or otalgia. Hoarseness may be an early sign of laryngeal cancer. Rare pts present with painless, rock-hard cervical or supraclavicular lymph node enlargement. Staging is based on the size of primary tumor and involvement of lymph nodes. Distant metastases occur in <10% of pts.

TREATMENT HEAD AND NECK CANCER

Three categories of disease are common: localized, locally or regionally advanced, and recurrent or metastatic. *Localized disease* occurs in about one-third of pts and is treated with curative intent by surgery or radiation therapy. Radiation therapy is preferred for localized larynx cancer to preserve organ function; surgery is used more commonly for oral cavity lesions. Overall 5-year survival is 60–90%, and most recurrences occur within 2 years. *Locally advanced disease* is the most common presentation (>50%). Combined-modality therapy using induction chemotherapy, then surgery followed by concomitant chemotherapy and radiation therapy, is most effective. The use of three cycles of cisplatin (75 mg/m^2 IV day 1) and docetaxel (75 mg/m^2 IV day 1) plus 5-fluorouracil (5-FU) (750 [mg/m^2]/d by 96- to 120-h continuous infusion) before or during radiation therapy is more effective than surgery plus radiation therapy, although mucositis is also more severe; 5-year survival is 34–50%. Cetuximab plus radiation therapy may be more effective than radiation therapy alone. Head and neck cancer pts are frequently malnourished and often have intercurrent illness. Those who obtain a remission often develop hypothyroidism. Pts with *recurrent* or *metastatic disease* (about 10% of pts) are treated palliatively with cisplatin plus 5FU or paclitaxel (200–250 mg/m^2 with granulocyte colony-stimulating factor support) or with single-agent chemotherapy (a taxane, methotrexate, cisplatin, or carboplatin). Response rates are usually 30–50% and median survival of about 3 months.

http://internalmedicinebook.com

PREVENTION

The most important intervention is to get the pts to stop smoking. Long-term survival is significantly better in those who stop smoking. Chemopreventive therapy with *cis*-retinoic acid (3 months of 1.5 [mg/kg]/d followed by 9 months of 0.5 [mg/kg]/d PO) may cause regression of leukoplakia but has no consistent effect on development of cancer.

For a more detailed discussion, see Vokes EE: Head and Neck Cancer, Chap. 106, p. 502, in HPIM-19.

69 Lung Cancer

INCIDENCE

Lung cancer was diagnosed in about 115,610 men and 105,590 women in the United States in 2015, and 86% of pts die within 5 years. Lung cancer, the leading cause of cancer death, accounts for 28% of all cancer deaths in men and 26% in women. Peak incidence occurs between ages 55 and 65 years. Incidence is decreasing in men and increasing in women.

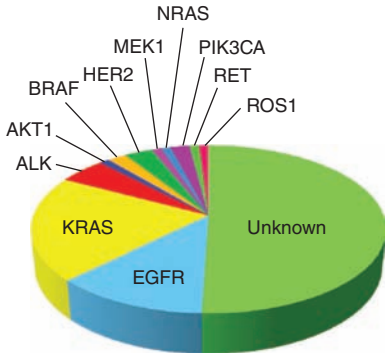
HISTOLOGIC CLASSIFICATION

Four major types account for 88% of primary lung cancers: epidermoid (squamous), 29%; adenocarcinoma (including bronchioloalveolar), 35%; large cell, 9%; and small cell (or oat cell), 18%. Histology (small-cell versus non-small-cell types) is a major determinant of treatment approach. Small cell is usually widely disseminated at presentation, whereas non-small cell may be localized. Epidermoid and small cell typically present as central masses, whereas adenocarcinomas and large cell usually present as peripheral nodules or masses. Epidermoid and large cell cavitate in 20–30% of pts.

ETIOLOGY

The major cause of lung cancer is tobacco use, particularly cigarette smoking. Lung cancer cells may have ≥10 acquired genetic lesions, most commonly point mutations in *ras* oncogenes; amplification, rearrangement, or transcriptional activation of *myc* family oncogenes; overexpression of *bcl*-2, *Her2/neu*, and telomerase; and deletions involving chromosomes 1p, 1q, 3p12-13, 3p14 (FHIT gene region), 3p21, 3p24-25, 3q, 5q, 9p (p16 and p15 cyclin-dependent kinase inhibitors), 11p13, 11p15, 13q14 (*rb* gene), 16q, and 17p13 (*p53* gene). Loss of 3p and 9p is the earliest event, detectable even in hyperplastic bronchial epithelium; *p53* abnormalities and *ras* point mutations are usually found only in invasive cancers. A small but significant subset of pts with adenocarcinoma have activating mutations in the gene for the epidermal growth factor (EGF) receptor, or activating fusion events involving the *alk* or *ros* gene. Driver mutations in lung cancer are depicted in Fig. 69-1.

http://internalmedicinebook.com



Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%

FIGURE 69-1 Driver mutations in adenocarcinomas.

CLINICAL MANIFESTATIONS

Only 5–15% are detected while asymptomatic. Central endobronchial tumors cause cough, hemoptysis, wheeze, stridor, dyspnea, pneumonitis. Peripheral lesions cause pain, cough, dyspnea, symptoms of lung abscess resulting from cavitation. Metastatic spread of primary lung cancer may cause tracheal obstruction, dysphagia, hoarseness, Horner's syndrome. Other problems of regional spread include superior vena cava syndrome, pleural effusion, respiratory failure. Extrathoracic metastatic disease affects 50% of pts with epidermoid cancer, 80% with adenocarcinoma and large cell, and >95% with small cell. Clinical problems result from brain metastases, pathologic fractures, liver invasion, and spinal cord compression. Paraneoplastic syndromes may be a presenting finding of lung cancer or first sign of recurrence (Chap. 76). Systemic symptoms occur in 30% and include weight loss, anorexia, fever. Endocrine syndromes occur in 12% and include hypercalcemia (epidermoid), syndrome of inappropriate antidiuretic hormone secretion (small cell), gynecomastia (large cell). Skeletal connective tissue syndromes include clubbing in 30% (most often non-small cell) and hypertrophic pulmonary osteoarthropathy in 1–10% (most often adenocarcinomas), with clubbing, pain, and swelling.

STAGING (TABLE 69-1)

Two parts to staging are: (1) determination of location (anatomic staging) and (2) assessment of pt's ability to withstand antitumor treatment (physiologic staging). Non-small-cell tumors are staged by the TNM/International Staging System (ISS). The T (tumor), N (regional node involvement), and M (presence or absence of distant metastasis) factors are taken together to define different stage groups. Small-cell tumors are staged by two-stage system: limited stage disease—confined to one hemithorax and regional lymph nodes; extensive disease—involvement beyond this. General staging procedures include careful ear, nose, and throat examination; chest x-ray (CXR); chest and abdominal CT scanning; and positron emission tomography scan. CT scans may suggest mediastinal lymph node involvement and pleural extension in non-small-cell lung cancer, but a definitive evaluation of mediastinal spread requires histologic examination. Routine radionuclide scans are not obtained in asymptomatic pts. If a mass lesion is on CXR and no obvious contraindications to curative surgical approach are noted, the mediastinum should be investigated. Major contraindications to curative surgery include extrathoracic metastases, superior vena cava syndrome, vocal cord and phrenic nerve paralysis, malignant pleural effusions, metastases to contralateral lung, and histologic diagnosis of small-cell cancer.

http://internalmedicinebook.com

TABLE 69-1 TUMOR, NODE, METASTASIS INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER

Comparison of Survival by Stage in TNM Sixth and Seventh Editions

Stage	TNM Sixth Edition	TNM Seventh Edition	5-Year Survival, %[a]
IA	T1N0M0	T1a-T1bN0M0	73
IB	T2N0M0	T2aN0M0	58
IIA	T1N1M0	T1a-T2aN1M0 *or* T2bN0M0	46
IIB	T2N1M0 *or* T3N0M0	T2bN1M0 *or* T3N0M0	36
IIIA	T3N1M0 *or* T1-3N2M0	T1a-T3N2M0 *or* T3N1M0 *or* T4N0-1M0	24
IIIB	Any T N3M0 T4 Any N M0	T4N2M0 *or* T1a-T4N3M0	9
IV	Any T Any N M1	Any T Any N M1a *or* M1b	13
	Sixth Edition	**Seventh Edition**	
Tumor (T)			
T1	Tumor ≤3 cm diameter without invasion more proximal than lobar bronchus	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus	
T1a		Tumor ≤2 cm in diameter	
T1b		Tumor >2 cm but ≤3 cm in diameter	
T2	Tumor >3 cm diameter *or* tumor of any size with any of the following: Visceral pleural invasion Atelectasis of less than entire lung Proximal extent at least 2 cm from carina	Tumor >3 cm but ≤7 cm with any of the following: Involves main bronchus, ≥2 cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis extending to hilar region but not involving the entire lung	
T2a		Tumor >3 cm but ≤5 cm in diameter	
T2b		Tumor >5 cm but ≤7 cm in diameter	
T3	Tumor of any size that invades any of the following: chest wall, diaphragm, mediastinal pleura, parietal pericardium Tumor <2 cm distal to carina	Tumor >7 cm or directly invades any of the following: chest wall (including superior sulcus tumors), phrenic nerve, mediastinal pleura, parietal pericardium Tumor <2 cm distal to carina but without involvement of carina Tumor with associated atelectasis or obstructive pneumonitis of entire lung Separate tumor nodule(s) in same lobe	

(*Continued*)

http://internalmedicinebook.com

TABLE 69-1 TUMOR, NODE, METASTASIS INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER (*CONTINUED*)

T4	Tumor of any size that invades any of the following: mediastinum, heart or great vessels, trachea, esophagus, vertebral body, carina	Tumor of any size that invades any of the following: mediastinum, heart or great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina
	Tumor with malignant pleural or pericardial effusion	Separate tumor nodule(s) in a different ipsilateral lobe
	Separate tumor nodules in same lobe	
Nodes (N)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or hilar lymph node(s)	Metastasis in ipsilateral peribronchial and/or hilar lymph node(s) and intrapulmonary node(s), including involvement by direct extensions
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)	Metastasis in contralateral mediastinal, hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
Metastasis (M)		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis (includes tumor nodules in different lobe from primary)	Distant metastasis
M1a		Separate tumor nodules in a contralateral lobe
		Tumor with pleural nodules or malignant pleural or pericardial effusion
M1b		Distant metastasis

[a]Survival according to the seventh edition.

Abbreviation: TNM, tumor-node-metastasis.

Source: Bottom portion of table reproduced with permission from P Goldstraw et al: *J Thorac Oncol* 2:706, 2007.

TREATMENT LUNG CANCER (TABLE 69-2)

1. Surgery in pts with localized disease and non-small-cell cancer; however, majority initially thought to have curative resection ultimately succumb to metastatic disease. Adjuvant chemotherapy (cisplatin, four cycles at 100 mg/m^2 plus a second active agent [etoposide, vinblastine, vinorelbine, vindesine, a taxane]) in pts with total resection of stage IIA and IIB diseases may modestly extend survival.

http://internalmedicinebook.com

TABLE 69-2 SUMMARY OF TREATMENT APPROACH TO PATIENTS WITH LUNG CANCER

Non-Small-Cell Lung Cancer
Stages IA, IB, IIA, IIB, and some IIIA:
Surgical resection for stages IA, IB, IIA, and IIB
Surgical resection with complete-mediastinal lymph node dissection and consideration of neoadjuvant CRx for stage IIIA disease with "minimal N2 involvement" (discovered at thoracotomy or mediastinoscopy)
Consider postoperative RT for pts found to have N2 disease
Stage IB: discussion of risk/benefits of adjuvant CRx; not routinely given
Stage II: Adjuvant CRx
Curative potential RT for "nonoperable" pts
Stage IIIA with selected types of stage T3 tumors:
Tumors with chest wall invasion (T3): en bloc resection of tumor with involved chest wall and consideration of postoperative RT
Superior sulcus (Pancoast's) (T3) tumors: preoperative RT (30–45 Gy) and CRx followed by en bloc resection of involved lung and chest wall with postoperative RT
Proximal airway involvement (<2 cm from carina) without mediastinal nodes: sleeve resection if possible preserving distal normal lung or pneumonectomy
Stages IIIA "advanced, bulky, clinically evident N2 disease" (discovered preoperatively) and IIIB disease that can be included in a tolerable RT port:
Curative potential concurrent RT + CRx if performance status and general medical condition are reasonable; otherwise, sequential CRx followed by RT, or RT alone
Stage IIIB disease with carinal invasion (T4) but without N2 involvement:
Consider pneumonectomy with tracheal sleeve resection with direct reanastomosis to contralateral mainstem bronchus
Stage IV and more advanced IIIB disease:
RT to symptomatic local sites
CRx for ambulatory pts; consider CRx and bevacizumab for selected pts
Chest tube drainage of large malignant pleural effusions
Consider resection of primary tumor and metastasis for isolated brain or adrenal metastases
Small-Cell Lung Cancer
Limited stage (good performance status): combination CRx + concurrent chest RT
Extensive stage (good performance status): combination CRx
Complete tumor responders (all stages): consider prophylactic cranial RT
Poor-performance-status pts (all stages):
Modified-dose combination CRx
Palliative RT
Bronchioloalveolar or Adenocarcinoma with EGF Receptor Mutations or ALK rearrangements
Gefitinib or erlotinib, inhibitors of EGF receptor kinase activity
Crizotinib, an alk inhibitor, or ceritinib

(*Continued*)

http://internalmedicinebook.com

TABLE 69-2 SUMMARY OF TREATMENT APPROACH TO PATIENTS WITH LUNG CANCER (*CONTINUED*)

All Pts
RT for brain metastases, spinal cord compression, weight-bearing lytic bony lesions, symptomatic local lesions (nerve paralyses, obstructed airway, hemoptysis, intrathoracic large venous obstruction, in non-small-cell lung cancer and in small-cell cancer not responding to CRx)
Appropriate diagnosis and treatment of other medical problems and supportive care during CRx
Encouragement to stop smoking
Entrance into clinical trial, if eligible

Abbreviations: CRx, chemotherapy; EGF, epidermal growth factor; RT, radiotherapy.

2. Solitary pulmonary nodule: factors suggesting resection include cigarette smoking, age ≥35 years, relatively large (>2 cm) lesion, lack of calcification, chest symptoms, and growth of lesion compared with old CXR. See Fig. 69-1.
3. For unresectable stage II non-small-cell lung cancer, combined thoracic radiation therapy and cisplatin-based chemotherapy reduces mortality by about 25% at 1 year.
4. For unresectable non-small-cell cancer, metastatic disease, or refusal of surgery, consider for radiation therapy; addition of cisplatin/taxane-based chemotherapy may reduce death risk by 13% at 2 years and improve quality of life. Pemetrexed has activity in pts with progressive disease.
5. Small-cell cancer: combination chemotherapy is standard mode of therapy; response after 6–12 weeks predicts median- and long-term survival.
6. Addition of radiation therapy to chemotherapy in limited-stage small-cell lung cancer can increase 5-year survival from about 11% to 20%.
7. Prophylactic cranial irradiation improves survival of limited-stage small-cell lung cancer by another 5%.
8. Laser obliteration of tumor through bronchoscopy in presence of bronchial obstruction.
9. Radiation therapy for brain metastases, spinal cord compression, symptomatic masses, bone lesions.
10. Encourage cessation of smoking.
11. Pts with adenocarcinoma carcinoma (3% of all pts with lung cancer): 7% of these have activating mutations in the EGF receptor. These pts often respond to gefitinib or erlotinib, EGF receptor inhibitors. About 5% of these have activating rearrangements of the *alk* gene and may respond to crizotinib.

PROGNOSIS

At time of diagnosis, only 20% of pts have localized disease. Overall 5-year survival is 30% for males and 50% for females with localized disease and 5% for pts with advanced disease. Survival as a function of stage is listed in Table 69-3.

SCREENING

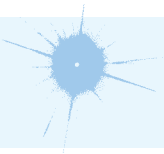
The National Cancer Institute study of lung cancer screening of high-risk pts (age 55–74 years with 30+ pack-year smoking history) with low-dose helical CT scan reduced lung cancer mortality by 20%, but had only a small effect on overall mortality.

http://internalmedicinebook.com

TABLE 69-3 FIVE-YEAR SURVIVAL BY STAGE AND TNM CLASSIFICATION OF NON-SMALL-CELL LUNG CANCER (SEVENTH EDITION)

Stage	TNM Seventh Edition	5-Year Survival (%)
IA	T1a-T1bN0M0	73%
IB	T2aN0M0	58%
IIA	T1a-T2aN1M0	46%
	T2bN0M0	
IIB	T2bN1M0	36%
	T3N0M0	
IIIA	T1a-T3N2M0	24%
	T3N1M0	
	T4N0-1M0	
IIIB	T4N2M0	9%
	T1a-T4N3M0	
IV	Any T	13%
	Any N plus M1a or M1b	

Abbreviation: TNM, tumor-node-metastasis.



For a more detailed discussion, see Horn L, Lovly CM, Johnson DH: Neoplasms of the Lung, Chap. 107, p. 506, in HPIM-19.

70 Breast Cancer

INCIDENCE AND EPIDEMIOLOGY

The most common tumor in women; 234,190 women in the United States were diagnosed in 2015 and 40,730 died with breast cancer. Men also get breast cancer; F:M is 150:1. Breast cancer is hormone dependent. Women with late menarche, early menopause, and first full-term pregnancy by age 18 years have a significantly reduced risk. The average American woman has about a one in nine lifetime risk of developing breast cancer. Dietary fat is a controversial risk factor. Oral contraceptives have little, if any, effect on risk and lower the risk of endometrial and ovarian cancer. Voluntary interruption of pregnancy does not increase risk. Estrogen replacement therapy may slightly increase the risk, but the beneficial effects of estrogen on quality of life, bone mineral density, and decreased risk of colorectal cancer appear to be somewhat outnumbered by increases in cardiovascular and thrombotic diseases. Women who received therapeutic radiation before age 30 years are at increased risk. Breast cancer risk is increased when a sister and mother also had the disease.

http://internalmedicinebook.com

GENETICS

Perhaps 8–10% of breast cancer is familial. *BRCA-1* mutations account for about 5%. *BRCA-1* maps to chromosome 17q21 and appears to be involved in transcription-coupled DNA repair. Ashkenazi Jewish women have a 1% chance of having a common mutation (deletion of adenine and guanine at position 185). The *BRCA-1* syndrome includes an increased risk of ovarian cancer in women and prostate cancer in men. *BRCA-2* on chromosome 11 may account for 2–3% of breast cancer. Mutations are associated with an increased risk of breast cancer in men and women. Germ-line mutations in p53 (Li-Fraumeni syndrome) are very rare, but breast cancer, sarcomas, and other malignancies occur in such families. Germ-line mutations in *PALB2, hCHK2*, and *PTEN* may account for some familial breast cancer. Sporadic breast cancers show many genetic alterations, including overexpression of *HER2/neu* in 25% of cases, p53 mutations in 40%, and loss of heterozygosity at other loci.

DIAGNOSIS

Breast cancer is usually diagnosed by biopsy of a nodule detected by mammogram or by palpation. Women should be strongly encouraged to examine their breasts monthly. In premenopausal women, questionable or nonsuspicious (small) masses should be reexamined in 2–4 weeks (Fig. 70-1). A mass in a premenopausal woman

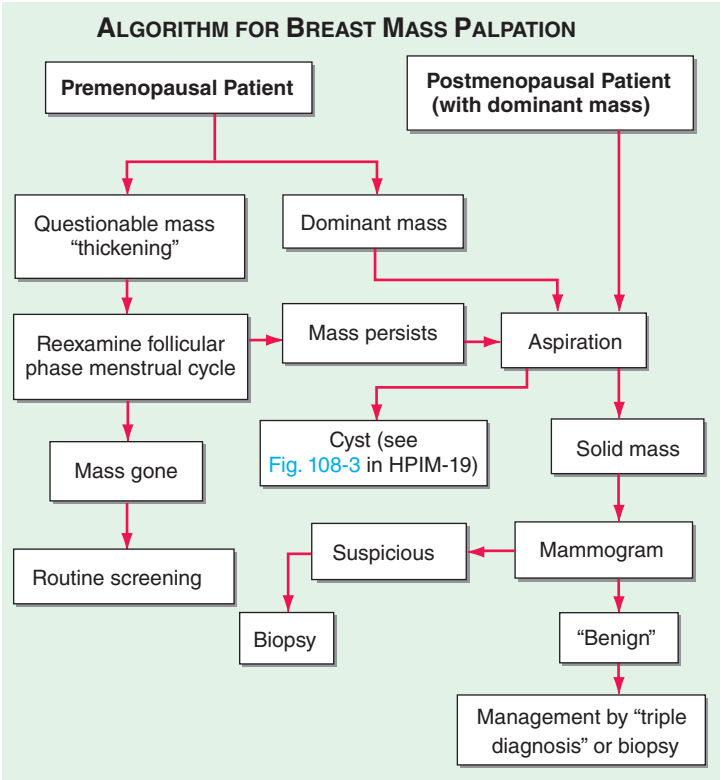


FIGURE 70-1 Approach to a palpable breast mass.

http://internalmedicinebook.com

that persists throughout her cycle and any mass in a postmenopausal woman should be aspirated. If the mass is a cyst filled with nonbloody fluid that goes away with aspiration, the pt is returned to routine screening. If the cyst aspiration leaves a residual mass or reveals bloody fluid, the pt should have a mammogram and excisional biopsy. If the mass is solid, the pt should undergo a mammogram and excisional biopsy. Screening mammograms performed every other year beginning at age 50 years have been shown to save lives. The controversy regarding screening mammograms beginning at age 40 years relates to the following facts: (1) the disease is much less common in the 40- to 49-year age group, and screening is generally less successful for less common problems; (2) workup of mammographic abnormalities in the 40- to 49-year age group less commonly diagnoses cancer; and (3) about 50% of women who are screened annually during their forties have an abnormality at some point that requires a diagnostic procedure (usually a biopsy), yet very few evaluations reveal cancer. However, many believe in the value of screening mammography beginning at age 40 years. After 13–15 years of follow-up, women who start screening at age 40 years have a small survival benefit. Women with familial breast cancer more often have false-negative mammograms. MRI is a better screening tool in these women. Women with dense breasts (>50% fibroglandular tissue) are said to be at increased risk (1.2- to 2-fold), but it is not clear that they require increased surveillance.

CLINICAL AND MOLECULAR STAGING

Therapy and prognosis are dictated by stage of disease (Table 70-1). Unless the breast mass is large or fixed to the chest wall, staging of the ipsilateral axilla is performed at the time of lumpectomy (see below). Within pts of a given stage, individual characteristics of the tumor may influence prognosis: expression of estrogen receptor improves prognosis, while overexpression of *HER2/neu*, mutations in p53,

TABLE 70-1 STAGING OF BREAST CANCER

Primary Tumor (T)	
T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor ≤2 cm
T1a	Tumor >0.1 cm but ≤0.5 cm
T1b	Tumor >0.5 but ≤1 cm
T1c	Tumor >1 cm but ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Extension to chest wall, inflammation, satellite lesions, ulcerations
Regional Lymph Nodes (N)	
PN0(i–)	No regional lymph node metastasis histologically, negative IHC
PN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster >0.2 mm
PN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
PN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
PN1	Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent

(*Continued*)

http://internalmedicinebook.com

TABLE 70-1 STAGING OF BREAST CANCER (*CONTINUED*)

PN1mi	Micrometastasis (>0.2 mm, none >2 mm)		
PN1a	Metastasis in one to three axillary lymph nodes		
PN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent* [a]		
PN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.[a] (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)		
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the *absence* of axillary lymph node metastasis		
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral subcarinal lymph nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis (includes spread to ipsilateral supraclavicular nodes)		
Stage Grouping			
Stage 0	TIS	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[a]Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase/polymerase chain reaction.

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th ed. New York, Springer, 2010; *www.springeronline.com*.

http://internalmedicinebook.com

high growth fraction, and aneuploidy worsen the prognosis. Molecular profiling has identified genetically distinct subsets including luminal A and B (estrogen receptor positive), normal breast-like, *HER2*-amplified, and basal (or triple-negative based on no expression of hormone receptors or overexpression of HER2. These subsets differ in prognosis. Breast cancer can spread almost anywhere but commonly goes to bone, lungs, liver, soft tissue, and brain.

TREATMENT BREAST CANCER

Five-year survival rate by stage is shown in Table 70-2. Treatment varies with stage of disease and expression of hormone receptors and HER2.

Ductal carcinoma in situ is noninvasive tumor present in the breast ducts. Treatment of choice is wide excision with breast radiation therapy. In one study, adjuvant tamoxifen further reduced the risk of recurrence.

Invasive breast cancer can be classified as operable, locally advanced, and metastatic. In operable breast cancer, the outcome of primary therapy is the same with modified radical mastectomy or lumpectomy followed by breast radiation therapy. Axillary dissection may be replaced with sentinel node biopsy to evaluate node involvement. The sentinel node is identified by injecting a dye in the tumor site at surgery; the first node in which dye appears is the sentinel node. Women with tumors <1 cm and negative axillary nodes require no additional therapy beyond their primary lumpectomy and breast radiation. Adjuvant combination chemotherapy for 6 months appears to benefit premenopausal women with positive lymph nodes, pre- and postmenopausal women with negative lymph nodes but with large tumors or poor prognostic features, and postmenopausal women with positive lymph nodes whose tumors do not express estrogen receptors. Estrogen receptor–positive tumors >1 cm with or without involvement of lymph nodes are treated with aromatase inhibitors. Women who began treatment with tamoxifen before aromatase inhibitors were approved should switch to an aromatase inhibitor after 5 years of tamoxifen and continue for another 5 years.

Adjuvant chemotherapy is added to hormonal therapy in estrogen receptor–positive, node-positive women and is used without hormonal therapy in estrogen receptor–negative node-positive women, whether they are pre- or postmenopausal. Various regimens have been used. The most effective regimen appears to be four cycles of doxorubicin, 60 mg/m^2, plus cyclophosphamide, 600 mg/m^2, IV on day 1 of each 3-week cycle followed by four cycles of paclitaxel, 175 mg/m^2, by 3-h infusion on day 1 of each 3-week cycle. In women with HER2+ tumors, trastuzumab augments the ability of chemotherapy to prevent recurrence. The activity of other combinations is being explored. In premenopausal women, ovarian ablation (e.g., with the luteinizing hormone–releasing hormone [LHRH] inhibitor goserelin) may be as effective as adjuvant chemotherapy.

TABLE 70-2 A 5-YEAR SURVIVAL RATE FOR BREAST CANCER BY STAGE

Stage	5-Year Survival (Percentage of Patients)
0	99
I	92
IIA	82
IIB	65
IIIA	47
IIIB	44
IV	14

Source: Modified from data of the National Cancer Institute—Surveillance, Epidemiology, and End Results (SEER).

http://internalmedicinebook.com

Tamoxifen adjuvant therapy (20 mg/d for 5 years) or an aromatase inhibitor (anastrozole, letrozole, exemestane) is used for postmenopausal women with tumors expressing estrogen receptors whose nodes are positive or whose nodes are negative but with large tumors or poor prognostic features. Breast cancer will recur in about half of pts with localized disease. High-dose adjuvant therapy with marrow support does not appear to benefit even women with high risk of recurrence.

Pts with locally advanced breast cancer benefit from neoadjuvant combination chemotherapy (e.g., CAF: cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and 5-fluorouracil 500 mg/m^2 all given IV on days 1 and 8 of a monthly cycle for 6 cycles) followed by surgery plus breast radiation therapy.

Treatment for metastatic disease depends on estrogen receptor status and treatment philosophy. No therapy is known to cure pts with metastatic disease. Randomized trials do not show that the use of high-dose therapy with hematopoietic stem cell support improves survival. Median survival is about 22 months with conventional treatment: aromatase inhibitors for estrogen receptor–positive tumors and combination chemotherapy for receptor-negative tumors. Pts whose tumors express *HER2/neu* have higher response rates by adding trastuzumab (anti-*HER2/neu*) to chemotherapy. Trastuzumab emtansine is a drug conjugate that targets HER2-expressing cells and has antitumor activity. Some advocate sequential use of active single agents in the setting of metastatic disease. Active agents in anthracycline- and taxane-resistant disease include capecitabine, vinorelbine, gemcitabine, irinotecan, and platinum agents. Pts progressing on adjuvant tamoxifen may benefit from an aromatase inhibitor such as letrozole or anastrozole. Half of pts who respond to one endocrine therapy will respond to another. Bisphosphonates reduce skeletal complications and may promote antitumor effects of other therapy. Radiation therapy is useful for palliation of symptoms.

PREVENTION

Women with breast cancer have a 0.5% per year risk of developing a second breast cancer. Women at increased risk of breast cancer can reduce their risk by 49% by taking tamoxifen or an aromatase inhibitor for 5 years. Women with *BRCA-1* mutations can reduce the risk by 90% with simple mastectomy.

For a more detailed discussion, see Lippman ME: Breast Cancer, Chap. 108, p. 523, in HPIM-19.

71 Tumors of the Gastrointestinal Tract

ESOPHAGEAL CARCINOMA

In 2015 in the United States, 16,980 cases and 15,590 deaths; less frequent in women than men. Highest incidence in focal regions of China, Iran, Afghanistan, Siberia, and Mongolia. In the United States, blacks more frequently affected than whites; usually

http://internalmedicinebook.com

presents sixth decade or later; 5-year survival <10% because most pts present with advanced disease.

Pathology

20% squamous cell carcinoma, most commonly in upper two-thirds; 75% adenocarcinoma, usually in distal third, arising in region of columnar metaplasia (Barrett's esophagus), glandular tissue, or as direct extension of proximal gastric adenocarcinoma; lymphoma and melanoma rare. 5% of all esophageal cancers occur in the upper third, 20% in the middle third, and 75% in the lower third. 15% of tumors express *HER2/neu*.

Risk Factors

Major risk factors for squamous cell carcinoma: ethanol abuse, smoking (combination is synergistic); other risks: lye ingestion and esophageal stricture, radiation exposure, head and neck cancer, achalasia, smoked opiates, Plummer-Vinson syndrome, tylosis, chronic ingestion of extremely hot tea, deficiency of vitamin A, zinc, molybdenum. Barrett's esophagus, chronic gastroesophageal reflux, obesity, and smoking are risk factors for adenocarcinoma.

Clinical Features

Progressive dysphagia (first with solids, then liquids), rapid weight loss common, chest pain (from mediastinal spread), odynophagia, pulmonary aspiration (obstruction, tracheoesophageal fistula), hoarseness (laryngeal nerve palsy), hypercalcemia (parathyroid hormone–related peptide hypersecretion by squamous carcinomas); bleeding infrequent, occasionally severe; examination often unremarkable.

Diagnosis

Double-contrast barium swallow useful as initial test in dysphagia; flexible esophagogastroscopy most sensitive and specific test; pathologic confirmation by combining endoscopic biopsy and cytologic examination of mucosal brushings (neither alone sufficiently sensitive); CT and endoscopic ultrasonography valuable to assess local and nodal spread. PET scanning can also assess mediastinal nodes and distant sites.

TREATMENT ESOPHAGEAL CARCINOMA

Surgical resection feasible in only 40% of pts; associated with high complication rate (fistula, abscess, aspiration). *Squamous cell carcinoma*: Surgical resection after chemotherapy [5-fluorouracil (5FU), cisplatin] plus radiation therapy prolongs survival and may provide improved cure rate. *Adenocarcinoma*: Curative resection rarely possible; <20% of pts with resectable tumors survive 5 years. Palliative measures include laser ablation, mechanical dilatation, radiotherapy, and a luminal prosthesis to bypass the tumor. Gastrostomy or jejunostomy are frequently required for nutritional support. Preoperative chemotherapy with concurrent radiation therapy is somewhat more effective but more toxic therapy.

GASTRIC CARCINOMA

Highest incidence in Japan, China, Chile, Ireland; incidence decreasing worldwide, eightfold in the United States over past 60 years; in 2015, 24,590 new cases and 10,720 deaths. Male:female = 2:1; peak incidence sixth and seventh decades; overall 5-year survival <15%.

Risk Factors

Increased incidence in lower socioeconomic groups; environmental component is suggested by studies of migrants and their offspring. Several dietary factors

http://internalmedicinebook.com

correlated with increased incidence: nitrates, smoked foods, heavily salted foods; genetic component suggested by increased incidence in first-degree relatives of affected pts; other risk factors: atrophic gastritis, *Helicobacter pylori* infection, Billroth II gastrectomy, gastrojejunostomy, adenomatous gastric polyps, pernicious anemia, hyperplastic gastric polyps (latter two associated with atrophic gastritis), Ménétrier's disease, slight increased risk with blood group A.

Pathology

Adenocarcinoma in 85%; usually focal (polypoid, ulcerative), two-thirds arising in antrum or lesser curvature, frequently ulcerative ("intestinal type"); less commonly diffuse infiltrative (linitis plastica) or superficial spreading (diffuse lesions more prevalent in younger pts; exhibit less geographic variation; have extremely poor prognosis); spreads primarily to local nodes, liver, peritoneum; systemic spread uncommon; lymphoma accounts for 15% (most frequent extranodal site in immunocompetent pts), either low-grade tumor of mucosa-associated lymphoid tissue (MALT) or aggressive diffuse large B cell lymphoma; leiomyosarcoma or gastrointestinal stromal tumor (GIST) is rare.

Clinical Features

Most commonly presents with progressive upper abdominal discomfort, frequently with weight loss, anorexia, nausea; acute or chronic GI bleeding (mucosal ulceration) common; dysphagia (location in cardia); vomiting (pyloric and widespread disease); early satiety; examination often unrevealing early in course; later, abdominal tenderness, pallor, and cachexia most common signs; palpable mass uncommon; metastatic spread may be manifest by hepatomegaly, ascites, left supraclavicular or scalene adenopathy, periumbilical, ovarian, or prerectal mass (Blumer's shelf), low-grade fever, skin abnormalities (nodules, dermatomyositis, acanthosis nigricans, or multiple seborrheic keratoses). Laboratory findings: iron-deficiency anemia in two-thirds of pts; fecal occult blood in 80%; rarely associated with pancytopenia and microangiopathic hemolytic anemia (from marrow infiltration), leukemoid reaction, migratory thrombophlebitis, or acanthosis nigricans.

Diagnosis

Double-contrast barium swallow useful but has been supplanted by the more sensitive and specific esophagogastroscopy and CT for staging and assessing resectability; pathologic confirmation by biopsy and cytologic examination of mucosal brushings; superficial biopsies less sensitive for lymphomas (frequently submucosal); important to differentiate benign from malignant gastric ulcers with multiple biopsies and follow-up examinations to demonstrate ulcer healing.

TREATMENT GASTRIC CARCINOMA

Adenocarcinoma: Gastrectomy offers only chance of cure (only possible in less than one-third); the rare tumors limited to mucosa are resectable for cure in 80%; deeper invasion, nodal metastases decrease 5-year survival to 20% of pts with resectable tumors in absence of obvious metastatic spread (Table 71-1). Subtotal gastrectomy has similar efficacy to total gastrectomy for distal stomach lesions, but with less morbidity; no clear benefit for resection of spleen and a portion of the pancreas, or for radical lymph node removal. Adjuvant chemotherapy (5FU/leucovorin) plus radiation therapy following primary surgery leads to a 7-month increase in median survival. Neoadjuvant chemotherapy with epirubicin or docetaxel with cisplatin, and 5FU or capecitabine may downstage tumors and increase the efficacy of surgery. Palliative therapy for pain, obstruction, and bleeding includes surgery, endoscopic dilatation, radiation therapy, chemotherapy, and ramucirumab, an antiangiogenic antibody.

http://internalmedicinebook.com

TABLE 71-1 STAGING SYSTEM FOR GASTRIC CARCINOMA

			Data from ACS	
Stage	**TNM**	**Features**	**No. of Cases, %**	**5-Year Survival, %**
0	T_{is}N0M0	Node negative; limited to mucosa	1	90
IA	T1N0M0	Node negative; invasion of lamina propria or submucosa	7	59
IB	T2N0M0 T1N1M0	Node negative; invasion of muscularis propria	10	44
II	T1N2M0 T2N1M0	Node positive; invasion beyond mucosa but within wall	17	29
		Or		
	T3N0M0	Node negative; extension through wall		
IIIA	T2N2M0 T3N1-2M0	Node positive; invasion of muscularis propria or through wall	21	15
IIIB	T4N0-1M0	Node negative; adherence to surrounding tissue	14	9
IIIC	T4N2-3M0	>3 nodes positive; invasion of serosa or adjacent structures		
	T3N3M0	7 or more positive nodes; penetrates wall without invading serosa or adjacent structures		
IV	T4N2M0	Node positive; adherence to surrounding tissue	30	3
		Or		
	T1-4N0-2-M1	Distant metastases		

Abbreviations: ACS, American Cancer Society; TNM, tumor-node-metastasis.

Lymphoma: Low-grade MALT lymphoma is caused by *H. pylori* infection, and eradication of the infection causes complete remissions in 50% of pts; rest are responsive to combination chemotherapy including cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) plus rituximab. Diffuse large B cell lymphoma may be treated with either CHOP plus rituximab or subtotal gastrectomy followed by chemotherapy; 50–60% 5-year survival.

Leiomyosarcoma: Surgical resection curative in most pts. Tumors expressing the *c-kit* tyrosine kinase (CD117)—GIST—respond to imatinib mesylate in a substantial fraction of cases.

http://internalmedicinebook.com

BENIGN GASTRIC TUMORS

Much less common than malignant gastric tumors; hyperplastic polyps most common, with adenomas, hamartomas, and leiomyomas rare; 30% of adenomas and occasional hyperplastic polyps are associated with gastric malignancy; polyposis syndromes include Peutz-Jeghers and familial polyposis (hamartomas and adenomas), Gardner's (adenomas), and Cronkhite-Canada (cystic polyps). See "Colonic Polyps," below.

Clinical Features

Usually asymptomatic; occasionally present with bleeding or vague epigastric discomfort.

TREATMENT BENIGN GASTRIC TUMORS

Endoscopic or surgical excision.

SMALL-BOWEL TUMORS

Clinical Features

Uncommon tumors (~5% of all GI neoplasms); usually present with bleeding, abdominal pain, weight loss, fever, or intestinal obstruction (intermittent or fixed); increased incidence of lymphomas in pts with gluten-sensitive enteropathy, Crohn's disease involving small bowel, AIDS, prior organ transplantation, autoimmune disorders.

Pathology

Usually benign; most common are adenomas (usually duodenal), leiomyomas (intramural), and lipomas (usually ileal); 50% of malignant tumors are adenocarcinoma, usually in duodenum (at or near ampulla of Vater) or proximal jejunum, commonly coexisting with benign adenomas; primary intestinal lymphomas (non-Hodgkin's) account for 25% and occur as focal mass (Western type), which is usually a T cell lymphoma associated with prior celiac disease, or diffuse infiltration (Mediterranean type), which is usually immunoproliferative small-intestinal disease (IPSID; α-heavy chain disease), a B cell MALT lymphoma associated with *Campylobacter jejuni* infection, which can present as intestinal malabsorption; carcinoid tumors (usually asymptomatic) occasionally produce bleeding or intussusception (see below).

Diagnosis

Endoscopy and biopsy most useful for tumors of duodenum and proximal jejunum; otherwise barium x-ray examination best diagnostic test; direct small-bowel instillation of contrast (enteroclysis) occasionally reveals tumors not seen with routine small-bowel radiography; angiography (to detect plexus of tumor vessels) or laparotomy often required for diagnosis; CT useful to evaluate extent of tumor (esp. lymphomas).

TREATMENT SMALL-BOWEL TUMORS

Surgical excision; adjuvant chemotherapy appears helpful for focal lymphoma; IPSID appears to be curable with combination chemotherapy used in aggressive lymphoma plus oral antibiotics (e.g., tetracycline); no proven role for chemotherapy or radiation therapy for other small-bowel tumors.

http://internalmedicinebook.com

COLONIC POLYPS

TUBULAR ADENOMAS

Present in ~30% of adults; pedunculated or sessile; usually asymptomatic; ~5% cause occult blood in stool; may cause obstruction; overall risk of malignant degeneration correlates with size (<2% if <1.5 cm in diameter; >10% if >2.5 cm in diameter) and is higher in sessile polyps; 65% found in rectosigmoid colon; diagnosis by barium enema, sigmoidoscopy, or colonoscopy. *Treatment*: Full colonoscopy to detect synchronous lesions (present in 30%); endoscopic resection (surgery if polyp large or inaccessible by colonoscopy); follow-up surveillance by colonoscopy every 2–3 years.

VILLOUS ADENOMAS

Generally larger than tubular adenomas at diagnosis; often sessile; high risk of malignancy (up to 30% when >2 cm); more prevalent in left colon; occasionally associated with potassium-rich secretory diarrhea. *Treatment*: As for tubular adenomas.

HYPERPLASTIC POLYPS

Asymptomatic; usually incidental finding at colonoscopy; rarely >5 mm; no malignant potential. No treatment required.

HEREDITARY POLYPOSIS SYNDROMES

See Table 71-2.

TABLE 71-2 HEREDITABLE (AUTOSOMAL DOMINANT) Gastrointestinal Polyposis Syndromes

Syndrome	Distribution of Polyps	Histologic Type	Malignant Potential	Associated Lesions
Familial adenomatous polyposis	Large intestine	Adenoma	Common	None
Gardner's syndrome	Large and small intestines	Adenoma	Common	Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment epithelium
Turcot's syndrome	Large intestine	Adenoma	Common	Brain tumors
Nonpolyposis syndrome (Lynch syndrome)	Large intestine (often proximal)	Adenoma	Common	Endometrial and ovarian tumors
Peutz-Jeghers syndrome	Small and large intestines, stomach	Hamartoma	Rare	Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium
Juvenile polyposis	Large and small intestines, stomach	Hamartoma, rarely progressing to adenoma	Rare	Various congenital abnormalities

http://internalmedicinebook.com

1. *Familial polyposis coli* (FPC): Diffuse pancolonic adenomatous polyposis (up to several thousand polyps); autosomal dominant inheritance associated with deletion in adenomatous polyposis coli (*APC*) gene on chromosome 5; colon carcinoma from malignant degeneration of polyp in 100% by age 40. *Treatment*: Prophylactic total colectomy or subtotal colectomy with ileoproctostomy before age 30; subtotal resection avoids ileostomy but necessitates frequent proctoscopic surveillance; periodic colonoscopic or annual radiologic screening of siblings and offspring of pts with FPC until age 35; sulindac and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause regression of polyps and inhibit their development.
2. *Gardner's syndrome:* Variant of FPC with associated soft tissue tumors (epidermoid cysts, osteomas, lipomas, fibromas, desmoids); higher incidence of gastroduodenal polyps, ampullary adenocarcinoma. *Treatment*: As for FPC; surveillance for small-bowel disease with fecal occult blood testing after colectomy.
3. *Turcot's syndrome:* Rare variant of FPC with associated malignant brain tumors. *Treatment*: As for FPC.
4. *Nonpolyposis syndrome:* Familial syndrome with up to 50% risk of colon carcinoma; peak incidence in fifth decade; associated with multiple primary cancers (esp. endometrial); autosomal dominant; due to defective DNA mismatch repair.
5. *Juvenile polyposis:* Multiple benign colonic and small-bowel hamartomas; intestinal bleeding common. Other symptoms: abdominal pain, diarrhea; occasional intussusception. Rarely recur after excision; low risk of colon cancer from malignant degeneration of interspersed adenomatous polyps. Prophylactic colectomy controversial.
6. *Peutz-Jeghers syndrome:* Numerous hamartomatous polyps of entire GI tract, though denser in small bowel than colon; GI bleeding common; somewhat increased risk for the development of cancer at GI and non-GI sites. Prophylactic surgery not recommended.

COLORECTAL CANCER

Second most common internal cancer in humans; accounts for 10% of cancer-related deaths in United States; incidence increases dramatically above age 50, nearly equal in men and women. In 2015, 132,700 new cases, 49,700 deaths.

Etiology and Risk Factors

Most colon cancers arise from adenomatous polyps. Genetic steps from polyp to dysplasia to carcinoma in situ to invasive cancer have been defined, including point mutation in K-*ras* proto-oncogene, hypomethylation of DNA leading to enhanced gene expression, allelic loss at the *APC* gene (a tumor suppressor), allelic loss at the *DCC* (deleted in colon cancer) gene on chromosome 18, and loss and mutation of p53 on chromosome 17. Hereditary nonpolyposis colon cancer arises from mutations in the DNA mismatch repair genes, *hMSH2* gene on chromosome 2 and *hMLH1* gene on chromosome 3. Mutations lead to colon and other cancers. Diagnosis requires three or more relatives with colon cancer, one of whom is a first-degree relative; one or more cases diagnosed before age 50; and involvement of at least two generations. Environmental factors also play a role including exposure to therapeutic radiation; smoking; increased prevalence in developed countries, urban areas, advantaged socioeconomic groups; increased risk in pts with hypercholesterolemia, coronary artery disease; correlation of risk with low-fiber, high-animal-fat diets, although direct effect of diet remains unproven; decreased risk with long-term dietary calcium supplementation and, possibly, daily aspirin ingestion. Risk increased in first-degree relatives of pts; families with increased prevalence of cancer; and pts with history of breast or gynecologic cancer, familial polyposis syndromes, >10-year history of ulcerative colitis or Crohn's colitis, >15-year history of ureterosigmoidostomy. Tumors in pts with strong family history of malignancy are frequently located in

http://internalmedicinebook.com

right colon and commonly present before age 50; high prevalence in pts with *Streptococcus bovis* bacteremia.

Pathology

Nearly always adenocarcinoma; 75% located distal to the splenic flexure (except in association with polyposis or hereditary cancer syndromes); may be polypoid, sessile, fungating, or constricting; subtype and degree of differentiation do not correlate with course. Degree of invasiveness at surgery (Dukes' classification) is single best predictor of prognosis (Fig. 71-1). Rectosigmoid tumors may spread to lungs early because of systemic paravertebral venous drainage of this area. Other predictors of poor prognosis: preoperative serum carcinoembryonic antigen (CEA) >5 ng/mL (>5 μg/L), poorly differentiated histology, bowel perforation, venous invasion, adherence to adjacent organs, aneuploidy, specific deletions in chromosomes 5, 17, 18, and mutation of *ras* proto-oncogene. 15% have defects in DNA repair.

Clinical Features

Left-sided colon cancers present most commonly with rectal bleeding, altered bowel habits (narrowing, constipation, intermittent diarrhea, tenesmus), and abdominal or back pain; cecal and ascending colon cancers more frequently present with symptoms of anemia, occult blood in stool, or weight loss; other complications: perforation, fistula, volvulus, inguinal hernia; laboratory findings: anemia in 50% of right-sided lesions.

Diagnosis

Early diagnosis aided by screening asymptomatic persons with fecal occult blood testing (see below); >50% of all colon cancers are within reach of a 60-cm flexible sigmoidoscope; air-contrast barium enema will diagnose ~85% of colon cancers not within reach of sigmoidoscope; colonoscopy most sensitive and specific, permits tumor biopsy and removal of synchronous polyps (thus preventing neoplastic conversion), but is more expensive. Radiographic or virtual colonoscopy has not been shown to be a better diagnostic method than colonoscopy.

TREATMENT COLORECTAL CANCER

Local disease: Surgical resection of colonic segment containing tumor; preoperative evaluation to assess prognosis and surgical approach includes full colonoscopy, chest films, biochemical liver tests, plasma CEA level, and possible abdominal CT. Resection of isolated hepatic metastases possible in selected cases. Adjuvant radiation therapy to pelvis (with or without concomitant 5FU chemotherapy) decreases local recurrence rate of rectal carcinoma (no apparent effect on survival); radiation therapy without benefit on colon tumors; preoperative radiation therapy may improve resectability and local control in pts with rectal cancer. Total mesorectal excision is more effective than conventional anteroposterior resection in rectal cancer. Adjuvant chemotherapy (5FU/leucovorin plus oxaliplatin, or FOLFOX plus bevacizumab, or 5FU/leucovorin plus irinotecan, or FOLFIRI) decreases recurrence rate and improves survival of stage C (III); survival benefit from adjuvant therapy is not so clear in stage B (II) tumors; periodic determination of serum CEA level useful to follow therapy and assess recurrence. *Follow-up after curative resection*: Yearly liver tests, complete blood count, follow-up radiologic or colonoscopic evaluation at 1 year—if normal, repeat every 3 years, with routine screening interim (see below); if polyps detected, repeat 1 year after resection. *Advanced tumor* (locally unresectable or metastatic): Systemic chemotherapy (5FU/leucovorin plus oxaliplatin plus bevacizumab), irinotecan usually used in second treatment; antibodies to the epidermal growth factor (EGF) receptor (cetuximab, panitumumab) appear to enhance the effect of chemotherapy

http://internalmedicinebook.com

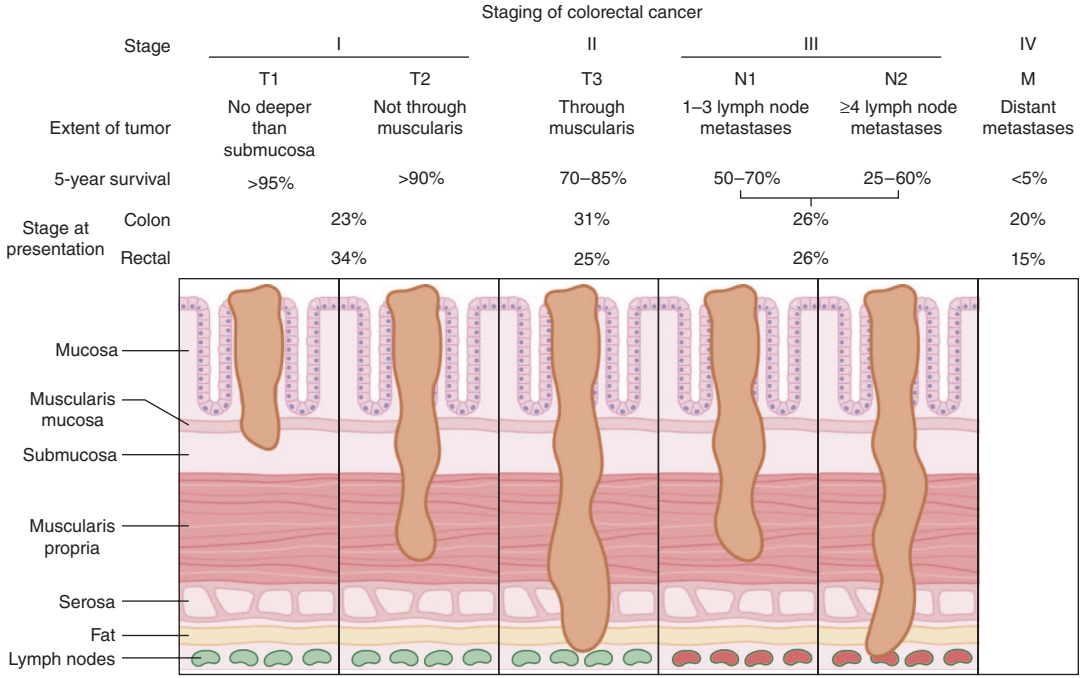


FIGURE 71-1 Staging and prognosis for pts with colorectal cancer.

http://internalmedicinebook.com

but are ineffective in tumors with *ras* mutations; intraarterial chemotherapy [floxuridine (FUDR)] and/or radiation therapy may palliate symptoms from hepatic metastases. Solitary hepatic metastases may be resected by partial hepatectomy with 25% 5-year survival.

Prevention

Early detection of colon carcinoma may be facilitated by routine screening of stool for occult blood (Hemoccult II, ColonCare, Hemosure); however, sensitivity only ~50% for carcinoma; specificity for tumor or polyp ~25–40%. Newer tests incorporating detection of blood and mutated genes may be more sensitive and specific. False positives: ingestion of red meat, iron, aspirin; upper GI bleeding. False negatives: vitamin C ingestion, intermittent bleeding. Annual digital rectal examination and fecal occult blood testing recommended for pts over age 40, screening by flexible sigmoidoscopy every 3 years after age 50, earlier in pts at increased risk (see above); careful evaluation of all pts with positive fecal occult blood tests (flexible sigmoidoscopy and air-contrast barium enema or colonoscopy alone) reveals polyps in 20–40% and carcinoma in ~5%; screening of asymptomatic persons allows earlier detection of colon cancer (i.e., earlier Dukes' stage) and achieves greater resectability rate; decreased overall mortality from colon carcinoma seen only after 13 years of follow-up. More intensive evaluation of first-degree relatives of pts with colon carcinoma frequently includes screening air-contrast barium enema or colonoscopy after age 40. NSAIDs and cyclooxygenase 2 inhibitors appear to prevent polyp development and induce regression in high-risk groups, but have not been recommended for average-risk pts at this time.

ANAL CANCER

Accounts for 1–2% of large-bowel cancer, 7270 cases and 1010 deaths in 2015; associated with chronic irritation, e.g., from condyloma acuminata, perianal fissures/fistulas, chronic hemorrhoids, leukoplakia, trauma from anal intercourse. Women are more commonly affected than men. Homosexual men are at increased risk. Human papillomavirus is etiologic. Presents with bleeding, pain, and perianal mass. Radiation therapy plus chemotherapy (5FU and mitomycin) leads to complete response in 80% when the primary lesion is <3 cm. Abdominoperineal resection with permanent colostomy is reserved for those with large lesions or whose disease recurs after chemoradiotherapy.

BENIGN LIVER TUMORS

Hepatocellular adenomas occur most commonly in women in the third or fourth decades who take birth control pills. Most are found incidentally but may cause pain; intratumoral hemorrhage may cause circulatory collapse. 10% may become malignant. Women with these adenomas should stop taking birth control pills. Large tumors near the liver surface may be resected. Focal nodular hyperplasia is also more common in women but seems not to be caused by birth control pills. Lesions are vascular on angiography and have septae and are usually asymptomatic.

HEPATOCELLULAR CARCINOMA

About 35,660 cases in the United States in 2015, but worldwide this may be the most common tumor; 24,550 deaths in 2015 in United States. Male:female = 4:1; tumor usually develops in cirrhotic liver in persons in fifth or sixth decade. High incidence in Asia and Africa is related to etiologic relationship between this cancer and hepatitis B and C infections. Effective vaccines for hepatitis B prevention and successful chemotherapy of hepatitis C should reduce the incidence. Aflatoxin exposure

http://internalmedicinebook.com

contributes to etiology and leaves a molecular signature, a mutation in codon 249 of the gene for p53.

Modes of Presentation

A pt with known liver disease develops an abnormality on ultrasound or rising α fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) due to absence of vitamin K; abnormal liver function tests; cachexia, abdominal pain, fever.

Physical Findings

Jaundice, asthenia, itching, tremors, disorientation, hepatomegaly, splenomegaly, ascites, peripheral edema.

TREATMENT HEPATOCELLULAR CARCINOMA

Surgical resection or liver transplantation is therapeutic option but rarely successful. Radiofrequency ablation, transcatheter arterial embolization (TACE), and ^{90}Yttrium can cause regression of small tumors. Sorafenib may produce partial responses lasting a few months.

Screening and Prevention

Screening populations at risk has given conflicting results. Hepatitis B vaccine prevents the disease. Interferon α (IFN-α) may prevent liver cancer in persons with chronic active hepatitis C disease and possibly in those with hepatitis B. Combination therapy with a viral protease inhibitor (e.g., ledipasvir) and a viral polumerase inhibitor (e.g., sofusbuvir) for 12–24 weeks cures most patients with chronic hepatitis C.

PANCREATIC CANCER

In 2015 in the United States, about 48,960 new cases and 40,560 deaths. The incidence is decreasing somewhat, but nearly all diagnosed cases are fatal. The tumors are ductal adenocarcinomas and are not usually detected until the disease has spread. About 70% of tumors are in the pancreatic head, 20% in the body, and 10% in the tail. Mutations in K-*ras* have been found in 85% of tumors, and the p16 cyclin-dependent kinase inhibitor on chromosome 9 may also be implicated. Long-standing diabetes, chronic pancreatitis, and smoking increase the risk; coffee-drinking, alcoholism, and cholelithiasis do not. Pts present with pain and weight loss, the pain often relieved by bending forward. Jaundice commonly complicates tumors of the head, due to biliary obstruction. Curative surgical resections are feasible in about 10%. Adjuvant chemotherapy (5FU) may benefit some pts after resection. Gemcitabine plus erlotinib or capecitabine may palliate symptoms in pts with advanced disease. Fit patients may obtain some benefit from the combination regimen, FOLFIRINOX, that includes 5FU, irinotecan, and oxaliplatin.

ENDOCRINE TUMORS OF THE GI TRACT AND PANCREAS

CARCINOID TUMOR

Carcinoid tumor accounts for 75% of GI endocrine tumors; incidence is about 15 cases per million population. 90% originate in Kulchitsky cells of the GI tract, most commonly the appendix, ileum, and rectum. Carcinoid tumors of the small bowel and bronchus have a more malignant course than tumors of other sites. About 5% of pts with carcinoid tumors develop symptoms of the carcinoid syndrome, the classic triad being cutaneous flushing, diarrhea, and valvular heart disease. For tumors of GI tract origin, symptoms imply metastases to liver.

http://internalmedicinebook.com

Diagnosis can be made by detecting the site of tumor or documenting production of >15 mg/d of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the urine. Octreotide scintigraphy identifies sites of primary and metastatic tumor in about two-thirds of cases.

TREATMENT CARCINOID TUMOR

Surgical resection where feasible. Symptoms may be controlled with histamine blockers, serotonin receptor antagonists, and octreotide, 150–1500 mg/d in three doses. Hepatic artery embolization and chemotherapy (5FU plus streptozocin or doxorubicin) have been used for metastatic disease. IFN-α at 3–10 million units SC three times a week may relieve symptoms. Everolimus, an mTOR inhibitor, and sunitinib, a kinase inhibitor, have antitumor effects. Prognosis ranges from 95% 5-year survival for localized disease to 20% 5-year survival for those with liver metastases. Median survival of pts with carcinoid syndrome is 2.5 years from the first episode of flushing.

PANCREATIC ISLET-CELL TUMORS

Gastrinoma, insulinoma, VIPoma, glucagonoma, and somatostatinoma account for the vast majority of pancreatic islet-cell tumors; their characteristics are shown in Table 71-3. The tumors are named for the dominant hormone they produce. They are generally slow-growing and produce symptoms related to hormone production. *Gastrinomas* and *peptic ulcer disease* constitute the Zollinger-Ellison syndrome. Gastrinomas are rare (4 cases per 10 million population), and in 25–50%, the tumor is a component of a multiple endocrine neoplasia type 1 (MEN 1) syndrome.

Insulinoma may present with Whipple's triad: fasting hypoglycemia, symptoms of hypoglycemia, and relief after IV glucose. Normal or elevated serum insulin levels

TABLE 71-3 GASTROINTESTINAL ENDOCRINE TUMOR SYNDROMES

Syndrome	Cell Type	Clinical Features	Percentage Malignant	Major Products
Carcinoid syndrome	Entero-chromaffin, enterochro-maffin-like	Flushing, diarrhea, wheezing, hypotension	~100	Serotonin, histamine, miscellaneous peptides
Zollinger-Ellison, gastrinoma	Non-β islet cell, duodenal G cell	Peptic ulcers, diarrhea	~70	Gastrin
Insulinoma	Islet β cell	Hypoglycemia	~10	Insulin
VIPoma (Verner-Morrison, WDHA)	Islet D_1 cell	Diarrhea, hypokalemia, hypochlorhy-dria	~60	Vasoactive intestinal peptide
Glucagonoma	Islet A cell	Mild diabetes mellitus, ery-thema necro-lytica migrans, glossitis	>75	Glucagon
Somatostati-noma	Islet D cell	Diabetes mel-litus, diarrhea, steatorrhea, gallstones	~70	Somatostatin

Abbreviation: WDHA, watery diarrhea, hypokalemia, achlorhydria.

http://internalmedicinebook.com

in the presence of fasting hypoglycemia are diagnostic. Insulinomas may also be associated with MEN 1.

Verner and Morrison described a syndrome of watery diarrhea, hypokalemia, achlorhydria, and renal failure associated with pancreatic islet tumors that produce vasoactive intestinal polypeptide (VIP). *VIPomas* are rare (1 case per 10 million) but often grow to a large size before producing symptoms.

Glucagonoma is associated with diabetes mellitus and necrolytic migratory erythema, a characteristic red, raised, scaly rash usually located on the face, abdomen, perineum, and distal extremities. Glucagon levels >1000 ng/L not suppressed by glucose are diagnostic.

The classic triad of *somatostatinoma* is diabetes mellitus, steatorrhea, and cholelithiasis.

Provocative tests may facilitate diagnosis of functional endocrine tumors: tolbutamide enhances somatostatin secretion by somatostatinomas; pentagastrin enhances calcitonin secretion from medullary thyroid (C cell) tumors; secretin enhances gastrin secretion from gastrinomas. If imaging techniques fail to detect tumor masses, angiography or selective venous sampling for hormone determination may reveal the site of tumor. Metastases to nodes and liver should be sought by CT or MRI.

TREATMENT PANCREATIC ISLET-CELL TUMORS

Tumor is surgically removed, if possible. Everolimus 10 mg PO qd or sunitinib 37.5 mg PO qd may produce meaningful delay (~12 months) in progressive disease and prolong survival in pts with metastatic disease. Octreotide inhibits hormone secretion in the majority of cases. IFN-α may reduce symptoms. Streptozotocin plus doxorubicin combination chemotherapy may produce responses in 60–90% of cases. Embolization or chemoembolization of hepatic metastases may be palliative.



For a more detailed discussion, see Mayer RJ: Upper Gastrointestinal Tract Cancers, Chap. 109, p. 532; Mayer RJ: Lower Gastrointestinal Cancers, Chap. 110, p. 537; Carr BI: Tumors of the Liver and Biliary Tree, Chap. 111, p. 544; Smyth E, Cunningham D: Pancreatic Cancer, Chap. 112, p. 554; and Jensen RT: Endocrine Tumors of the Gastrointestinal Tract and Pancreas, Chap. 113, p. 557, in HPIM-19.

72 Genitourinary Tract Cancer

BLADDER CANCER

INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 74,000 cases with 16,000 deaths. Median age is 65 years. Smoking accounts for 50% of the risk. Exposure to polycyclic aromatic hydrocarbons increases the risk, especially in slow acetylators. Risk is

http://internalmedicinebook.com

increased in chimney sweeps, dry cleaners, and those involved in aluminum manufacturing. Chronic cyclophosphamide exposure increases risk ninefold. *Schistosoma haematobium* infection also increases risk, especially of squamous histology.

ETIOLOGY

Lesions involving chromosome 9q are an early event. Deletions in 17p (p53), 18q (the DCC locus), 13q (RB), 3p, and 5q are characteristic of invasive lesions. Overexpression of epidermal growth factor receptors and *HER2/neu* receptors is common.

PATHOLOGY

Over 90% of tumors are derived from transitional epithelium; 3% are squamous, 2% are adenocarcinomas, and <1% are neuroendocrine small cell tumors. Field effects are seen that place all sites lined by transitional epithelium at risk, including the renal pelvis, ureter, bladder, and proximal two-thirds of the urethra; 90% of tumors are in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra. Histologic grade influences survival. Lesion recurrence is influenced by size, number, and growth pattern of the primary tumor.

CLINICAL PRESENTATION

Hematuria is the initial sign in 80–90%; however, cystitis is a more common cause of hematuria (22% of all hematuria) than is bladder cancer (15%). Pts are initially staged and treated by endoscopy. Superficial tumors are removed at endoscopy; muscle invasion requires more extensive surgery.

TREATMENT BLADDER CANCER

Management is based on extent of disease: superficial, invasive, or metastatic. Frequency of presentation is 75% superficial, 20% invasive, and 5% metastatic. Superficial lesions are resected at endoscopy. Although complete resection is possible in 80%, 30–80% of cases recur; grade and stage progression occur in 30%. Intravesical instillation of bacille Calmette-Guérin (BCG) reduces the risk of recurrence by 40–45%. Recurrence is monitored every 3 months.

The standard management of muscle-invasive disease is radical cystectomy. 5-year survival is 70% for those without invasion of perivesicular fat or lymph nodes, 50% for those with invasion of fat but not lymph nodes, 35% for those with one node involved, and 10% for those with six or more involved nodes. Pts who cannot withstand radical surgery may have 30–35% 5-year survival with 5000- to 7000-cGy external beam radiation therapy. Bladder sparing may be possible in up to 45% of pts with two cycles of chemotherapy with CMV (methotrexate, 30 mg/m^2 days 1 and 8, vinblastine, 4 mg/m^2 days 1 and 8, cisplatin, 100 mg/m^2 day 2, q21d) followed by 4000-cGy radiation therapy given concurrently with cisplatin.

Metastatic disease is treated with combination chemotherapy. Useful regimens include CMV (see above), M-VAC (methotrexate, 30 mg/m^2 days 1, 15, 22; vinblastine, 3 mg/m^2 days 2, 15, 22; doxorubicin, 30 mg/m^2 day 2; cisplatin, 70 mg/m^2 day 2; q28d) or cisplatin (70 mg/m^2 day 2) plus gemcitabine (1000 mg/m^2 days 1, 8, 15 of a 28-day cycle) or carboplatin plus paclitaxel. About 70% of pts respond to treatment, and 20% have a complete response; 10–15% have long-term disease-free survival.

RENAL CANCER

INCIDENCE AND EPIDEMIOLOGY

Annual incidence in the United States is about 62,000 cases with 14,000 deaths. Cigarette smoking accounts for 20–30% of cases. Risk is increased in acquired renal

http://internalmedicinebook.com

cystic disease. There are two familial forms: a rare autosomal dominant syndrome and von Hippel–Lindau disease. About 35% of pts with von Hippel–Lindau disease develop renal cancer. Incidence is also increased in those with tuberous sclerosis and polycystic kidney disease.

ETIOLOGY

Most cases are sporadic; however, the most frequent chromosomal abnormality (occurs in 60%) is deletion or rearrangement of 3p21-26. The von Hippel–Lindau gene has been mapped to that region and appears to have ubiquitin ligase activities that influence regulation of speed of transcription and turnover of damaged proteins. It is unclear how lesions in the gene lead to cancer.

PATHOLOGY

Five variants are recognized: clear cell tumors (75%), papillary tumors (15%), chromophobic tumors (5%), oncocytic tumors (3%), and collecting duct tumors (2%). Clear cell tumors arise from cells of the proximal convoluted tubules. Papillary tumors tend to be bilateral and multifocal and often show trisomy 7 and/or trisomy 17. Chromophobic and eosinophilic tumors less frequently have chromosomal aberrations and follow a more indolent course.

CLINICAL PRESENTATION

The classic triad of hematuria, flank pain, and flank mass is seen in only 10–20% of pts; hematuria (40%), flank pain (40%), palpable mass (33%), and weight loss (33%) are the most common individual symptoms. Paraneoplastic syndromes of erythrocytosis (3%), hypercalcemia (5%), and nonmetastatic hepatic dysfunction (Stauffer's syndrome) (15%) may also occur. Workup should include IV pyelography, renal ultrasonography, CT of abdomen and pelvis, chest x-ray (CXR), urinalysis, and urine cytology. Stage I is disease restricted to the kidney, stage II is disease contained within Gerota's fascia, stage III is locally invasive disease involving nodes and/or inferior vena cava, stage IV is invasion of adjacent organs or metastatic sites. Prognosis is related to stage: 66% 5-year survival for I, 64% for II, 42% for III, and 11% for IV.

TREATMENT RENAL CANCER

Radical nephrectomy is standard for stage I, II, and most stage III pts. Surgery may also be indicated in the setting of metastatic disease for intractable local symptoms (bleeding, pain). Response rates of 40–48% have been noted with five different single agents, sunitinib (50 mg/d 4 weeks out of 6), sorafenib (400 mg bid), and temsirolimus (25 mg IV weekly) and the related drug, everolimus (10 mg PO daily), the PD1 inhibitor, nivolumab and cabozantinib (60 mg PO daily), an inhibitor of MET, AXL and the vascular endothelial growth factor receptor. Sunitinib and sorafenib are thought to be antiangiogenic through inhibition of kinases in tumor cells. Temsirolimus is an inhibitor of mTOR. Nivolumab allows activation of T cells that kill the tumor cells. About 10–15% of pts with advanced-stage disease may benefit from interleukin 2 and/or interferon α (IFN-α). Addition of bevacizumab to IFN-α improves the response rate. Some remissions are durable. Chemotherapy is of little or no benefit.

TESTICULAR CANCER

INCIDENCE AND EPIDEMIOLOGY

Annual incidence is about 8430 cases with 380 deaths. Peak age incidence is 20–40. Occurs 4–5 times more frequently in white than black men. Cryptorchid testes are

http://internalmedicinebook.com

at increased risk. Early orchiopexy may protect against testis cancer. Risk is also increased in testicular feminization syndromes, and Klinefelter syndrome is associated with mediastinal germ cell tumor.

ETIOLOGY

The cause is unknown. Disease is associated with a characteristic cytogenetic defect, isochromosome 12p.

PATHOLOGY

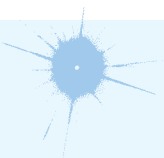
Two main subtypes are noted: seminoma and nonseminoma. Each accounts for ~50% of cases. Seminoma has a more indolent natural history and is highly sensitive to radiation therapy. Four subtypes of nonseminoma are defined: embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus (yolk sac) tumor.

CLINICAL PRESENTATION

Painless testicular mass is the classic initial sign. In the presence of pain, differential diagnosis includes epididymitis or orchitis; a brief trial of antibiotics may be undertaken. Staging evaluation includes measurement of serum tumor markers α fetoprotein (AFP) and β-human chorionic gonadotropin (hCG), CXR, and CT scan of abdomen and pelvis. Lymph nodes are staged at resection of the primary tumor through an inguinal approach. Stage I disease is limited to the testis, epididymis, or spermatic cord; stage II involves retroperitoneal nodes; and stage III is disease outside the retroperitoneum. Among seminoma pts, 70% are stage I, 20% are stage II, and 10% are stage III. Among nonseminoma germ cell tumor pts, 33% are found in each stage. hCG may be elevated in either seminoma or nonseminoma, but AFP is elevated only in nonseminoma. 95% of pts are cured if treated appropriately. Primary nonseminoma in the mediastinum is associated with acute leukemia or other hematologic disorders and has a poorer prognosis than testicular primaries (~33%).

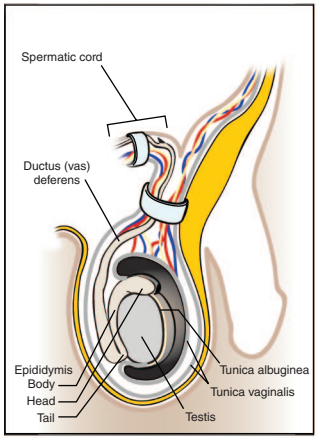
TREATMENT TESTICULAR CANCER (FIGURE 72-1)

For stages I and II seminoma, inguinal orchiectomy followed by retroperitoneal radiation therapy to 2500–3000 cGy is effective. For stages I and II nonseminoma germ cell tumors, inguinal orchiectomy followed by retroperitoneal lymph node dissection is effective. For pts of either histology with bulky nodes or stage III disease, chemotherapy is given. Cisplatin (20 mg/m^2 days 1–5), etoposide (100 mg/m^2 days 1–5), and bleomycin (30 U days 2, 9, 16) given every 21 days for four cycles is the standard therapy. If tumor markers return to zero, residual masses are resected. Most are necrotic debris or teratomas. Salvage therapy rescues about 25% of those not cured with primary therapy.

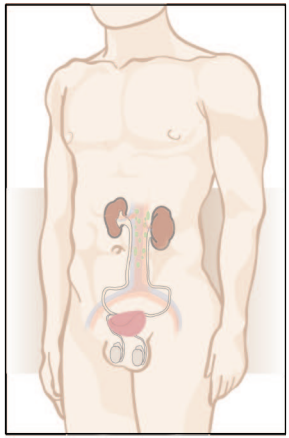


For a more detailed discussion, see Scher HI, Rosenberg JE, Motzer RJ: Bladder and Renal Cell Carcinomas, Chap. 114, p. 575; and Motzer RJ, Fedlman DR, Bosl GJ: Testicular Cancer, Chap. 116, p. 588, in HPIM-19.

http://internalmedicinebook.com



Stage	Extent of Disease
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion; tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion



		Treatment Option	
Stage	Extent of Disease	Seminoma	Nonseminoma
IA	Testis only, no vascular/lymphatic invasion (T1)	Observation Chemotherapy or RT	Observation
IB	Testis only, with vascular/lymphatic invasion (T2), or extension through tunica albuginea (T2), or involvement of spermatic cord (T3) or scrotum (T4)	Observation Chemotherapy or RT	RPLND or Chemotherapy
IIA	Retroperitoneal Nodes <2 cm	RT	RPLND +/– adjuvant Chemotherapy or Chemotherapy, often followed by RPLND
IIB	Retroperitoneal Nodes 2–5 cm	RT or Chemotherapy	Chemotherapy, often followed by RPLND
IIC	Retroperitoneal Nodes >5 cm	Chemotherapy	Chemotherapy, often followed by RPLND
Distant Metastases			
III	Common sites include distant (or extra-abdominal) lymph nodes, lung, liver, bone, and brain	Chemotherapy	Chemotherapy, often followed by surgery (biopsy or resection)

FIGURE 72-1 Germ cell tumor staging and treatment. RPLND, retroperitoneal lymph node dissection; RT, radiotherapy.

http://internalmedicinebook.com

73 Gynecologic Cancer

OVARIAN CANCER

INCIDENCE AND EPIDEMIOLOGY

Annually in the United States, about 21,290 new cases are found and 14,180 women die of ovarian cancer. Incidence begins to rise in the fifth decade, peaking in the eighth decade. Risk is increased in nulliparous women and reduced by pregnancy (risk decreased about 10% per pregnancy) and oral contraceptives. About 5% of cases are familial.

GENETICS

Mutations in *BRCA-1* and *BRCA-2* predispose women to both breast and ovarian cancer. Cytogenetic analysis of epithelial ovarian cancers that are not familial often reveals complex karyotypic abnormalities, including structural lesions on chromosomes 1 and 11 and loss of heterozygosity for loci on chromosomes 3q, 6q, 11q, 13q, and 17. C-*myc*, H-*ras*, K-*ras*, and *HER2/neu* are often mutated or overexpressed. Unlike in colon cancer, a stepwise pathway to ovarian carcinoma is not apparent. Ovarian cancers may also occur in the setting of Lynch syndrome, inherited nonpolyposis colorectal cancer, due to mutations in the genes that repair DNA mismatches. The subset of women with endometrioid histology often have a mutation in *ARID1A*, a DNA repair complex component.

SCREENING

No benefit has been seen from screening women of average risk. Hereditary ovarian cancer accounts for 10% of all cases. Women with *BRCA-1* or *-2* mutations should consider prophylactic bilateral salpingo-oophorectomy by age 40.

CLINICAL PRESENTATION

Most pts present with abdominal pain, bloating, urinary symptoms, and weight gain indicative of disease spread beyond the true pelvis. Localized ovarian cancer is usually asymptomatic and detected on routine pelvic examination as a palpable nontender adnexal mass. Most ovarian masses detected incidentally in ovulating women are ovarian cysts that resolve over one to three menstrual cycles. Adnexal masses in postmenopausal women are more often pathologic and should be surgically removed. CA-125 serum levels are ≥35 U/mL in 80–85% of women with ovarian cancer, but other conditions may also cause elevations.

PATHOLOGY

Half of ovarian tumors are benign, one-third are malignant, and the rest are tumors of low malignant potential. These borderline lesions have cytologic features of malignancy but do not invade. Malignant epithelial tumors may be of five different types: serous (50%), mucinous (25%), endometrioid (15%), clear cell (5%), and Brenner tumors (1%, derived from urothelial or transitional epithelium). The remaining 4% of ovarian tumors are stromal or germ cell tumors, which are managed like testicular cancer in men (Chap. 72). Histologic grade is an important prognostic factor for the epithelial varieties.

STAGING

Extent of disease is ascertained by a surgical procedure that permits visual and manual inspection of all peritoneal surfaces and the diaphragm. Total abdominal

http://internalmedicinebook.com

TABLE 73-1 STAGING AND SURVIVAL IN GYNECOLOGIC MALIGNANCIES

Stage	Ovarian	5-Year Survival, %	Endometrial	5-Year Survival, %	Cervical	5-Year Survival, %
0	—		—		Carcinoma in situ	100
I	Confined to ovary	90–95	Confined to corpus	89	Confined to uterus	85
II	Confined to pelvis	70–80	Involves corpus and cervix	73	Invades beyond uterus but not pelvic wall	65
III	Intraabdominal spread	25–50	Extends outside the uterus but not outside the true pelvis	52	Extends to pelvic wall and/or lower third of vagina, or hydronephrosis	35
IV	Spread outside abdomen	1–5	Extends outside the true pelvis or involves the bladder or rectum	17	Invades mucosa of bladder or rectum or extends beyond the true pelvis	7

hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, pelvic and paraaortic lymph node sampling, and peritoneal washings should be performed. The staging system and its influence on survival are shown in Table 73-1. About 23% of pts are stage I, 13% are stage II, 47% are stage III, and 16% are stage IV.

TREATMENT OVARIAN CANCER

Pts with stage I disease, no residual tumor after surgery, and well- or moderately differentiated tumors need no further treatment after surgery and have a 5-year survival of >95%. For stage II pts totally resected and stage I pts with poor histologic grade, adjuvant therapy with single-agent cisplatin or cisplatin plus paclitaxel produces 5-year survival of 80%. In the setting of bulky disease, maximal surgical cytoreduction is attempted. Those in whom no gross residual disease is left have a median survival of 39 months; those left with visible tumor, 17 months. Giving chemotherapy before definitive surgery (neoadjuvant) may increase the fraction of pts whose gross disease is resectable. Advanced-stage pts should receive paclitaxel, 175 mg/m^2 by 3-h infusion, followed by carboplatin dosed to an area under the curve (AUC) of 6 every 3 or 4 weeks. Carboplatin dose is calculated by the Calvert formula: dose = target AUC × (glomerular filtration rate + 25). Some data support intraperitoneal delivery of the chemotherapy. The complete response rate is about 55%, and median survival is 38 months.

http://internalmedicinebook.com

ENDOMETRIAL CANCER

INCIDENCE AND EPIDEMIOLOGY

The most common gynecologic cancer—54,870 cases are diagnosed in the United States and 10,170 pts die annually. It is primarily a disease of postmenopausal women. Obesity, altered menstrual cycles, infertility, late menopause, and postmenopausal bleeding are commonly encountered in women with endometrial cancer. Women taking tamoxifen to prevent breast cancer recurrence and those taking estrogen replacement therapy are at a modestly increased risk. Peak incidence is in the sixth and seventh decades.

CLINICAL PRESENTATION

Abnormal vaginal discharge (90%), abnormal vaginal bleeding (80%), and leukorrhea (10%) are the most common symptoms.

PATHOLOGY

Endometrial cancers are adenocarcinomas in 75–80% of cases. The remaining cases include mucinous carcinoma; papillary serous carcinoma; and secretory, ciliate, and clear cell varieties. Prognosis depends on stage, histologic grade, and degree of myometrial invasion.

STAGING

Total abdominal hysterectomy and bilateral salpingo-oophorectomy constitute both the staging procedure and the treatment of choice. The staging scheme and its influence on prognosis are shown in Table 73-1. About 75% of pts are stage I, 13% are stage II, 9% are stage III, and 3% are stage IV.

TREATMENT ENDOMETRIAL CANCER

In women with poor histologic grade, deep myometrial invasion, or extensive involvement of the lower uterine segment or cervix, intracavitary or external-beam radiation therapy is given. If cervical invasion is deep, preoperative radiation therapy may improve the resectability of the tumor. Stage III disease is managed with surgery and radiation therapy. Stage IV disease is usually treated palliatively. Progestational agents such as hydroxyprogesterone or megestrol and the antiestrogen tamoxifen may produce responses in 20% of pts. Doxorubicin, 60 mg/m^2 IV day 1, and cisplatin, 50 mg/m^2 IV day 1, every 3 weeks for 8 cycles produces a 45% response rate.

CERVICAL CANCER

INCIDENCE AND EPIDEMIOLOGY

In the United States, about 12,900 cases of invasive cervical cancer are diagnosed each year and 50,000 cases of carcinoma in situ are detected by Pap smear. Cervical cancer kills 4100 women a year, 85% of whom never had a Pap smear. It is a major cause of disease in underdeveloped countries and is more common in lower socioeconomic groups, in women with early sexual activity and/or multiple sexual partners, and in smokers. Human papilloma virus (HPV) types 16 and 18 are the major types associated with cervical cancer. The virus attacks the G_1 checkpoint of the cell cycle; its E7 protein binds and inactivates Rb protein, and E6 induces the degradation of p53. Risk factors include a large number of sexual partners, early age at first intercourse, a history of venereal disease, HIV infection, and heavy smoking.

http://internalmedicinebook.com

SCREENING

Women should begin screening when they begin sexual activity or at age 20. After two consecutive negative annual Pap smears, the test should be repeated every 3 years. Abnormal smears dictate the need for a cervical biopsy, usually under colposcopy, with the cervix painted with 3% acetic acid, which shows abnormal areas as white patches. If there is evidence of carcinoma in situ, a cone biopsy is performed, which is therapeutic.

PREVENTION

Women, men, and children age 9–26 should obtain vaccination with Gardasil to prevent infection with two serotypes of virus (16 and 18) that cause 70% of the cervical cancer in the United States.

CLINICAL PRESENTATION

Pts present with abnormal bleeding or postcoital spotting or menometrorrhagia or intermenstrual bleeding. Vaginal discharge, low back pain, and urinary symptoms also may be present.

STAGING

Staging is clinical and consists of a pelvic examination under anesthesia with cystoscopy and proctoscopy. Chest x-ray, IV pyelography, and abdominal CT are used to search for metastases. The staging system and its influence on prognosis are shown in Table 73-1. At presentation, 47% of pts are stage I, 28% are stage II, 21% are stage III, and 4% are stage IV.

TREATMENT CERVICAL CANCER

Carcinoma in situ is cured with cone biopsy. Stage I disease may be treated with radical hysterectomy or radiation therapy. Stages II–IV disease are usually treated with radiation therapy, often with both brachytherapy and teletherapy, or combined-modality therapy. Pelvic exenteration is used uncommonly to control the disease, especially in the setting of centrally recurrent or persistent disease. Women with locally advanced (stage IIB–IVA) disease usually receive concurrent chemotherapy and radiation therapy. The chemotherapy acts as a radiosensitizer. Hydroxyurea, 5-fluorouracil (5FU), and cisplatin have all shown promising results given concurrently with radiation therapy. Cisplatin, 75 mg/m^2 IV over 4 h on day 1, and 5FU, 4 g given by 96-h infusion on days 1–5 of radiation therapy, is a common regimen. Relapse rates are reduced 30–50% by such therapy. Advanced-stage disease is treated palliatively with single agents (cisplatin, irinotecan, ifosfamide). Bevacizumab may improve the antitumor effects of chemotherapy.



For a more detailed discussion, see Seiden MV: Gynecologic Malignancies, Chap. 117, p. 592, in HPIM-19.

http://internalmedicinebook.com

74 Prostate Hyperplasia and Carcinoma

PROSTATE HYPERPLASIA

Enlargement of the prostate is nearly universal in aging men. Hyperplasia usually begins by age 45 years, occurs in the area of the prostate gland surrounding the urethra, and produces urinary outflow obstruction. Symptoms develop on average by age 65 in whites and 60 in blacks. Symptoms develop late because hypertrophy of the bladder detrusor compensates for ureteral compression. As obstruction progresses, urinary stream caliber and force diminish, hesitancy in stream initiation develops, and postvoid dribbling occurs. Dysuria and urgency are signs of bladder irritation (perhaps due to inflammation or tumor) and are usually not seen in prostate hyperplasia. As the postvoid residual increases, nocturia and overflow incontinence may develop. Common medications such as tranquilizing drugs and decongestants, infections, or alcohol may precipitate urinary retention. Because of the prevalence of hyperplasia, the relationship to neoplasia is unclear.

On digital rectal examination (DRE), a hyperplastic prostate is smooth, firm, and rubbery in consistency; the median groove may be lost. Prostate-specific antigen (PSA) levels may be elevated but are ≤10 ng/mL unless cancer is also present (see below). Cancer may also be present at lower levels of PSA.

TREATMENT PROSTATE HYPERPLASIA

Asymptomatic pts do not require treatment, and those with complications of urethral obstruction such as inability to urinate, renal failure, recurrent urinary tract infection, hematuria, or bladder stones clearly require surgical extirpation of the prostate, usually by transurethral resection (TURP). However, the approach to the remaining pts should be based on the degree of incapacity or discomfort from the disease and the likely side effects of any intervention. If the pt has only mild symptoms, watchful waiting is not harmful and permits an assessment of the rate of symptom progression. If therapy is desired by the pt, two medical approaches may be helpful: terazosin, an α_1-adrenergic blocker (1 mg at bedtime, titrated to symptoms up to 20 mg/d), relaxes the smooth muscle of the bladder neck and increases urine flow; finasteride (5 mg/d) or dutasteride (2.5 mg/d), inhibitors of 5α-reductase, block the conversion of testosterone to dihydrotestosterone and cause an average decrease in prostate size of ~24%. TURP has the greatest success rate but also the greatest risk of complications. Transurethral microwave thermotherapy (TUMT) may be comparably effective to TURP. Direct comparison has not been made between medical and surgical management.

PROSTATE CARCINOMA

Prostate cancer has been diagnosed in 220,800 men in 2015 in the United States—an incidence comparable to that of breast cancer. About 27,540 men have died of prostate cancer in 2015. The early diagnosis of cancers in mildly symptomatic men found on screening to have elevated serum levels of PSA has complicated management. Like most other cancers, incidence is age-related. The disease is more common in blacks than whites. Symptoms are generally similar to and indistinguishable from those of prostate hyperplasia, but those with cancer more often have dysuria and back or hip pain. On histology, 95% are adenocarcinomas. Biologic behavior is affected by histologic grade (Gleason score).

http://internalmedicinebook.com

In contrast to hyperplasia, prostate cancer generally originates in the periphery of the gland and may be detectable on DRE as one or more nodules on the posterior surface of the gland, hard in consistency and irregular in shape. An approach to diagnosis is shown in Fig. 74-1. Those with a negative DRE and PSA ≤4 ng/mL may be followed annually. Those with an abnormal DRE or a PSA >10 ng/mL should undergo transrectal ultrasound (TRUS)-guided biopsy. Those with normal DRE and PSA of 4.1–10 ng/mL may be handled differently in different centers. Some would perform TRUS and biopsy any abnormality or follow if no abnormality were found. Some would repeat the PSA in a year and biopsy if the increase over that period were >0.75 ng/mL. Other methods of using PSA to distinguish early cancer from hyperplasia include quantitating bound and free PSA and relating the PSA to the size of the prostate (PSA density). Perhaps one-third of persons with prostate cancer do not have PSA elevations.

Lymphatic spread is assessed surgically; it is present in only 10% of those with Gleason grade 5 or lower and in 70% of those with grade 9 or 10. PSA level also correlates with spread; only 10% of those with PSA <10 ng/mL have lymphatic spread. Bone is the most common site of distant metastasis. Whitmore-Jewett staging includes A: tumor not palpable but detected at TURP; B: palpable tumor in one (B1) or both (B2) lobes; C: palpable tumor outside capsule; and D: metastatic disease.

TREATMENT PROSTATE CARCINOMA

For pts with stages A through C disease, surgery (radical retropubic prostatectomy) and radiation therapy (conformal three-dimensional fields) are said to have similar outcomes; however, most pts are treated surgically. Both modalities are associated with impotence. Surgery is more likely to lead to incontinence. Radiation therapy is more likely to produce proctitis, perhaps with bleeding or stricture. Addition of hormonal therapy (goserelin) to radiation therapy of pts with localized disease appears to improve results. Pts usually must have a 5-year life expectancy to undergo radical prostatectomy. Stage A pts have survival identical to age-matched controls without cancer. Stage B and C pts have a 10-year survival of 82% and 42%, respectively.

Pts treated surgically for localized disease who develop rising PSA may undergo Prostascint scanning (antibody to a prostate-specific membrane antigen). If no uptake is seen, the pt is observed. If uptake is seen in the prostate bed, local recurrence is implied and external beam radiation therapy is delivered to the site. (If the pt was initially treated with radiation therapy, this local recurrence may be treated with surgery.) However, in most cases, a rising PSA after local therapy indicates systemic disease. It is not clear when to intervene in such pts. Treatment is often initiated if the PSA doubling time is <12 months.

For pts with metastatic disease, androgen deprivation is the treatment of choice. Surgical castration is effective, but most pts prefer to take leuprolide, 7.5 mg depot form IM monthly (to inhibit pituitary gonadotropin production), plus flutamide, 250 mg PO tid (an androgen receptor blocker). The value of added flutamide is debated. Alternative approaches include adrenalectomy, hypophysectomy, estrogen administration, and medical adrenalectomy with aminoglutethimide. The median survival of stage D pts is 33 months. Pts occasionally respond to withdrawal of hormonal therapy with tumor shrinkage. Second hormonal manipulations act by blocking androgen production in the tumor; abiraterone, a CYP17 inhibitor that blocks androgen synthesis and enzalutamide, an antiandrogen, improve overall survival. Many pts who progress on hormonal therapy have androgen-independent tumors, often associated with genetic changes in the androgen receptor and new expression of *bcl*-2, which may contribute to chemotherapy resistance. Chemotherapy is used for palliation in prostate cancer. Mitoxantrone, estramustine, and taxanes, particularly cabazitaxel, appear to be active single agents, and combinations of drugs are being tested.

http://internalmedicinebook.com

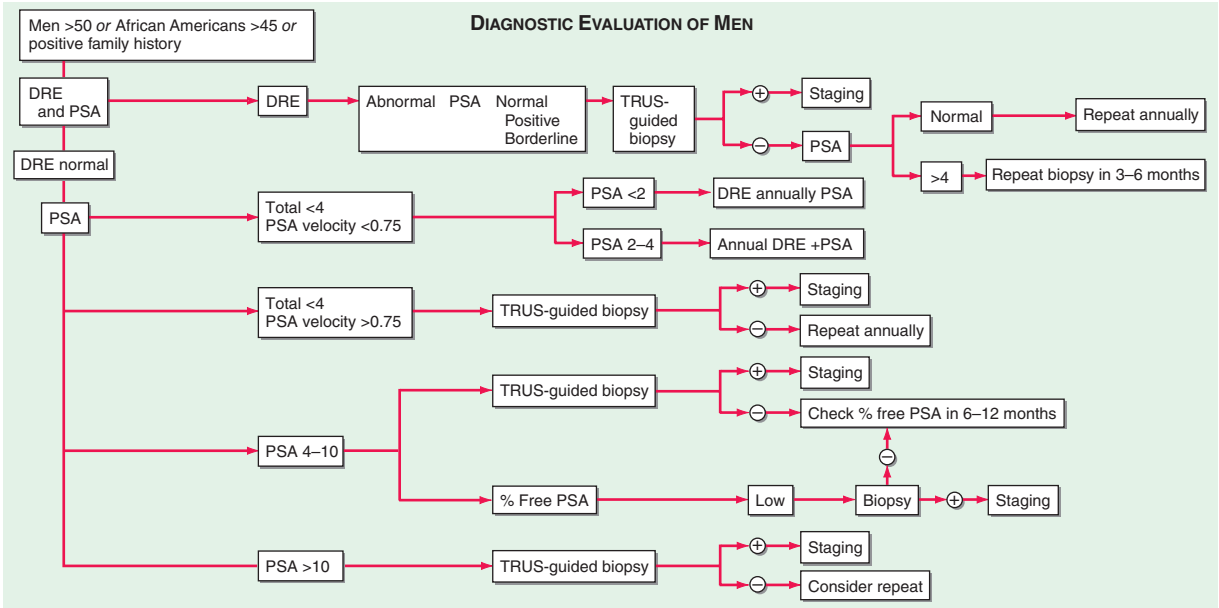


FIGURE 74-1 The use of the annual digital rectal examination (DRE) and measurement of prostate-specific antigen (PSA) as guides for deciding which men should have transrectal ultrasound (TRUS)-guided prostate biopsy. There are at least three schools of thought about what to do if the DRE is negative and the PSA is equivocal (4.1–10 ng/mL).

http://internalmedicinebook.com

Chemotherapy-treated pts are more likely to have pain relief than those receiving supportive care alone. Sipuleucel-T, an active specific immunotherapy, improves survival by about 4 months in hormone-refractory disease without producing any measureable change in the tumor. Bone pain from metastases may be palliated with strontium-89 or samarium-153. Bisphosphonates decrease the incidence of skeletal events.

PROSTATE CANCER PREVENTION

Finasteride and dutasteride have been shown to reduce the incidence of prostate cancer by 25%, but no effect on overall survival has been seen with limited follow-up. In addition, the cancers that do occur appear to be shifted to higher Gleason grades, but the clinical course of disease does not seem to be altered.

For a more detailed discussion, see Scher HI, Eastham JA: Benign and Malignant Diseases of the Prostate, Chap. 115, p. 579, in HPIM-19.

75 Cancer of Unknown Primary Site

Cancer of unknown primary site (CUPS) is defined as follows: biopsy-proven malignancy; primary site unapparent after history, physical examination, chest x-ray, abdominal and pelvic CT, complete blood count, chemistry survey, mammography (women), β-human chorionic gonadotropin (hCG) levels (men), α-fetoprotein (AFP) levels (men), and prostate-specific antigen (PSA) levels (men); and histologic evaluation not consistent with a primary tumor at the biopsy site. CUPS incidence is declining, probably because of better pathology diagnostic criteria; it accounts for about 3% of all cancers today, down from 10–15% 15 years ago. Most pts are over age 60. The tumors are often aneuploid. Cell lines derived from such tumors frequently have abnormalities in chromosome 1.

Clinical Presentation

Pts may present with fatigue, weight loss, pain, bleeding, abdominal swelling, subcutaneous masses, and lymphadenopathy. Once metastatic malignancy is confirmed, diagnostic efforts should be confined to evaluating the presence of potentially curable tumors, such as lymphoma, Hodgkin's disease, germ cell tumor, ovarian cancer, head and neck cancer, and primitive neuroectodermal tumor, or tumors for which therapy may be of significant palliative value such as breast cancer or prostate cancer. In general, efforts to evaluate the presence of these tumor types depend more on the pathologist than on expensive clinical diagnostic testing. Localizing symptoms, a history of carcinogen exposure, or a history of fulguration of skin lesion may direct some clinical testing; however, the careful light microscopic, ultrastructural, immunologic, karyotypic, and molecular biologic examination of adequate volumes of tumor tissue is the most important feature of the diagnostic workup in the absence of suspicious findings on history and physical examination (Table 75-1).

http://internalmedicinebook.com

TABLE 75-1 POSSIBLE PATHOLOGIC EVALUATION OF BIOPSY SPECIMENS FROM PATIENTS WITH METASTATIC CANCER OF UNKNOWN PRIMARY SITE

Evaluation/Findings	Suggested Primary Site or Neoplasm
Histology (hematoxylin and eosin staining)	
Psammoma bodies, papillary configuration	Ovary, thyroid
Signet ring cells	Stomach
Immunohistology	
Leukocyte common antigen (LCA, CD45)	Lymphoid neoplasm
Leu-M1	Hodgkin's disease
Epithelial membrane antigen	Carcinoma
Cytokeratin	Carcinoma
CEA	Carcinoma
HMB45	Melanoma
Desmin	Sarcoma
Thyroglobulin	Thyroid carcinoma
Calcitonin	Medullary carcinoma of the thyroid
Myoglobin	Rhabdomyosarcoma
PSA/prostatic acid phosphatase	Prostate
AFP	Liver, stomach, germ cell
Placental alkaline phosphatase	Germ cell
β-human chorionic gonadotropin	Germ cell
B, T cell markers	Lymphoid neoplasm
S-100 protein	Neuroendocrine tumor, melanoma
Gross cystic fluid protein	Breast, sweat gland
Estrogen and progesterone receptors	Breast
Factor VIII	Kaposi's sarcoma, angiosarcoma
Thyroid transcription factor 1 (TTF-1)	Lung adenocarcinoma, thyroid
Calretinin, mesothelin	Mesothelioma
URO-III, thrombomodulin	Bladder
Flow Cytometry	
B, T cell markers	Lymphoid neoplasm
Ultrastructure	
Actin-myosin filaments	Rhabdomyosarcoma
Secretory granules	Neuroendocrine tumors
Desmosomes	Carcinoma
Premelanosomes	Melanoma
Cytogenetics	
Isochromosome 12p; 12q(–)	Germ cell
t(11;22)	Ewing's sarcoma, primitive neuroectodermal tumor
t(8;14)[a]	Lymphoid neoplasm
3p(–)	Small cell lung carcinoma; renal cell carcinoma, mesothelioma
t(X;18)	Synovial sarcoma

(*Continued*)

http://internalmedicinebook.com

TABLE 75-1 POSSIBLE PATHOLOGIC EVALUATION OF BIOPSY SPECIMENS FROM PATIENTS WITH METASTATIC CANCER OF UNKNOWN PRIMARY SITE (*CONTINUED*)

Evaluation/Findings	Suggested Primary Site or Neoplasm
t(12;16)	Myxoid liposarcoma
t(12;22)	Clear cell sarcoma (melanoma of soft parts)
t(2;13)	Alveolar rhabdomyosarcoma
1p(–)	Neuroblastoma
Receptor Analysis	
Estrogen/progesterone receptor	Breast
Molecular Biologic Studies	
Immunoglobulin, *bcl*-2, T cell receptor gene rearrangement	Lymphoid neoplasm

[a]Or any other rearrangement involving an antigen-receptor gene.
Abbreviations: AFP, α-fetoprotein; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen.

Histology

About 60% of CUPS tumors are adenocarcinomas, 5% are squamous cell carcinomas, and 30% are poorly differentiated neoplasms not further classified on light microscopy. Expression of cytokeratin subtypes may narrow the range of possible diagnoses (Fig. 75-1).

Prognosis

Pts with squamous cell carcinoma have a median survival of 9 months; those with adenocarcinoma or unclassifiable tumors have a median survival of 4–6 months. Pts in whom a primary site is identified usually have a better prognosis. Limited sites of involvement and neuroendocrine histology are favorable prognostic factors. Pts without a primary diagnosis should be treated palliatively with radiation therapy to symptomatic lesions. All-purpose chemotherapy regimens rarely produce responses but always produce toxicity. Certain clinical features may permit individualized therapy.

SYNDROME OF UNRECOGNIZED EXTRAGONADAL GERM CELL CANCER

In pts <50 years with tumor involving midline structures, lung parenchyma, or lymph nodes and evidence of rapid tumor growth, germ cell tumor is a possible diagnosis. Serum tumor markers may or may not be elevated. Cisplatin, etoposide, and bleomycin (Chap. 72) chemotherapy may induce complete responses in ≥25%,

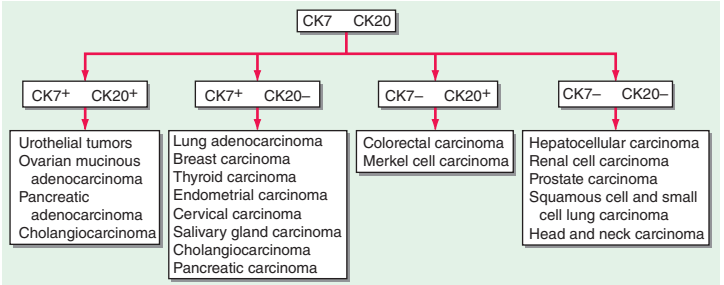


FIGURE 75-1 Approach to cytokeratin (CK7 and CK20) markers used in CUP.

http://internalmedicinebook.com

and ~15% may be cured. A trial of such therapy should probably also be undertaken in pts whose tumors have abnormalities in chromosome 12.

PERITONEAL CARCINOMATOSIS IN WOMEN

Women who present with pelvic mass or pain and an adenocarcinoma diffusely throughout the peritoneal cavity, but without a clear site of origin, have primary peritoneal papillary serous carcinoma. The presence of psammoma bodies in the tumor or elevated CA-125 levels may favor ovarian origin. Such pts should undergo debulking surgery followed by paclitaxel plus cisplatin or carboplatin combination chemotherapy (Chap. 73). About 20% of pts will respond, and 10% will survive at least 2 years.

CARCINOMA IN AN AXILLARY LYMPH NODE IN WOMEN

Such women should receive adjuvant breast cancer therapy appropriate for their menopausal status even in the absence of a breast mass on physical examination or mammography and undetermined or negative estrogen and progesterone receptors on the tumor (Chap. 70). Unless the ipsilateral breast is radiated, up to 50% of these pts will later develop a breast mass. Although this is a rare clinical situation, long-term survival similar to women with stage II breast cancer is possible.

OSTEOBLASTIC BONE METASTASES IN MEN

The probability of prostate cancer is high; a trial of empirical hormonal therapy (leuprolide and flutamide) is warranted (Chap. 74).

CERVICAL LYMPH NODE METASTASES

Even if panendoscopy fails to reveal a head and neck primary, treatment of such pts with cisplatin and 5-fluorouracil chemotherapy may produce a response; some responses are long-lived (Chap. 68).

For a more detailed discussion, see Varadhachary GR, Abbruzzese JL: Carcinoma of Unknown Primary, Chap. 120e, in HPIM-19.

76 Paraneoplastic Endocrine Syndromes

Both benign and malignant tumors of nonendocrine tissue can secrete a variety of hormones, principally peptide hormones, and many tumors produce more than one hormone (Table 76-1). At the clinical level, ectopic hormone production is important for two reasons.

First, endocrine syndromes that result may either be the presenting manifestations of the neoplasm or occur late in the course. The endocrine manifestations in some instances are of greater significance than the tumor itself, as in pts with benign or slowly growing malignancies that secrete corticotropin-releasing hormone and cause fulminant Cushing's syndrome. The frequency with which ectopic hormone production is recognized varies with the criteria used for diagnosis. The most common syndromes of clinical import are those of adrenocorticotropic hormone

http://internalmedicinebook.com

TABLE 76-1 PARANEOPLASTIC SYNDROMES CAUSED BY ECTOPIC HORMONE PRODUCTION

Paraneoplastic Syndrome	Ectopic Hormone	Typical Tumor Types[a]
Common		
Hypercalcemia of malignancy	PTHrP	Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal
	1,25 dihydroxyvitamin D	Lymphomas
	PTH (rare)	Lung, ovary
	PGE_2 (rare)	Renal, lung
SIADH	Vasopressin	Lung (squamous, small cell), gastrointestinal, genitourinary, ovary
Cushing's syndrome	ACTH	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma
	CRH (rare)	Pancreatic islet, carcinoid, lung, prostate
	Ectopic expression of GIP, LH/hCG, other G protein–coupled receptors (rare)	Macronodular adrenal hyperplasia
Less common		
Nonislet cell hypoglycemia	IGF-II	Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate
	Insulin (rare)	Cervix (small cell carcinoma)
Male feminization	hCG[b]	Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet
Diarrhea or intestinal hypermotility	Calcitonin[c]	Lung, colon, breast, medullary thyroid carcinoma
	VIP	Pancreas, pheochromocytoma, esophagus
Rare		
Oncogenic osteomalacia	Phosphatonin (FGF23)	Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung
Acromegaly	GHRH	Pancreatic islet, bronchial and other carcinoids
	GH	Lung, pancreatic islet

(*Continued*)

http://internalmedicinebook.com

TABLE 76-1 PARANEOPLASTIC SYNDROMES CAUSED BY ECTOPIC HORMONE PRODUCTION (*CONTINUED*)

Paraneoplastic Syndrome	Ectopic Hormone	Typical Tumor Types[a]
Hyperthyroidism	TSH	Hydatidiform mole, embryonal tumors, struma ovarii
Hypertension	Renin	Juxtaglomerular tumors, kidney, lung, pancreas, ovary

[a]Only the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones.
[b]hCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor.
[c]Calcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker.
Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FGF23, fibroblast growth factor 23; GH, growth hormone; GHRH, Growth hormone–releasing hormone; GIP, gastric inhibitory peptide; hCG, human chorionic gonadotropin; IGF, insulin-like growth factor; LH, luteinizing hormone; PGE_2, prostaglandin E_2; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone; VIP, vasoactive intestinal peptide.

(ACTH) hypersecretion, hypercalcemia, and hypoglycemia. Indeed, ectopic ACTH secretion is responsible for 15–20% of pts with Cushing's syndrome, and ~50% of pts with persistent hypercalcemia have a malignancy rather than hyperparathyroidism. Because of the rapidity of development of hormone secretion in some rapidly growing tumors, diagnosis may require a high index of suspicion, and hormone levels may be elevated out of proportion to the manifestations.

Second, ectopic hormones serve as valuable peripheral markers for neoplasia. Because of the broad spectrum of ectopic hormone secretion, screening measurements of plasma hormone levels for diagnostic purposes are not cost effective. However, in pts with malignancies that are known to secrete hormones, serial measurements of circulating hormone levels can serve as markers for completeness of tumor excision and for effectiveness of radiation therapy or chemotherapy. Likewise, tumor recurrence may be heralded by reappearance of elevated plasma hormone levels before mass effects of the tumor are evident. However, some tumors at recurrence do not secrete hormones, so hormone measurements cannot be relied on as the sole evidence of tumor activity.

TREATMENT PARANEOPLASTIC ENDOCRINE SYNDROMES

Therapy of ectopic hormone-secreting tumors should be directed when possible toward removal of the tumor. When the tumor cannot be removed or is incurable, specific therapy can be directed toward inhibiting hormone secretion (octreotide for ectopic acromegaly or mitotane to inhibit adrenal steroidogenesis in the ectopic ACTH syndrome) or blocking the action of the hormone at the tissue level (demeclocycline for inappropriate vasopressin secretion).

http://internalmedicinebook.com

HYPERCALCEMIA

The most common paraneoplastic syndrome, hypercalcemia of malignancy accounts for 40% of all hypercalcemia. Of cancer pts with hypercalcemia, 80% have humoral hypercalcemia mediated by parathyroid hormone–related peptide; 20% have local osteolytic hypercalcemia mediated by cytokines such as interleukin 1 and tumor necrosis factor. Many tumor types may produce hypercalcemia (Table 76-1). Pts may have malaise, fatigue, confusion, anorexia, bone pain, polyuria, weakness, constipation, nausea, and vomiting. At high calcium levels, confusion, lethargy, coma, and death may ensue. Median survival of hypercalcemic cancer pts is 1–3 months. Treatment with saline hydration, furosemide diuresis, and pamidronate (60–90 mg IV) or zoledronate (4–8 mg IV) controls calcium levels within 2 days and suppresses calcium release for several weeks. Calcitonin (2–8 U/kg) may be useful if rapid action is needed. Oral bisphosphonates can be used for chronic treatment. In the setting of hematologic malignancies, hypercalcemia may respond to glucocorticoids.

HYPONATREMIA

Most commonly discovered in asymptomatic individuals as a result of serum electrolyte measurements, hyponatremia is usually due to tumor secretion of arginine vasopressin, a condition called *syndrome of inappropriate antidiuretic hormone secretion* (SIADH). Atrial natriuretic hormone also may produce hyponatremia. SIADH occurs most commonly in small cell lung cancer (15%) and head and neck cancer (3%). A number of drugs may produce the syndrome. Symptoms of fatigue, poor attention span, nausea, weakness, anorexia, and headache may be controlled by restricting fluid intake to 500 mL/d or blocking the effects of the hormone with 600- to 1200-mg demeclocycline a day. Conivaptan, a vasopressin receptor blocker, is effective PO (20–120 mg bid) or IV (10–40 mg), especially in combination with fluid restriction. With severe hyponatremia (<115 meq/L) or in the setting of mental status changes, normal saline infusion plus furosemide may be required; rate of correction should be <1 meq/L per hour to prevent complications.

ECTOPIC ACTH SYNDROME

When pro-opiomelanocortin mRNA in the tumor is processed into ACTH, excessive secretion of glucocorticoids and mineralocorticoids may ensue. Pts develop Cushing's syndrome with hypokalemic alkalosis, weakness, hypertension, and hyperglycemia. About half the cases occur in small cell lung cancer. ACTH production adversely affects prognosis. Ketoconazole (400–1200 mg/d) or metyrapone (1–4 g/d) may be used to inhibit adrenal steroid synthesis.



For a more detailed discussion, see Jameson JL, Longo, DL: Paraneoplastic Syndromes: Endocrinologic/Hematologic, Chap. 121, p. 608, in HPIM-19.

http://internalmedicinebook.com

77 Neurologic Paraneoplastic Syndromes

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system; caused by mechanisms other than metastasis or by complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of pts the neurologic symptoms precede cancer diagnosis. PNDs occur in 0.5–1% of all cancer pts, but they occur in 2–3% of pts with neuroblastoma or small cell lung cancer (SCLC), and in 30–50% of pts with thymoma or sclerotic myeloma.

CLINICAL FEATURES

Recognition of a distinctive paraneoplastic syndrome (Table 77-1) should prompt a search for cancer, because treatment of tumor may improve the course of PNDs; many of these disorders also occur without cancer. Diagnosis is based on the clinical pattern, exclusion of other cancer-related disorders, confirmatory serum or CSF antibodies, or occasionally electrodiagnostic testing. Most PNDs are mediated by immune responses triggered by neuronal proteins expressed by tumors. PNDs associated with immune responses against intracellular antigens often respond poorly to treatment (Table 77-2), whereas those associated with antibodies to synaptic or neuronal cell surface proteins are more responsive to immunotherapy (Table 77-3). For any type of PND, if antibody testing is negative, the diagnosis rests on the

TABLE 77-1 PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

Classic Syndromes: Usually Occur with Cancer Association	Nonclassic Syndromes: May Occur with and Without Cancer Association
Encephalomyelitis	Brainstem encephalitis
Limbic encephalitis	Stiff-person syndrome
Cerebellar degeneration (adults)	Necrotizing myelopathy
Opsoclonus-myoclonus	Motor neuron disease
Subacute sensory neuronopathy	Guillain-Barré syndrome
Gastrointestinal paresis or pseudo-obstruction	Subacute and chronic mixed sensory-motor neuropathies
Dermatomyositis (adults)	Neuropathy associated with plasma cell dyscrasias and lymphoma
Lambert-Eaton myasthenic syndrome	Vasculitis of nerve
Cancer- or melanoma-associated retinopathy	Pure autonomic neuropathy
	Acute necrotizing myopathy
	Polymyositis
	Vasculitis of muscle
	Optic neuropathy
	BDUMP

Abbreviation: BDUMP, bilateral diffuse uveal melanocytic proliferation.

http://internalmedicinebook.com

TABLE 77-2 ANTIBODIES TO INTRACELLULAR ANTIGENS, SYNDROMES, AND ASSOCIATED CANCERS

Antibody	Associated Neurologic Syndrome(s)	Tumors
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin, bipolar cell antibodies, others[a]	CAR MAR	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndromes, limbic encephalitis	Infrequent tumor association (thymoma)

[a]A variety of target antigens have been identified.
Abbreviations: CAR, cancer-associated retinopathy; CRMP, collapsing response-mediator protein; MAR, melanoma-associated retinopathy; SCLC, small cell lung cancer.

demonstration of cancer and the exclusion of other cancer-related or independent disorders. Combined whole-body CT and PET scans often uncover tumors undetected by other tests.

PNDs of the Central Nervous System and Dorsal Root Ganglia

MRI and CSF studies are important to rule out neurologic complications due to direct spread of cancer. In most PNDs the MRI findings are nonspecific. CSF findings typically consist of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands.

- *Paraneoplastic encephalomyelitis and focal encephalitis* describe an inflammatory process with multifocal involvement of the nervous system. Clinical manifestations depend on area involved, and syndromes may occur alone or in combination.
- *Cortical encephalitis*, which may present as "epilepsia partialis continua."
- *Limbic encephalitis*, characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities).
- *Brainstem encephalitis* presents with eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction.

http://internalmedicinebook.com

TABLE 77-3 ANTIBODIES TO CELL SURFACE OR SYNAPTIC ANTIGENS, SYNDROMES, AND ASSOCIATED TUMORS

Antibody	Neurologic Syndrome	Tumor Type When Associated
Anti-AChR (muscle)[a]	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)[a]	Autonomic ganglionopathy	SCLC
Anti-VGCC[b]	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR[a]	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1[c]	Limbic encephalitis, hyponatremia, faciobrachial tonic, or dystonic seizures	Rarely thymoma
Anti-Caspr2[c]	Morvan's syndrome, neuromyotonia	Thymoma, prostate cancer
Anti-$GABA_BR$[d]	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-$GABA_AR$[d]	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Rarely thymoma
Anti-AMPAR[d]	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor[d]	Encephalomyelitis with rigidity, stiff-person syndrome	Rarely, thymoma, lung cancer
Anti-DPPX[d]	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia

[a]A direct pathogenic role of these antibodies has been demonstrated.
[b]Anti-VGCC antibodies are pathogenic for LEMS.
[c]Previously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable).
[d]These antibodies are strongly suspected to be pathogenic.
Abbreviations: AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, *N*-methyl-D-aspartate receptor; SCLC, small cell lung cancer; VGCC, voltage-gated calcium channel.

- *Opsoclonus-myoclonus syndrome* consists of involuntary, chaotic eye movements in all directions of gaze plus myoclonus; it is frequently associated with ataxia.
- *Paraneoplastic cerebellar degeneration* begins as dizziness, oscillopsia, blurry or double vision, nausea, and vomiting; a few days or weeks later, dysarthria, gait and limb ataxia, and variable dysphagia can appear.
- *Myelitis*, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms.
- *Autonomic dysfunction* occurs as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves. Cardiac

http://internalmedicinebook.com

arrhythmias, postural hypotension, and central hypoventilation are frequent causes of death.

- *Encephalitis with antibodies to cell-surface or synaptic proteins* can occur without tumor association and may occur predominantly in children or young adults. An example is *N*-methyl-D-aspartate (NMDA) receptor autoantibodies that present as a virus-like syndrome followed by a prominent psychiatric disturbance with involuntary movements; in young women, ovarian teratomas are frequently present. Despite dramatic severity at times, patients usually respond to treatment of the tumor (if found) and immunotherapy.
- *Cancer-associated retinopathies* involve cone and rod dysfunction with photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG).
- *Dorsal root ganglionopathy* (sensory neuronopathy) is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes; all modalities of sensation can be involved.

PNDs of Nerve and Muscle

These disorders may develop anytime during the course of the neoplastic disease. Serum and urine immunofixation studies should be considered in pts with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to anti-CV_2/CRMP5 and anti-Hu.

Myasthenia gravis is discussed in Chap. 194 and dermatomyositis in Chap. 195.

TREATMENT **PARANEOPLASTIC NEUROLOGIC DISORDERS**

- Treatment of PNDs focuses mainly on recognition and control of the underlying malignancy; a stabilization or improvement of symptoms has been reported in some pts with successful tumor control.
- Variable responses have been described following treatment with glucocorticoids and other immunosuppressive agents as well as intravenous immunoglobulin (IVIg) and plasma exchange.
- Those PNDs caused by antibodies to cell surface or synaptic antigens have a much more favorable response to therapy.



For a more detailed discussion, see Dalmau J, Rosenfeld MR: Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis, Chap. 122, p. 614, in HPIM-19.

http://internalmedicinebook.com

This page intentionally left blank

http://internalmedicinebook.com

78 Infections Acquired in Health Care Facilities

Hospital-acquired or *nosocomial* infections (defined as those not present or incubating at the time of admission to the hospital) and other health care–associated infections affect an estimated 1.7 million pts, cost $28–33 billion, and contribute to 99,000 deaths in U.S. hospitals each year. Although efforts to lower infection risks have been challenged by the growing numbers of immunocompromised pts, antibiotic-resistant bacteria, fungal and viral superinfections, and invasive procedures and devices, the "zero-tolerance" viewpoint of consumer advocates holds that nearly all health care–associated infections should be avoidable. Accordingly, federal legislation now exists to prevent U.S. hospitals from upgrading Medicare charges to pay hospital costs resulting from at least 14 specific nosocomial events.

PREVENTION OF HOSPITAL-ACQUIRED INFECTIONS

Nosocomial pathogens have reservoirs, are transmitted by largely predictable routes, and require susceptible hosts—features that allow the implementation of monitoring and prevention strategies.

- *Surveillance:* review of microbiology laboratory results, surveys of nursing wards, and use of other mechanisms to keep track of infections acquired after hospital admission. Most hospitals aim surveillance at infections associated with high-level morbidity or great expense. Results of surveillance are expressed as rates and should include a denominator indicating the number of pts exposed to a specific risk (e.g., pts using a mechanical ventilator) or the number of intervention days (e.g., 1000 pt days on a ventilator).
- *Prevention and control measures:* Hand hygiene is the single most important measure to prevent cross-infection.
  - Health care workers' rates of adherence to hand-hygiene recommendations are abysmally low at <50%.
  - Other measures include identifying and eradicating reservoirs of infection and minimizing use of invasive procedures and catheters.
- *Isolation techniques:* Isolation of infectious pts is a standard component of infection control programs.
  - *Standard precautions:* include hand hygiene and use of gloves when there is a potential for contact with blood, other body fluids, nonintact skin, or mucous membranes during the care of all pts. In certain cases, masks, eye protection, and gowns are used as well.
  - *Transmission-based guidelines:* Airborne, droplet, or contact precautions—for which personnel don (at a minimum) N95 respirators, surgical face masks, or gowns and gloves, respectively—are used to prevent transmission of disease from pts with contagious clinical syndromes. More than one precaution can be used for diseases that have more than one mode of transmission (e.g., contact and airborne isolation for varicella).

http://internalmedicinebook.com

NOSOCOMIAL AND DEVICE-RELATED INFECTIONS

Nosocomial infections are due to the combined effect of the pt's own flora and the presence of invasive devices in 25–50% of cases. Intensive education, "bundling" of evidence-based interventions, and use of checklists to facilitate adherence can reduce infection rates. Table 78-1 summarizes effective interventions to reduce the incidence of the more common nosocomial infections.

- *Urinary tract infections:* Thirty to forty percent of nosocomial infections are UTIs, contributing ~15% to prolongation of hospital stay with an attributable cost of ~$1300.
  - Most nosocomial UTIs are associated with prior instrumentation or indwelling bladder catheterization. The 3–7% risk of infection for each day a catheter remains in place is due to the ascent of bacteria from the periurethral area or via intraluminal contamination of the catheter.
  - In men, condom catheters may lessen the risk of UTI.
  - The most common pathogens are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and (particularly for pts in the ICU) *Candida*.
  - For suspected infection in the setting of chronic catheterization, the catheter should be replaced and a freshly voided urine specimen obtained for culture to confirm actual infection as opposed to simple colonization of the catheter.
  - As with all nosocomial infections, it is useful to repeat the culture to confirm the persistence of infection at the time therapy is initiated.
- *Pneumonia:* Accounting for 10–15% of nosocomial infections, pneumonia increases the duration of hospital stay by 10 days, accounts for ~$23,000 in extra costs, and is associated with more deaths than are infections at any other body site. Of pts using mechanical ventilation, 5–10% develop ventilator-associated events.
  - Bacterial nosocomial pneumonia is caused by aspiration of endogenous or hospital-acquired oropharyngeal flora.
  - Risk factors include events that increase colonization with potential pathogens, such as prior antibiotic use, contaminated ventilator equipment, or decreased gastric acidity; events that increase risk of aspiration, such as nasogastric or endotracheal intubation or decreased level of consciousness; and conditions that compromise host defense mechanisms in the lung, such as chronic obstructive pulmonary disease, extremes of age, or upper abdominal surgery.
  - Etiologic organisms include community-acquired pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) early during hospitalization and *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter*, and *Acinetobacter* later in the hospital stay. In all, 20–40% of cases are polymicrobial.
  - Diagnosis can be difficult, as clinical criteria (e.g., fever, leukocytosis, purulent secretions, and new or changing pulmonary infiltrates on CXR) have high sensitivity but low specificity.
    - An etiology should be sought by studies of lower respiratory tract samples protected from upper-tract contamination; quantitative cultures have diagnostic sensitivities in the range of 80%.
    - Febrile pts with nasogastric or nasotracheal tubes should also have sinusitis or otitis media ruled out.
- *Surgical wound infections:* Making up ~15–20% of nosocomial infections, surgical wound infections increase the length of hospital stay by 7–10 days and increase costs by $3000–$29,000.
  - These infections often become evident after pts have left the hospital; thus, it is difficult to assess the true incidence.
  - Risk factors include the pt's underlying conditions (e.g., diabetes mellitus or obesity) and age, inappropriate timing of antibiotic prophylaxis, the presence of drains, prolonged preoperative hospital stays, shaving of the operative site the day before surgery (rather than just before the procedure), long duration of surgery, and infection at remote sites.

http://internalmedicinebook.com

TABLE 78-1 EXAMPLES OF EVIDENCE-BASED "BUNDLED INTERVENTIONS" TO PREVENT COMMON HEALTH CARE–ASSOCIATED INFECTIONS AND OTHER ADVERSE EVENTS

Prevention of Central Venous Catheter Infections
Catheter insertion bundle:
Educate personnel about catheter insertion and care.
Use chlorhexidine to prepare the insertion site.
Use maximal barrier precautions and asepsis during catheter insertion.
Consolidate insertion supplies (e.g., in an insertion kit or cart).
Use a checklist to enhance adherence to the "insertion bundle."
Empower nurses to halt insertion if asepsis is breached.
Catheter maintenance bundle:
Cleanse pts daily with chlorhexidine.
Maintain clean, dry dressings.
Enforce hand hygiene among health care workers.
Ask daily: Is the catheter needed? Remove catheter if not needed or used.
Prevention of Ventilator-Associated Events
Elevate head of bed to 30–45°.
Decontaminate oropharynx regularly with chlorhexidine (controversial).
Give "sedation vacation" and assess readiness to extubate daily.
Use peptic ulcer disease prophylaxis.
Use deep-vein thrombosis prophylaxis (unless contraindicated).
Prevention of Surgical-Site Infections
Choose a surgeon wisely.
Administer prophylactic antibiotics within 1 h before surgery; discontinue within 24 h.
Limit any hair removal to the time of surgery; use clippers or do not remove hair at all.
Prepare surgical site with chlorhexidine-alcohol.
Maintain normal perioperative glucose levels (cardiac surgery pts).[a]
Maintain perioperative normothermia (colorectal surgery pts).[a]
Prevention of Urinary Tract Infections
Place bladder catheters only when absolutely needed (e.g., to relieve obstruction), not solely for the provider's convenience.
Use aseptic technique for catheter insertion and urinary tract instrumentation.
Minimize manipulation or opening of drainage systems.
Ask daily: Is the bladder catheter needed? Remove catheter if not needed.
Prevention of Pathogen Cross-Transmission
Cleanse hands with alcohol hand rub before and after all contacts with pts or their environments.

[a]These components of care are supported by clinical trials and experimental evidence in the specified populations; they may prove valuable for other surgical pts as well.

Source: Adapted from information presented at the following websites: *www.cdc.gov/hicpac/pubs.html*; *www.cdc.gov/HAI/prevent/prevention.html*; *www.ihi.org*.

http://internalmedicinebook.com

  - These infections are typically caused by the pt's endogenous or hospital-acquired flora.
    - *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria are the most common pathogens.
    - A group A streptococcal or clostridial etiology should be considered in rapidly progressing postoperative infections (manifesting within 24–48 h of a procedure).
  - Clinical assessment of the surgical site may reveal obvious cellulitis or abscess formation; diagnosis of deeper infections requires a high index of suspicion and radiographic imaging.
  - Treatment of postoperative wound infections requires source control (drainage or surgical excision of infected or necrotic material) and use of antibiotics aimed at the most likely or laboratory-confirmed pathogens.
- *Intravascular device infections:* Intravascular device–related infections cause 10–15% of nosocomial infections, increase the duration of hospital stay by 12 days, add $3700–$29,000 to hospital costs, and have an attributable mortality rate of 12–25%.
  - Catheterization of the femoral vessels is associated with a higher risk of infection in adults.
    - These infections are largely due to the skin flora at the site of catheter insertion, with pathogens migrating extraluminally to the catheter tip.
    - Contamination of the infusate is rare.
    - Coagulase-negative staphylococci, *S. aureus* (≥50% methicillin-resistant isolates), enterococci, nosocomial gram-negative bacilli, and *Candida* are the pathogens most frequently associated with these bacteremias.
  - Infection is suspected on the basis of the catheter site's appearance and/or the presence of fever or bacteremia without another source. The diagnosis is confirmed by isolation of the same bacteria from peripheral-blood cultures and from semiquantitative or quantitative cultures of samples from the vascular catheter tip.
  - In addition to the initiation of appropriate antibiotic treatment, considerations include the level of risk for endocarditis (relatively high in pts with *S. aureus* bacteremia) and the decision regarding catheter removal, which is often necessary to cure infection.
    - The decision to remove a surgically implanted catheter should be based on the severity of the pt's illness, the strength of evidence that the device is infected, the presence of local or systemic complications, an assessment of the specific pathogens, and the pt's response to antimicrobial therapy if the catheter is initially retained.
    - If salvage of the catheter is attempted, the "antibiotic lock" technique (allowing a concentrated antibiotic solution to dwell in the catheter lumen along with systemic antibiotic administration) should be used.

EPIDEMIC AND EMERGING PROBLEMS

Although outbreaks and emerging pathogens often receive a great deal of press, they account for <5% of nosocomial infections.

- *Influenza:* The main components of infection control—vaccination of the general public and health care workers, early use of antiviral agents for control of outbreaks, and adherence to surveillance and droplet precautions for symptomatic pts—have been effective in controlling influenza, including the 2009 H1N1 pandemic.
- *Nosocomial diarrhea:* Rates of health care–associated diarrhea have been increasing in recent years.
  - Rates of infection with *Clostridium difficile*—particularly the more virulent BI/NAP1/027 strain—are increasing, especially among older pts. Important

http://internalmedicinebook.com

infection-control components include judicious use of antibiotics (particularly fluoroquinolones); heightened suspicion in cases with atypical presentations; and early diagnosis, treatment, and implementation of contact precautions.
  - Outbreaks of norovirus infection should be suspected in bacterial culture–negative diarrheal syndromes in which nausea and vomiting are prominent aspects. Contact precautions may need to be augmented by environmental cleaning and active exclusion of ill staff and visitors, who often represent index cases.
- *Chickenpox:* Routine vaccination of children and VZV-susceptible employees has made nosocomial spread less common.
  - If VZV exposure occurs, postexposure prophylaxis with varicella-zoster immune globulin (VZIG) is considered for immunocompromised or pregnant contacts.
  - Varicella vaccine or preemptive administration of acyclovir is an alternative for other susceptible persons.
  - Susceptible employees are furloughed for 8–21 days (or for 28 days if VZIG has been given).
- *Tuberculosis:* Prompt recognition and isolation of cases, use of negative-pressure private rooms with 100% exhaust and at least 6–12 air changes per hour, use of approved N95 respirators, and follow-up serologic or skin testing of susceptible, exposed personnel are required.
- *Group A streptococcal infections:* One or two nosocomial cases, usually involving surgical wounds and the presence of an asymptomatic carrier in the operating room, should trigger an investigation. Health care workers linked to nosocomial transmission of group A streptococci should not be permitted to return to pt care settings until eradication of carriage via antimicrobial therapy has been documented.
- *Fungal infections:* Hospital renovations and disturbance of dusty surfaces can cause fungal spores to become airborne. Routine surveillance of neutropenic pts for infections with filamentous fungi (e.g., *Aspergillus*, *Fusarium*) helps determine whether there are extensive environmental risks.
- *Legionellosis:* If nosocomial cases are detected, environmental samples (e.g., tap water) should be cultured; eradication measures should be pursued if typing of clinical and environmental isolates reveals a correlation.
- *Antibiotic-resistant bacterial infection:* Close laboratory surveillance, strict infection-control practices, and aggressive antibiotic-control policies are the cornerstones of resistance-control efforts.
  - Molecular typing can help distinguish an outbreak of a single isolate (which necessitates an emphasis on hand hygiene and an evaluation of common-source exposures) from a polyclonal outbreak (which necessitates re-emphasis on antibiotic prudence and device bundles).
  - Organisms that raise concerns include methicillin-resistant *S. aureus*, gram-negative organisms that produce carbapenemases and/or extended-spectrum β-lactamases, pan-resistant strains of *Acinetobacter*, and vancomycin-resistant enterococci.
- *Bioterrorism preparedness:* Education, effective systems of internal and external communication, and risk assessment capabilities are key features.



For a more detailed discussion, see Weinstein RA: Infections Acquired in Health Care Facilities, Chap. 168, p. 911, in HPIM-19.

http://internalmedicinebook.com

79 Infections in the Immunocompromised Host

The immunocompromised pt is at increased risk for infection with both common and opportunistic pathogens.

INFECTIONS IN CANCER PTS

Table 79-1 lists the normal barriers to infection whose disruption may permit infections in immunocompromised pts, with particular relevance for the noted cancers. Infection-associated mortality rates among cancer pts have decreased as a result of an evolving approach entailing early use of empirical broad-spectrum antibiotics; empirical antifungal therapy in neutropenic pts who, after 4–7 days of antibiotic treatment, remain febrile without positive cultures; and use of antibiotics for afebrile neutropenic pts as broad-spectrum prophylaxis against infections.

SYSTEM-SPECIFIC SYNDROMES

- *Skin infections:* Skin lesions of various types are common in pts with cancer and may be the first sign of bacterial or fungal sepsis, particularly in neutropenic pts (those with <500 functional neutrophils/μL).
  - *Cellulitis:* most often caused by group A *Streptococcus* and *Staphylococcus aureus*. Unusual organisms (e.g., *Escherichia coli*, *Pseudomonas*, fungi) may be involved in neutropenic pts.
  - *Macules or papules:* due to bacteria (e.g., *Pseudomonas aeruginosa* causing ecthyma gangrenosum) or fungi (e.g., *Candida*)
  - *Sweet's syndrome or febrile neutrophilic dermatosis:* Most often seen in neutropenic pts (particularly those with acute myeloid leukemia), it presents as red or bluish-red papules or nodules that form sharply bordered plaques; high fever; and an elevated ESR. The skin lesions are most common on the face, neck, and arms.
  - *Erythema multiforme with mucous membrane involvement:* Often due to HSV infection, it is distinct from Stevens-Johnson syndrome, which is associated with drugs and has a more widespread distribution. Both conditions are common in pts with cancer.
  - *Drug rashes:* Rashes associated with drugs, particularly cytokines used in cancer therapy, complicate the differential diagnosis of rashes in pts with cancer.
- *Catheter-related infections:* Exit-site infections, often with erythema around the insertion site, are most common.
  - Infections caused by coagulase-negative staphylococci can often be treated medically without catheter removal.
  - Infections caused by other organisms, including *S. aureus*, *P. aeruginosa*, *Candida*, *Stenotrophomonas*, and *Bacillus*, usually require catheter removal.
  - If a red streak develops over the SC part of a "tunneled" catheter, the device must be removed to prevent extensive cellulitis and tissue necrosis.
- *Upper GI infections:* Breakdown of mucosal surfaces due to chemotherapy and infection is common.
  - Oral mucositis is associated with viridans streptococci and HSV.
  - Oral candidal infections (thrush) are common.
  - Esophagitis can be caused by *Candida albicans* and HSV.
- *Lower GI infections:* Transmigration of bowel flora across the intestinal epithelium can lead to severe conditions.

http://internalmedicinebook.com

TABLE 79-1 DISRUPTION OF NORMAL BARRIERS THAT MAY PREDISPOSE TO INFECTIONS IN PTS WITH CANCER

Type of Defense	Specific Lesion	Cells Involved	Organisms	Cancer Association(s)	Disease(s)
Physical barrier	Breaks in skin	Skin epithelial cells	Staphylococci, streptococci	Head and neck, squamous cell carcinoma	Cellulitis, extensive skin infection
Emptying of fluid collections	Occlusion of orifices: ureters, bile duct, colon	Luminal epithelial cells	Gram-negative bacilli	Renal, ovarian, biliary tree, metastatic diseases of many cancers	Rapid, overwhelming bacteremia; urinary tract infection
Lymphatic function	Node dissection	Lymph nodes	Staphylococci, streptococci	Breast cancer surgery	Cellulitis
Splenic clearance of microorganisms	Splenectomy	Splenic reticuloendothelial cells	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Babesia, Capnocytophaga canimorsus*	Hodgkin's disease, leukemia	Rapid, overwhelming sepsis
Phagocytosis	Lack of granulocytes	Granulocytes (neutrophils)	Staphylococci, streptococci, enteric organisms, fungi	Acute myeloid and acute lymphocytic leukemias, hairy cell leukemia	Bacteremia
Humoral immunity	Lack of antibody	B cells	*S. pneumoniae, H. influenzae, N. meningitidis*	Chronic lymphocytic leukemia, multiple myeloma	Infections with encapsulated organisms, sinusitis, pneumonia
Cellular immunity	Lack of T cells	T cells and macrophages	*Mycobacterium tuberculosis, Listeria,* herpesviruses, fungi, intracellular parasites	Hodgkin's disease, leukemia, T-cell lymphoma	Infections with intracellular bacteria, fungi, parasites; virus reactivation

http://internalmedicinebook.com

- *Chronic disseminated candidiasis:* results from seeding of organs (e.g., liver, spleen, kidneys) during neutropenia in pts with hematologic malignancy and generally presents symptomatically when neutropenia resolves. Pts have persistent fever unresponsive to antibiotics, abdominal pain, and increased alkaline phosphatase levels. Although biopsies may reveal granulomas, yeasts, or pseudohyphae, the diagnosis is often made on the basis of radiographic studies (CT, MRI). Treatment should be directed to the causative agent; *C. albicans* is usually responsible, but *C. tropicalis* or other *Candida* species are sometimes involved.
- *Typhlitis (necrotizing colitis):* more common among children than among adults and among pts with acute myeloid leukemia or acute lymphocytic leukemia than among pts with other forms of cancer. Pts have fever, RLQ tenderness, and diarrhea that is often bloody. The diagnosis is confirmed by documentation of a thickened cecal wall via imaging. Treatment should include antibiotics directed against bowel flora and surgery (in the case of perforation).

- *CNS infections:* The susceptibility of pts to specific infections depends on whether they have prolonged neutropenia, defects in cellular immunity (e.g., due to high-dose glucocorticoid therapy or cytotoxic chemotherapy), or defects in humoral immunity (e.g., pts with chronic lymphocytic leukemia, those who have previously undergone splenectomy or bone marrow transplantation [BMT]).
  - *Meningitis:* Consider *Cryptococcus* or *Listeria*, particularly for pts with defects in cellular immunity. Pts with defects in humoral immunity are also at risk for infection with encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.
  - *Encephalitis:* Pts with defects in cellular immunity are particularly prone to infection with VZV, JC virus (the cause of progressive multifocal leukoencephalopathy), CMV, *Listeria*, HSV, and human herpesvirus type 6.
  - *Brain masses:* most often present as headache with or without fever or neurologic abnormalities. Pts with prolonged neutropenia are at increased risk for a brain abscess due to *Aspergillus*, *Nocardia*, or *Cryptococcus*. Pts with defects in cellular immunity are at increased risk for infection with *Toxoplasma* and EBV (lymphoproliferative disease). A definitive diagnosis may require a biopsy.
- *Pulmonary infections:* Pneumonia can be difficult to diagnose in immunocompromised pts, given that many of the conventional findings (e.g., purulent sputum, physical findings suggestive of chest consolidation) rely on the presence of neutrophils. Radiographic patterns of infiltration can help narrow the differential diagnosis.
  - *Localized infiltrate:* Consider bacterial pneumonia (including *Legionella* and mycobacteria), local hemorrhage or embolism, and tumor.
  - *Nodular infiltrate:* Consider fungal infection (e.g., *Aspergillus*, *Mucor*), *Nocardia* infection, and recurrent tumor. In pts with *Aspergillus* infection, hemoptysis may be an ominous sign. A biopsy performed with direct visualization may be required for definitive diagnosis.
  - *Diffuse infiltrates:* Consider infection with viruses (particularly CMV), *Chlamydia*, *Pneumocystis*, *Toxoplasma*, or mycobacteria. Viruses that cause URIs in immunocompetent hosts (e.g., influenza, respiratory syncytial) can cause fatal pneumonitis in immunocompromised pts. Noninfectious causes include radiation pneumonitis, CHF, diffuse alveolar hemorrhage (after BMT), and drug-induced lung injury (e.g., bleomycin, alkylating agents).
- *Renal and ureteral infections:* These infections are usually associated with obstructing tumor masses.
  - *Candida* has a predilection for the kidneys, reaching this site via either hematogenous seeding or retrograde spread from the bladder. Persistent funguria should prompt a search for infection in the kidney (e.g., fungus ball).
  - BK virus and adenovirus can cause hemorrhagic cystitis.

http://internalmedicinebook.com

APPROACH TO THE PATIENT: **Febrile Neutropenia**

Approach to Diagnosis and Treatment of Febrile Neutropenic Pts Figure 79-1 presents an algorithm for the diagnosis and treatment of pts with febrile neutropenia.

- The initial regimen should be refined on the basis of culture data; surface cultures of skin and mucous membranes may be misleading.
- Adding antibiotics to the initial regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Administering additional antibiotics

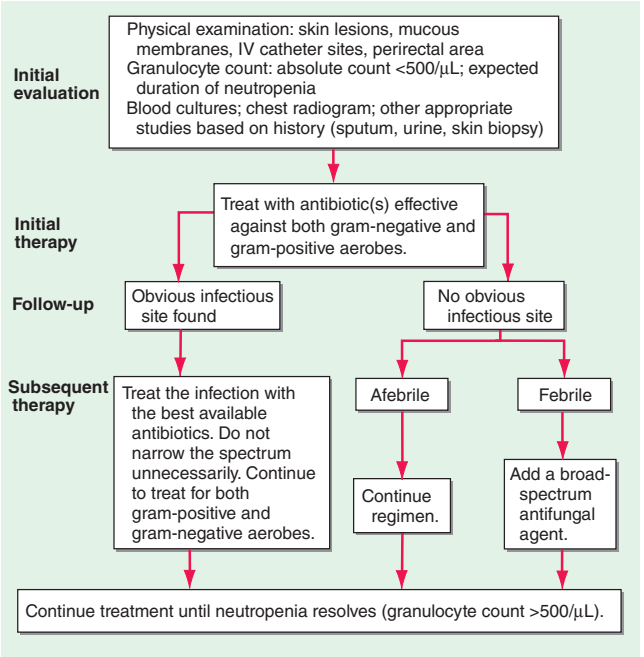


FIGURE 79-1 Algorithm for the diagnosis and treatment of fever and neutropenia. Several general guidelines are useful in the initial treatment of febrile neutropenic pts: (1) The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital. (2) A single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals (if the pattern of resistance justifies its use). (3) Most standard regimens are designed for pts who have not previously received prophylactic antibiotics. The development of fever in a pt who has received antibiotics affects the choice of subsequent therapy (which should target resistant organisms and organisms known to cause infections in pts being treated with the antibiotics already administered). (4) Randomized trials have indicated that it is safe to use oral antibiotic regimens to treat "low-risk" pts who have fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.

http://internalmedicinebook.com

for fear of a gram-negative infection (e.g., "double coverage," synergistic addition of aminoglycosides to β-lactam therapy) does not enhance efficacy (but does increase toxicity), even for infections involving *P. aeruginosa*.

- For empirical antifungal treatment, amphotericin B deoxycholate is being supplanted by liposomal formulations of amphotericin B, newer azoles (e.g., voriconazole or posaconazole), and echinocandins (e.g., caspofungin). Echinocandins are useful against infections with azole-resistant *Candida*.
- Clinical experience related to antiviral therapy is most extensive with acyclovir for HSV and VZV infections. Newer agents (e.g., cidofovir, foscarnet) with a broader spectrum of action have heightened the focus on treatment of viral infections.
  - Prophylactic antibiotics (e.g., fluoroquinolones) in pts expected to have prolonged neutropenia or antifungal agents (e.g., fluconazole) in pts with hematopoietic stem cell transplants (see below) may prevent infections. *Pneumocystis* prophylaxis is mandatory for pts with acute lymphocytic leukemia and for those receiving glucocorticoid-containing regimens.

INFECTIONS IN TRANSPLANT RECIPIENTS

Evaluation of infections in transplant recipients must involve consideration of infectious agents harbored by the donor organ and the recipient's immunosuppressive drug regimen, which increases susceptibility to latent infections (among other infections).

- Pretransplantation evaluation of the donor should include a thorough serologic evaluation for viral pathogens (e.g., HSV-1, HSV-2, VZV, CMV, EBV, HIV, and hepatitis A, B, and C viruses) and mycobacterial disease; other evaluations should be directed by the donor's history, including diet, exposures, and travel.
- Pretransplantation evaluation of the recipient is generally more comprehensive than that of the donor and should include assessment for respiratory viruses and GI pathogens. Given the effects of underlying chronic disease and chemotherapy, serologic testing of the recipient may not be reliable.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

- *Pathogenesis:* The myeloablative processes involved in HSCT result in the complete absence of innate and adaptive immune cells. This transient state of complete immunologic incompetence and the reconstitution that follows make the host extremely susceptible to infections.
- *Etiology:* Most infections occur in a predictable time frame after HSCT (Table 79-2).
  - *Bacterial infections:* Neutropenia-related infectious complications are most common during the first month. Some centers give prophylactic antibiotics (e.g., quinolones) that may decrease the risk of gram-negative bacteremia but increase the risk of *Clostridium difficile* colitis.
    - Skin and bowel flora (e.g., *S. aureus*, coagulase-negative staphylococci, *E. coli*) are responsible for most infections in the first few days following HSCT, after which nosocomial pathogens and filamentous bacteria (e.g., vancomycin-resistant enterococci, *Acinetobacter*, antibiotic-resistant gram-negative bacteria, and *Nocardia* species) become more common.
    - In the late posttransplantation period (>6 months after reconstitution), bacteremia due to encapsulated organisms is most common, particularly among pts who are asplenic or hypogammaglobulinemic.
  - *Fungal infections:* Fungal infections are increasingly common beyond the first week after HSCT, particularly among pts who receive broad-spectrum antibiotics. Infections with *Candida* species are most common, although resistant fungi (e.g.,

http://internalmedicinebook.com

TABLE 79-2 COMMON SOURCES OF INFECTIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

	Period after Transplantation		
Infection Site	**Early (<1 Month)**	**Middle (1–4 Months)**	**Late (>6 Months)**
Disseminated	Aerobic bacteria (gram-negative, gram-positive)	*Candida, Aspergillus,* EBV	Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*)
Skin and mucous membranes	HSV	HHV-6	VZV, HPV (warts)
Lungs	Aerobic bacteria (gram-negative, gram-positive), *Candida, Aspergillus,* other molds, HSV	CMV, seasonal respiratory viruses, *Pneumocystis, Toxoplasma*	*Pneumocystis, Nocardia, S. pneumoniae*
Gastrointestinal tract	*Clostridium difficile*	CMV, adenovirus, *Bradyrhizobium enterica* (cord blood cells)	EBV, CMV, *B. enterica* (cord blood cells)
Kidney		BK virus, adenovirus	
Brain		HHV-6, *Toxoplasma*	*Toxoplasma,* JC virus (rare)
Bone marrow		CMV, HHV-6	CMV, HHV-6

Abbreviations: HHV-6, human herpesvirus type 6; HPV, human papillomavirus.

Aspergillus, *Fusarium*) are becoming more common because of the increased use of prophylactic fluconazole.

- Prolonged treatment with glucocorticoids or other immunosuppressive agents increases the risk of infection with *Candida* or *Aspergillus* and of reactivation of endemic fungi even after resolution of neutropenia.
- Maintenance prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg/d starting 1 month after engraftment and continuing for at least 1 year) is recommended to prevent *Pneumocystis jirovecii* pneumonia.

– *Parasitic infections:* Prophylaxis with TMP-SMX is also protective against disease caused by *Toxoplasma* as well as against late infections caused by certain bacteria, including *Nocardia*, *Listeria monocytogenes*, *S. pneumoniae*, and *H. influenzae*.

- Given increasing international travel, parasitic diseases (e.g., caused by *Strongyloides*, *Leishmania*, *Giardia*, *Cryptosporidium*) that are typically restricted to particular environments may be more likely to be reactivated in pts after HSCT.

– *Viral infections:* Prophylactic acyclovir or valacyclovir for HSV-seropositive pts reduces rates of mucositis and prevents pneumonia and other HSV manifestations.

- Zoster generally occurs several months after HSCT and usually is managed readily with acyclovir.
- Human herpesvirus type 6 delays monocyte and platelet engraftment and may be linked to encephalitis or pneumonitis; the efficacy of antiviral treatment has not been well studied.

http://internalmedicinebook.com

- CMV disease (e.g., interstitial pneumonia, bone marrow suppression, colitis, and graft failure) usually occurs 30–90 days after HSCT. Severe disease is more common among allogeneic transplant recipients and is often associated with graft-versus-host disease, with pneumonia as the foremost cause of death. Preemptive therapy (initiation of antiviral therapy only after CMV is detected in blood) has supplanted prophylactic therapy (treatment of all transplant recipients when either the recipient or the donor is seropositive) because of the toxic side effects associated with ganciclovir.
- EBV lymphoproliferative disease as well as infections caused by respiratory viruses (e.g., respiratory syncytial virus, parainfluenza virus, metapneumovirus, influenza virus, adenovirus) can occur. BK virus (a polyomavirus) has been found in the urine of pts after HSCT and may be associated with hemorrhagic cystitis.

SOLID ORGAN TRANSPLANTATION

- *Pathogenesis:* After solid organ transplantation, pts do not go through a stage of neutropenia like that seen after HSCT; thus the infections in these two groups of pts differ. However, solid organ transplant recipients are immunosuppressed for longer periods with agents that chronically impair T-cell immunity. Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.
- *Etiology:* As in HSCT, the infection risk depends on the interval since transplantation.
  - *Early infections (<1 month):* Infections are most commonly caused by extracellular organisms, which originate in surgical wound or anastomotic sites.
  - *Middle-period infections (1–6 months):* The consequences of suppressing cell-mediated immunity become apparent, and infections result from acquisition—or reactivation—of viruses, mycobacteria, endemic fungi, and parasites.
    - CMV can cause severe systemic disease or infection of transplanted organs; the latter increases the risk of organ rejection, prompting increased immunosuppression that, in turn, increases CMV replication.
    - Diagnosis, treatment, and prophylaxis of CMV infection are the keys to interrupting this cycle.
  - *Late infections (>6 months):* Infections in this period are similar to those in pts with chronically impaired T-cell immunity (e.g., *Listeria*, *Nocardia*, *Rhodococcus*, mycobacteria, various fungi, other intracellular organisms).
    - EBV lymphoproliferative disease occurs most commonly in pts who receive a heart or lung transplant (as well as the most intense immunosuppressive regimens); in these cases, immunosuppression should be decreased or discontinued, if possible, and consideration should be given to treatment with anti–B cell antibodies.
    - Prophylaxis against *Pneumocystis* pneumonia for at least 1 year is generally recommended for all solid organ transplant recipients.
    - The incidence of tuberculosis within the first 12 months after solid organ transplantation is greater than that after HSCT and reflects the prevalence of tuberculosis in the local population.
- *Specific issues:* While the above information is generally valid for all organ transplants, there are some organ-specific considerations.
  - *Kidney transplantation:* TMP-SMX prophylaxis for the first 4–6 months decreases the incidence of early and middle-period infections, particularly UTIs related to anatomic alterations resulting from surgery. CMV is the predominant pathogen in the middle period; disease is evident in 50% of renal transplant pts presenting with fever 1–4 months after transplantation, prompting many centers to use valganciclovir prophylaxis for high-risk pts. BK viruria and viremia, often diagnosed as a late-onset disease, are associated with ureteral strictures, nephropathy, and vasculopathy and require a reduction of immunosuppression to lower rates of graft loss.
  - *Heart transplantation:* Mediastinitis, generally caused by typical skin flora and rarely caused by *Mycoplasma hominis*, is an early complication of heart transplantation. The overall incidence of toxoplasmosis (a middle-period infec-

http://internalmedicinebook.com

tion) is so high in the setting of heart transplantation that serologic screening and some prophylaxis (e.g., TMP-SMX) are always warranted.

– *Lung transplantation:* Pts receiving a lung transplant are predisposed to pneumonia and mediastinitis in the early period. The high incidence of CMV disease (75–100% if either the donor or the recipient is seropositive) indicates the importance of antiviral prophylaxis; late disease may occur once prophylaxis is discontinued, although the pt is generally better able to handle it because of reduced immunosuppression.
– *Liver transplantation:* Bacterial abscesses and peritonitis are common early complications and often result from biliary leaks. Pts receiving a liver transplant have a high incidence of fungal infections correlated with preoperative glucocorticoid use, long-term antimicrobial use, and a high degree of immunosuppression. Recurrent (reactivated) hepatitis B and C infections are problematic; while hepatitis B immunoglobulin administration and prophylaxis with antiviral agents active against hepatitis B virus have been successful in preventing reinfection with hepatitis B virus, reinfection with hepatitis C virus occurs in all pts.

IMMUNIZATIONS IN IMMUNOSUPPRESSED PTS

Recommendations for vaccination of cancer pts receiving chemotherapy, pts with Hodgkin's disease, and hematopoietic stem cell transplant recipients are listed in Table 79-3. In solid organ transplant recipients, the usual vaccines and boosters should be given before immunosuppression. Pts with continued immunosuppression should have pneumococcal vaccination repeated every 5 years and should not receive live vaccines.

TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a]

	Use in Indicated Pts		
Vaccine	**Intensive Chemotherapy**	**Hodgkin's Disease**	**Hematopoietic Stem Cell Transplantation**
Diphtheria-tetanus[b]	Primary series and boosters as necessary	No special recommendation	Three doses given 6–12 months after transplantation
Poliomyelitis[c]	Complete primary series and boosters	No special recommendation	Three doses given 6–12 months after transplantation
Haemophilus influenzae type b conjugate	Primary series and booster for children	Single dose for adults	Three doses given 6–12 months after transplantation (separated by 1 month)
HPV	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations.	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations.	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations.

(*Continued*)

http://internalmedicinebook.com

TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a] (*CONTINUED*)

Vaccine	Use in Indicated Pts		
	Intensive Chemotherapy	**Hodgkin's Disease**	**Hematopoietic Stem Cell Transplantation**
Hepatitis A	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle
Hepatitis B	Same as for normal hosts	As indicated for normal hosts on the basis of occupation and lifestyle	Three doses given 6–12 months after transplantation
PCV13 PPSV23[d]	Finish series prior to chemotherapy if possible	Pts with splenectomy should receive PPSV23.	Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose can be given 5 years later.
Quadrivalent meningococcal vaccine[e]	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.	Should be administered to splenectomized pts and to pts living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization (A seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended.)
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in pts without graft-versus-host disease

(*Continued*)

http://internalmedicinebook.com

TABLE 79-3 VACCINATION OF CANCER AND TRANSPLANT PTS RECEIVING CHEMOTHERAPY[a] (*CONTINUED*)

Vaccine	Use in Indicated Pts		
	Intensive Chemotherapy	Hodgkin's Disease	Hematopoietic Stem Cell Transplantation
Varicella-zoster virus[f]	Contraindicated[g]	Contraindicated	Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.)

[a]The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at *http://www.cdc.gov/vaccines*.
[b]A single dose of tetanus–diphtheria–acellular pertussis (TDaP), followed by a booster dose of tetanus-diphtheria (Td) every 10 years, is recommended for adults.
[c]Live-virus vaccine is contraindicated; inactivated vaccine should be used.
[d]Two types of vaccine are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants eradicates immunologic memory, revaccination is recommended for all such pts. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, recipients of stem cell transplants should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised pts, including transplant recipients, as well as pts with Hodgkin's disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time.
[e]Meningococcal conjugate vaccine MenACWY is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥ 56 years old.
[f]Includes both varicella vaccine for children and zoster vaccine for adults.
[g]Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.
Abbreviations: CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.



For a more detailed discussion, see Finberg RW: Infections in Patients with Cancer, Chap. 104, p. 484; and Finberg RW, Fingeroth J: Infections in Transplant Recipients, Chap. 169, p. 919, in HPIM-19.

http://internalmedicinebook.com

80 Infective Endocarditis

Acute endocarditis is a febrile illness that rapidly damages cardiac structures, seeds extracardiac sites hematogenously, and can progress to death within weeks. *Subacute* endocarditis follows an indolent course, rarely causes metastatic infection, and progresses gradually unless complicated by a major embolic event or a ruptured mycotic aneurysm.

- *Epidemiology:* In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year, with higher rates among the elderly.
  - Predisposing conditions include congenital heart disease, illicit IV drug use, degenerative valve disease, and the presence of intracardiac devices.
  - Chronic rheumatic heart disease is a risk factor in low-income countries.
  - Of endocarditis cases, 16–30% involve prosthetic valves, with the greatest risk during the first 6–12 months after valve replacement.
- *Etiology and microbiology:* Because of their different portals of entry, the causative microorganisms vary among clinical types of endocarditis.
  - In native valve endocarditis (NVE), viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus* spp., *Aggregatibacter spp.*, *Cardiobacterium hominis*, *Eikenella corrodens,* and *Kingella kingae*) enter the bloodstream from oral, skin, and upper respiratory tract portals. *Streptococcus gallolyticus* subspecies *gallolyticus* (formerly *S. bovis* biotype 1) originates from the gut and is associated with polyps or colon cancer.
  - Health care–associated NVE, frequently due to *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have a nosocomial onset (55%) or a community onset (45%) in pts who have had extensive contact with the health care system in the preceding 90 days.
  - Prosthetic valve endocarditis (PVE) developing within 2 months of surgery is due to intraoperative contamination or a bacteremic postoperative complication and is typically caused by CoNS, *S. aureus*, facultative gram-negative bacilli, diphtheroids, or fungi. Cases beginning >1 year after valve surgery are caused by the same organisms that cause community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection.
  - Cardiovascular implantable electronic device (CIED)–related endocarditis involves the device itself or the endothelium at points of device contact, with occasional concurrent aortic or mitral valve infection. One-third of cases of CIED endocarditis present within 3 months after device implantation or manipulation, one-third present at 4–12 months, and one-third present at >1 year. *S. aureus* and CoNS (often methicillin-resistant strains) cause the majority of cases.
  - Endocarditis occurring among IV drug users, especially that involving the tricuspid valve, is commonly caused by *S. aureus* (often a methicillin-resistant strain). Left-sided valve infections among IV drug users are caused by *Pseudomonas aeruginosa* and *Candida*, *Bacillus*, *Lactobacillus*, and *Corynebacterium* spp. in addition to the usual causes of endocarditis.
  - About 5–15% of endocarditis cases are culture negative, and one-third to one-half of these cases are due to prior antibiotic exposure. The remainder of culture-negative cases represent infection by fastidious organisms, such as the nutritionally variant bacteria *Granulicatella* and *Abiotrophia* spp., HACEK organisms, *Coxiella burnetii*, *Brucella* spp., and *Tropheryma whipplei*.
- *Pathogenesis:* Endothelial injury allows direct infection by more virulent pathogens (e.g., *S. aureus*) or the development of a platelet-fibrin thrombus [referred to as *nonbacterial thrombotic endocarditis* (NBTE)] that may become infected during

http://internalmedicinebook.com

transient bacteremia. NBTE arises from cardiac conditions (e.g., mitral regurgitation, aortic stenosis, aortic regurgitation), hypercoagulable states (giving rise to marantic endocarditis, which consists of uninfected vegetations), and the antiphospholipid antibody syndrome. After entering the bloodstream, organisms adhere to the endothelium or sites of NBTE via surface adhesin molecules. The clinical manifestations of endocarditis arise from cytokine production, damage to intracardiac structures, embolization of vegetation fragments, hematogenous infection of sites during bacteremia, and tissue injury due to the deposition of immune complexes.

- *Clinical manifestations:* The clinical syndrome is variable and spans a continuum between acute and subacute presentations. The temporal course of disease is dictated in large part by the causative organism: *S. aureus*, β-hemolytic streptococci, pneumococci, and *Staphylococcus lugdunensis* typically present acutely, whereas viridans streptococci, enterococci, CoNS (other than *S. lugdunensis*), and the HACEK group typically present subacutely.
  - *Constitutional symptoms:* generally nonspecific, but may include fever, chills, weight loss, myalgias, or arthralgias
  - *Cardiac manifestations:* Heart murmurs, particularly new or worsened regurgitant murmurs, are ultimately heard in 85% of pts with acute NVE.
    - CHF develops in 30–40% of pts and is usually due to valvular dysfunction.
    - Extension of infection can result in perivalvular abscesses, which in turn may cause intracardiac fistulae. Abscesses may burrow from the aortic root into the ventricular septum and interrupt the conduction system or may burrow through the epicardium and cause pericarditis.
  - *Noncardiac manifestations:* Arterial emboli, one-half of which precede the diagnosis of endocarditis, are present in 50% of pts, with hematogenously seeded focal infection most often evident in the skin, spleen, kidneys, bones, and meninges.
    - The risk of embolization increases with endocarditis caused by *S. aureus*, vegetations >10 mm in diameter, and infection involving the mitral valve (particularly the anterior leaflet).
    - Cerebrovascular emboli presenting as stroke or encephalopathy complicate 15–35% of cases, with one-half of these cases preceding the diagnosis of endocarditis.
      - The incidence of stroke decreases dramatically with antibiotic therapy and does not correlate with change in vegetation size; 3% of strokes occur after 1 week of effective therapy, but these late-occurring embolic events do not specifically constitute evidence of failed antimicrobial therapy.
      - Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to ruptured mycotic aneurysms (focal dilations of arteries at points in the artery wall that have been weakened by infection or where septic emboli have lodged) or hemorrhagic infarcts, seizures, and microabscesses (especially with *S. aureus*).
    - Immune complex deposition on the glomerular basement membrane causes glomerulonephritis and renal dysfunction, which improve with antibiotic therapy.
    - Nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions, Roth's spots) are related to duration of infection and are now rare because of early diagnosis and treatment.
  - *Manifestations of specific predisposing conditions:* Underlying conditions may affect the presenting signs and symptoms.
    - *IV drug use:* ~50% of endocarditis cases associated with IV drug use are limited to the tricuspid valve and present as fever, faint or no murmur, septic pulmonary emboli (evidenced by cough, pleuritic chest pain, nodular pulmonary infiltrates, or occasional pyopneumothorax), and the absence of peripheral manifestations. Pts with left-sided cardiac infections present with the typical clinical features of endocarditis.
    - *Health care–associated endocarditis:* Manifestations are typical in the absence of a retained intracardiac device. Endocarditis associated with a transvenous

http://internalmedicinebook.com

pacemaker or an implanted defibrillator may be associated with a generator pocket infection and result in fever, minimal murmur, and pulmonary symptoms due to septic emboli.
  - *PVE:* In cases of endocarditis occurring within 60 days of valve surgery, typical symptoms may be masked by comorbidity associated with recent surgery. Paravalvular infection is common in PVE, resulting in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.
- *Diagnosis:* A diagnosis of infective endocarditis is established definitively only when vegetations are examined histologically and microbiologically.
  - The modified Duke criteria (Table 80-1) constitute a highly sensitive and specific diagnostic schema that emphasizes the roles of bacteremia and echocardiographic findings.
    - A clinical diagnosis of definite endocarditis requires fulfillment of two major criteria, one major criterion plus three minor criteria, or five minor criteria.
    - A diagnosis of possible endocarditis requires documentation of one major criterion plus one minor criterion or three minor criteria.
  - For antibiotic-naïve pts, three 2-bottle sets of blood culture samples—separated from one another by at least 2 h—should be obtained from different sites within the first 24 h. If blood cultures are negative after 48–72 h, two or three additional sets of samples should be cultured.
  - Serology is helpful in implicating *Brucella, Bartonella*, *Legionella*, *Chlamydia psittaci*, or *C. burnetii* in endocarditis. Examination of the vegetation by histology, culture, direct fluorescent antibody techniques, and/or PCR may be helpful in identifying the causative organism in the absence of a positive blood culture.
  - Echocardiography should be performed to confirm the diagnosis, to verify the size of vegetations, to detect intracardiac complications, and to assess cardiac function.
    - Transthoracic echocardiography (TTE) does not detect vegetations <2 mm in diameter, is not adequate for evaluation of prosthetic valves or detection of intracardiac complications, and is technically inadequate in 20% of pts because of emphysema or body habitus; however, TTE may suffice when pts have a low pretest likelihood of endocarditis.
    - Transesophageal echocardiography (TEE) detects vegetations in >90% of cases of definite endocarditis and is optimal for evaluation of prosthetic valves and detection of abscesses, valve perforation, or intracardiac fistulas.
    - When endocarditis is likely, a negative TEE result does not exclude the diagnosis but warrants repetition of the study once or twice in 7–10 days.
    - Routine echocardiography (preferably TEE) is recommended in pts with *S. aureus* bacteremia.

TREATMENT ENDOCARDITIS

ANTIMICROBIAL THERAPY

- Antimicrobial therapy must be bactericidal and prolonged. See Table 80-2 for organism-specific regimens.
  - Blood cultures should be repeated until sterile, and results should be rechecked if there is recrudescent fever and at 4–6 weeks after therapy to document cure.
  - If pts are febrile for 7 days despite antibiotic therapy, an evaluation for paravalvular or extracardiac abscesses should be performed.
- Pts with acute endocarditis require antibiotic treatment as soon as three sets of blood culture samples are obtained, but pts with subacute disease who are clinically stable should have antibiotics withheld until a diagnosis is made.
- Pts treated with vancomycin or an aminoglycoside should have serum drug levels monitored. Tests to detect renal, hepatic, and/or hematologic toxicity should be performed periodically.

http://internalmedicinebook.com

TABLE 80-1 THE MODIFIED DUKE CRITERIA FOR THE CLINICAL DIAGNOSIS OF INFECTIVE ENDOCARDITIS[a]

Major Criteria

1. Positive blood culture
   - Typical microorganism for infective endocarditis from two separate blood cultures
     - Viridans streptococci, *Streptococcus gallolyticus*, HACEK group organisms, *Staphylococcus aureus*, *or*
     - Community-acquired enterococci in the absence of a primary focus,
     - ***or***
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
     - Blood cultures drawn >12 h apart; *or*
     - All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart
     - ***or***
   - Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement
   - Positive echocardiogram[b]
     - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*
     - Abscess, *or*
     - New partial dehiscence of prosthetic valve,
     - ***or***
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

1. Predisposition: predisposing heart conditions[c] or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,[d] *or* serologic evidence of active infection with an organism consistent with infective endocarditis

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.
[b]Transesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.
[c]Valvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.
[d]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.
Source: Adapted from JS Li et al: *Clin Infect Dis* 30:633, 2000. With permission from Oxford University Press.

http://internalmedicinebook.com

TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a]

Organism	Drug (Dose, Duration)	Comments
Streptococci		
Penicillin-susceptible[b] streptococci, *S. gallolyticus*	• Penicillin G (2–3 mU IV q4h for 4 weeks)	—
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use ceftriaxone in pts with nonimmediate penicillin allergy.
	• Vancomycin[c] (15 mg/kg IV q12h for 4 weeks)	Use vancomycin in pts with severe or immediate β-lactam allergy.
	• Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 2 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic valve or complicated endocarditis.
Relatively penicillin-resistant[f]	• Penicillin G (4 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 4 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of ≤0.1 μg/mL.
	• Vancomycin[c] as noted above for 4 weeks	—
Moderately penicillin-resistant[g] streptococci, nutritionally variant organisms, or *Gemella* species	• Penicillin G (4–5 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 6 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM as a single dose[e] *or* divided into equal doses q8h for 6 weeks)	Preferred for prosthetic valve endocarditis caused by streptococci with penicillin MICs of >0.1 μg/mL
	• Vancomycin[c] as noted above for 4 weeks	Regimen is preferred by some.
Enterococci[h]		
	• Penicillin G (4–5 mU IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin
	• Ampicillin (2 g IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	—

(*Continued*)

http://internalmedicinebook.com

TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a] (*CONTINUED*)

Organism	Drug (Dose, Duration)	Comments
	• Vancomycin[c] (15 mg/kg IV q12h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Use vancomycin plus gentamicin for penicillin-allergic pts (or desensitize to penicillin) and for isolates resistant to penicillin/ampicillin.
	• Ampicillin (2 g IV q4h) *plus* ceftriaxone (2 g IV q12h), both for 6 weeks	Use for *E. faecalis* isolates with high-level resistance to gentamicin and streptomycin or for pts at high risk for aminoglycoside nephrotoxicity
Staphylococci		
MSSA infecting native valves (no foreign devices)	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 4–6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin-susceptible (does not produce β-lactamase).
	• Cefazolin (2 g IV q8h for 4–6 weeks)	Can use cefazolin regimen for pts with nonimmediate penicillin allergy
	• Vancomycin[c] (15 mg/kg IV q12h for 4–6 weeks)	Use vancomycin for pts with immediate (urticarial) or severe penicillin allergy.
MRSA infecting native valves (no foreign devices)	• Vancomycin[c] (15 mg/kg IV q8–12h for 4–6 weeks)	No role for routine use of rifampin. Consider alternative treatment (see text) for MRSA with vancomycin MIC >1.0 or persistent bacteremia during vancomycin therapy.
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** • Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin; if pt is highly allergic to penicillin, use regimen for MRSA; if β-lactam allergy is of the minor nonimmediate type, cefazolin can be substituted for oxacillin/nafcillin.
MRSA infecting prosthetic valves	• Vancomycin[c] (15 mg/kg IV q12h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin.

(*Continued*)

http://internalmedicinebook.com

TABLE 80-2 ANTIBIOTIC TREATMENT FOR INFECTIVE ENDOCARDITIS CAUSED BY COMMON ORGANISMS[a] (*CONTINUED*)

Organism	Drug (Dose, Duration)	Comments
HACEK Organisms		
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use another third-generation cephalosporin at comparable dosage
	• Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	—
Coxiella burnetii		
	• Doxycycline (100 mg PO q12h) *plus* hydroxychloroquine (200 mg PO q8h), both for 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (anti–phase I IgG and IgA decreased 4-fold and IgM anti–phase II negative) and thereafter for relapse.
Bartonella spp.		
	• Ceftriaxone (2 g IV q24h) *or* ampicillin (2 g IV q4h) *or* doxycycline (100 mg PO q12h) for 6 weeks ***plus*** Gentamicin (1 mg/kg IV q8h for 3 weeks)	If pt is highly allergic to β-lactams, use doxycycline.

[a]Doses are for adults with normal renal function. Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet).
[b]MIC, ≤0.1 μg/mL.
[c]Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections.
[d]Aminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 μg/mL and <10 μg/mL, respectively.
[e]Netilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin.
[f]MIC, >0.1 μg/mL and <0.5 μg/mL.
[g]MIC, ≥0.5 μg/mL and <8 μg/mL.
[h]Antimicrobial susceptibility must be evaluated; see text.
[i]Rifampin increases warfarin and dicumarol requirements for anticoagulation.
Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus.*

ORGANISM-SPECIFIC THERAPIES

- Endocarditis due to group B, C, or G streptococci should be treated with the regimen recommended for relatively penicillin-resistant streptococci (Table 80-2).
- Killing of enterococci requires the synergistic activity of a cell wall–active agent and an aminoglycoside (gentamicin or streptomycin) to which the isolate does

http://internalmedicinebook.com

not exhibit high-level resistance. The aminoglycoside can be discontinued in those pts who have responded satisfactorily if toxicity develops after 2–3 weeks of treatment. If there is high-level resistance to both aminoglycosides, the cell wall–active agent should be given alone for 8–12 weeks, or—for *Enterococcus faecalis*—high-dose ampicillin plus ceftriaxone or cefotaxime can be given. If the isolate is resistant to all commonly used agents, surgical therapy is advised (see below and Table 80-3).

- For staphylococcal NVE, the addition of 3–5 days of gentamicin to a β-lactam antibiotic does not improve survival rates and is not recommended.
- Although this regimen has not yet been approved by the U.S. Food and Drug Administration, daptomycin (6 mg/kg IV qd; or, as some experts prefer, 8–10 mg/kg IV qd) has been recommended for endocarditis caused by *S. aureus* isolates with a vancomycin minimal inhibitory concentration (MIC) of ≥2 μg/mL. These isolates should be tested to document daptomycin sensitivity.

TABLE 80-3 TIMING OF CARDIAC SURGICAL INTERVENTION IN PTS WITH ENDOCARDITIS

	Indication for Surgical Intervention	
Timing	**Strong Supporting Evidence**	**Conflicting Evidence, but Majority of Opinions Favor Surgery**
Emergent (same day)	Acute aortic regurgitation plus preclosure of mitral valve	
	Sinus of Valsalva abscess ruptured into right heart	
	Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation	Major embolus plus persisting large vegetation (>10 mm in diameter)
	Unstable (dehisced) prosthesis	
	Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV)	
	Septal perforation	
	Perivalvular extension of infection with or without new electrocardiographic conduction system changes	
	Lack of effective antibiotic therapy	
Elective (earlier usually preferred)	Vegetation diameter >10 mm plus severe aortic or mitral valve dysfunction[a]	Staphylococcal prosthetic valve endocarditis
	Progressive paravalvular prosthetic regurgitation	Early prosthetic valve endocarditis (≤2 months after valve surgery)
	Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy	Fungal endocarditis (*Candida* spp.)
	Fungal (mold) endocarditis	Antibiotic-resistant organisms

[a]Supported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment.

Source: Adapted from L Olaison, G Pettersson: *Infect Dis Clin North Am* 16:453, 2002.

http://internalmedicinebook.com

- Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen. Rifampin is important because it kills organisms adherent to foreign material. The inclusion of two other agents in addition to rifampin helps prevent the emergence of rifampin resistance in vivo. Testing for gentamicin susceptibility should be performed before rifampin is given; if the strain is resistant, another aminoglycoside, a fluoroquinolone, or another active agent should be substituted.
- Empirical therapy (either before culture results are known or when cultures are negative) depends on epidemiologic clues to etiology (e.g., endocarditis in an IV drug user, health care–associated endocarditis).
  - In the setting of no prior antibiotic therapy and negative blood cultures, *S. aureus*, CoNS, and enterococcal infection are unlikely; empirical therapy in this situation should target nutritionally variant organisms, the HACEK group, and *Bartonella*.
  - If negative cultures are confounded by prior antibiotic therapy, broader empirical therapy is indicated and should cover pathogens inhibited by the prior therapy.

SURGICAL TREATMENT

- The timing and indications for surgical intervention are listed in Table 80-3; most of these indications are not absolute, and recommendations are derived from observational studies and expert opinion. Moderate or severe refractory CHF is the major indication for surgical treatment of endocarditis.
- Cardiac surgery should be delayed for 2–3 weeks if possible when the pt has had a nonhemorrhagic embolic stroke and for 4 weeks when the pt has had a hemorrhagic embolic stroke. Ruptured mycotic aneurysms should be treated prior to cardiac surgery.
- The duration of antibiotic therapy after cardiac surgery depends on the indication for surgery.
  - For cases of uncomplicated NVE caused by susceptible organisms with negative valve cultures at surgery, the duration of pre- and postoperative treatment should equal the total duration of recommended therapy, with ~2 weeks of treatment given postoperatively.
  - For endocarditis with paravalvular abscess, partially treated PVE, or culture-positive valves, pts should receive a full course of therapy postoperatively.

- *Outcome:* Death and other poor outcomes are related not to failure of antibiotic therapy but rather to interactions of comorbidities and endocarditis-related end-organ complications.
  - Survival rates are 85–90% for NVE due to viridans streptococci, HACEK organisms, or enterococci as opposed to 55–70% for NVE due to *S. aureus* in pts who are not IV drug users.
  - PVE beginning within 2 months of valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases.
- *Prevention:* The American Heart Association and the European Society of Cardiology have narrowed recommendations for antibiotic prophylaxis, limiting its use to pts at highest risk of severe morbidity and death from endocarditis.
  - Prophylaxis is recommended only for those dental procedures involving manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including respiratory tract surgery). Prophylaxis is not advised for pts undergoing GI or genitourinary tract procedures unless the genitourinary tract is infected.
  - Table 80-4 lists the high-risk cardiac lesions for which prophylaxis is advised, and Table 80-5 lists the recommended antibiotic regimens for this purpose.

http://internalmedicinebook.com

TABLE 80-4 HIGH-RISK CARDIAC LESIONS FOR WHICH ENDOCARDITIS PROPHYLAXIS IS ADVISED BEFORE DENTAL PROCEDURES

Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac transplantation[a]

[a]Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.

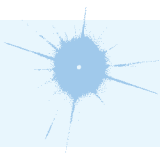
Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: *Circulation* 116:1736, 2007; and G Habib et al: *Eur Heart J* 30:2369, 2009).

TABLE 80-5 ANTIBIOTIC REGIMENS FOR PROPHYLAXIS OF ENDOCARDITIS IN ADULTS WITH HIGH-RISK CARDIAC LESIONS[a,b]

A. Standard oral regimen
   Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
   Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
   1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
   2. Cephalexin[c]: 2 g PO 1 h before procedure
   3. Clindamycin: 600 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
   1. Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure
   2. Clindamycin: 600 mg IV or IM 1 h before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV.
[b]For high-risk lesions, see Table 80-4. Prophylaxis is not advised for other lesions.
[c]Do not use cephalosporins in pts with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: *Circulation* 116:1736, 2007; and G Habib et al: *Eur Heart J* 30:2369, 2009).



For a more detailed discussion, see Karchmer AW: Infective Endocarditis, Chap. 155, p. 816, in HPIM-19.

http://internalmedicinebook.com

81 Intraabdominal Infections

Intraperitoneal infections result when normal anatomic barriers are disrupted. Organisms contained within the bowel or an intraabdominal organ enter the sterile peritoneal cavity, causing peritonitis and—if the infection goes untreated and the pt survives—abscesses.

PERITONITIS

Peritonitis is a life-threatening event that is often accompanied by bacteremia and sepsis. Primary peritonitis has no apparent source, whereas secondary peritonitis is caused by spillage from an intraabdominal viscus; the etiologic organisms and the clinical presentations of these two processes are different.

PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

- *Epidemiology:* Primary bacterial peritonitis (PBP) is most common among pts with cirrhosis (usually due to alcoholism) and preexisting ascites, but ≤10% of these pts develop PBP. PBP is also described in other settings (e.g., malignancy, hepatitis).
- *Pathogenesis:* PBP is due to hematogenous spread of organisms to ascitic fluid in pts in whom a diseased liver and altered portal circulation compromise the liver's filtration function.
- *Microbiology:* Enteric gram-negative bacilli such as *Escherichia coli* or gram-positive organisms such as streptococci, enterococci, and pneumococci are the most common etiologic agents.
  - A single organism is typically isolated.
  - If a polymicrobial infection including anaerobes is identified, the diagnosis of PBP should be reconsidered and a source of secondary peritonitis sought.
- *Clinical manifestations:* Although some pts experience acute-onset abdominal pain or signs of peritoneal irritation, other pts have only nonspecific and nonlocalizing manifestations (e.g., malaise, fatigue, encephalopathy). Fever is common (~80% of pts).
- *Diagnosis:* PBP is diagnosed if peritoneal fluid is sampled and contains >250 PMNs/μL.
  - Culture yield is improved if a 10-mL volume of peritoneal fluid is placed directly into blood culture bottles.
  - Blood cultures should be performed because bacteremia is common.
- *Prevention:* Up to 70% of pts have a recurrence of PBP within 1 year. Prophylaxis with fluoroquinolones (e.g., ciprofloxacin, 750 mg weekly) or trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) reduces this rate to 20%, but increases the risk of serious staphylococcal infections over time.

TREATMENT PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

A third-generation cephalosporin (e.g., ceftriaxone, 2 g q24h IV; or cefotaxime, 2 g q8h IV) or piperacillin/tazobactam (3.375 g qid IV) constitutes appropriate empirical treatment.

- The regimen should be narrowed after the etiology is identified.
- Treatment should continue for at least 5 days, but longer courses (up to 2 weeks) may be needed for pts with coexisting bacteremia or for those whose improvement is slow.
- Albumin (1.5 g/kg of body weight within 6 h of detection and 1.0 g/kg on day 3) improves survival rates among pts with serum creatinine levels ≥1 mg/dL, BUN levels ≥30 mg/dL, or total bilirubin levels ≥4 mg/dL.

http://internalmedicinebook.com

SECONDARY PERITONITIS

- *Pathogenesis:* Secondary peritonitis develops when bacteria contaminate the peritoneum as a result of spillage from an intraabdominal viscus.
- *Microbiology:* Infection almost always involves a mixed flora in which gram-negative bacilli and anaerobes predominate, especially when the contaminating source is colonic. The specific organisms depend on the flora present at the site of the initial process.
- *Clinical manifestations:* Initial symptoms may be localized or vague and depend on the primary organ involved. Once infection has spread to the peritoneal cavity, pain increases; pts lie motionless, often with knees drawn up to avoid stretching the nerve fibers of the peritoneal cavity. Coughing or sneezing causes severe, sharp pain. There is marked voluntary and involuntary guarding of anterior abdominal musculature, tenderness (often with rebound), and fever.
- *Diagnosis:* Although recovery of organisms from peritoneal fluid is easier in secondary than in primary peritonitis, radiographic studies to find the source of peritoneal contamination or immediate surgical intervention should usually be part of the initial diagnostic evaluation. Abdominal taps are done only to exclude hemoperitoneum in trauma cases.

TREATMENT SECONDARY PERITONITIS

- Antibiotics aimed at the inciting flora—e.g., penicillin/β-lactamase inhibitor combinations or a combination of a fluoroquinolone or a third-generation cephalosporin plus metronidazole—should be administered early.
  - For critically ill pts in the ICU, imipenem (500 mg q6h IV) or d*rug combinations such as ampicillin plus metronidazol*e plus ciprofloxacin should be used.
  - Surgical intervention is often needed.

PERITONITIS IN PTS UNDERGOING CAPD

- *Pathogenesis:* In a phenomenon similar to that seen in intravascular device–related infections, organisms migrate along the catheter, a foreign body that serves as an entry point.
- *Microbiology:* CAPD-associated peritonitis usually involves skin organisms, with *Staphylococcus* spp. such as coagulase-negative staphylococci and *Staphylococcus aureus* accounting for ~45% of cases; gram-negative bacilli and fungi (e.g., *Candida*) are occasionally identified. A polymicrobial infection should prompt evaluation for secondary peritonitis.
- *Clinical manifestations:* CAPD-associated peritonitis presents similarly to secondary peritonitis, in that diffuse pain and peritoneal signs are common.
- *Diagnosis:* Several hundred milliliters of removed dialysis fluid should be centrifuged and sent for culture.
  - Use of blood culture bottles improves the diagnostic yield.
  - The dialysate is usually cloudy and contains >100 WBCs/μL, with >50% neutrophils; the percentage of neutrophils is more important than the absolute WBC count.

TREATMENT PERITONITIS IN PTS UNDERGOING CAPD

- Empirical therapy should be directed against staphylococcal species and gram-negative bacilli (e.g., cefazolin plus a fluoroquinolone or a third-generation cephalosporin such as ceftazidime). Vancomycin should be used instead of cefazolin if methicillin resistance is prevalent, if the pt has an overt exit-site infection, or if the pt appears toxic.
  - Antibiotics are given by the IP route either continuously (e.g., with each exchange) or intermittently (e.g., once daily, with the dose allowed to remain

http://internalmedicinebook.com

in the peritoneal cavity for 6 h). Severely ill pts should be given the same regimen by the IV route.
- Catheter removal should be considered in fungal infection, for pts with exit-site or tunnel infection, or if the pt's condition does not improve within 48–96 h.
- Uncomplicated CAPD-associated peritonitis should be treated for 14 days; up to 21 days may be necessary in pts with exit-site or tunnel infection.

INTRAABDOMINAL ABSCESSES

Intraabdominal abscesses are generally diagnosed through radiographic studies, of which abdominal CT is typically most useful.

INTRAPERITONEAL ABSCESSES

- *Epidemiology:* Of intraabdominal abscesses, 74% are IP or retroperitoneal, not visceral.
- *Pathogenesis:* Most IP abscesses arise from colonic sources. Abscesses develop in untreated peritonitis as an extension of the disease process and represent host defense activity aimed at containing the infection.
- *Microbiology:* Infection is typically polymicrobial; the most frequently isolated anaerobe is *Bacteroides fragilis*.

TREATMENT INTRAPERITONEAL ABSCESSES

- Antimicrobial therapy is adjunctive to drainage and/or surgical correction of an underlying lesion or process.
  - Diverticular abscesses usually wall off locally, and surgical intervention is not routinely needed.
  - Antimicrobial agents with activity against gram-negative bacilli and anaerobic organisms are indicated (see "Secondary Peritonitis," above).

VISCERAL ABSCESSES

Liver Abscess

- *Epidemiology, Pathogenesis, and Microbiology:* Liver abscesses account for up to half of visceral intraabdominal abscesses and are caused most commonly by biliary tract disease (due to aerobic gram-negative bacilli or enterococci) and less often by local spread from pelvic and other IP sources (due to mixed flora including aerobic and anaerobic species, among which *B. fragilis* is most common) or hematogenous seeding (infection with a single species, usually *S. aureus* or streptococci such as *S. milleri*).
  - Amebic liver abscesses are not uncommon, with positive serology in >95% of affected pts.
- *Clinical manifestations:* Pts have fever, anorexia, weight loss, nausea, and vomiting, but only ~50% have signs localized to the RUQ, such as tenderness, hepatomegaly, and jaundice. Serum levels of alkaline phosphatase are elevated in ~70% of pts, and leukocytosis is common. One-third to one-half of pts are bacteremic.

TREATMENT LIVER ABSCESS

- Drainage is the mainstay of treatment, but medical management with long courses of antibiotics can be successful.
  - Empirical therapy is the same as for intraabdominal sepsis and secondary bacterial peritonitis.

http://internalmedicinebook.com

– Percutaneous drainage tends to fail in cases with multiple, sizable abscesses; with viscous abscess contents that plug the pigtail catheter; with associated disease (e.g., of the biliary tract) requiring surgery; with the presence of yeast; or with lack of response in 4–7 days.

Splenic Abscess

- *Epidemiology and Pathogenesis:* Splenic abscesses are much less common than liver abscesses and usually develop via hematogenous spread of infection (e.g., due to endocarditis). The diagnosis is often made only after the pt's death; the condition is frequently fatal if left untreated.
- *Microbiology:* Splenic abscesses are most often caused by streptococci; *S. aureus* is the next most common cause. Gram-negative bacilli can cause splenic abscess in pts with urinary tract foci, with associated bacteremia, or with infection from another intraabdominal source; salmonellae are fairly commonly isolated, particularly from pts with sickle cell disease.
- *Clinical manifestations:* Abdominal pain or splenomegaly occurs in ~50% of cases and pain localized to the LUQ in ~25%. Fever and leukocytosis are common.

TREATMENT SPLENIC ABSCESS

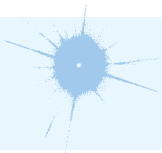
Pts with multiple or complex multilocular abscesses should undergo splenectomy, receive adjunctive antibiotics, and be vaccinated against encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*). Percutaneous drainage has been successful for single, small (<3-cm) abscesses and may also be useful for pts at high surgical risk.

Perinephric and Renal Abscesses

- *Epidemiology and Pathogenesis:* Perinephric and renal abscesses are uncommon. More than 75% of these abscesses are due to ascending infection and are preceded by pyelonephritis. The most important risk factor is the presence of renal calculi that produce local obstruction to urinary flow.
- *Microbiology: E. coli*, *Proteus* spp. (associated with struvite stones), and *Klebsiella* spp. are the most common etiologic agents; *Candida* spp. are sometimes identified.
- *Clinical manifestations:* Clinical signs are nonspecific and include flank pain, abdominal pain, and fever. This diagnosis should be considered if pts with pyelonephritis have persistent fever after 4 or 5 days of treatment, if a urine culture yields a polymicrobial flora, if the pt has known renal stone disease, or if fever and pyuria occur in conjunction with a sterile urine culture.

TREATMENT PERINEPHRIC AND RENAL ABSCESSES

Drainage and the administration of antibiotics active against the organisms recovered are essential. Percutaneous drainage is usually successful for perinephric abscesses.



For a more detailed discussion, see Barshak MB, Kasper DL: Intraabdominal Infections and Abscesses, Chap. 159, p. 846, in HPIM-19.

http://internalmedicinebook.com

82 Infectious Diarrheas

Acute diarrheal disease, which is associated with ~1.4 million deaths per year, is the second most common infectious cause of death worldwide among children <5 years old (after lower respiratory tract infection). The wide range of clinical manifestations is matched by the wide variety of infectious agents involved (Table 82-1). An approach to pts with infectious diarrhea is presented in Fig. 82-1.

NONINFLAMMATORY DIARRHEA

BACTERIAL FOOD POISONING

If there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the timing of diarrhea after a meal can provide clues to the bacterial cause of the illness.

TABLE 82-1 GASTROINTESTINAL PATHOGENS CAUSING ACUTE DIARRHEA

Mechanism	Location	Illness	Stool Findings	Examples of Pathogens Involved
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes; mild or no increase in fecal lactoferrin	*Vibrio cholerae*, enterotoxigenic *Escherichia coli* (LT and/or ST), enteroaggregative *E. coli*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, rotavirus, norovirus, enteric adenoviruses, *Giardia lamblia*, *Cryptosporidium* spp., *Cyclospora* spp., microsporidia
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin	*Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, enterohemorrhagic *E. coli*, enteroinvasive *E. coli*, *Yersinia enterocolitica*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Clostridium difficile*, *A. hydrophila*, *P. shigelloides*, *Entamoeba histolytica*, *Klebsiella oxytoca*
Penetrating	Distal small bowel	Enteric fever	Fecal mononuclear leukocytes	*Salmonella typhi*, *Y. enterocolitica*

Abbreviations: LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

http://internalmedicinebook.com

- *Staphylococcus aureus:* Enterotoxin is elaborated in food left at room temperature (e.g., at picnics).
  - The incubation period is 1–6 h. Disease lasts <12 h and consists of diarrhea, nausea, vomiting, and abdominal cramping, usually without fever.
  - Most cases are due to contamination from infected human carriers.
- *Bacillus cereus:* Either an *emetic* or a *diarrheal* form of food poisoning can occur.
  - The emetic form presents like *S. aureus* food poisoning, is due to a staphylococcal type of enterotoxin, has an incubation period of 1–6 h, and is associated with contaminated fried rice.
  - The diarrheal form has an incubation period of 8–16 h, is caused by an enterotoxin resembling *Escherichia coli* heat-labile toxin (LT), and presents as diarrhea and abdominal cramps without vomiting.
- *Clostridium perfringens:* Ingestion of heat-resistant spores in undercooked meat, poultry, or legumes leads to toxin production in the intestinal tract. The incubation period is 8–14 h, after which pts develop ≤24 h of diarrhea and abdominal cramps, without vomiting or fever.

CHOLERA

Microbiology

Cholera is caused by *Vibrio cholerae* serogroups O1 (classic and El Tor biotypes) and O139—highly motile, facultatively anaerobic, curved gram-negative rods. The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries. Toxin production causes disease manifestations.

Epidemiology

Currently, >90% of cases reported to the World Health Organization (WHO) are from Africa; however, most cases go unreported or do not have a specific bacterial etiology identified.

- It is estimated that there are >3 million cases annually, with >100,000 deaths.
- Spread takes place by fecal contamination of water and food sources. Infection requires ingestion of a relatively large inoculum (compared with that required for other pathogens) of $>10^5$ organisms.

Clinical Manifestations

After an incubation period of 24–48 h, pts develop painless watery diarrhea and vomiting that can cause profound, rapidly progressive dehydration and death within hours.

- Volume loss can be >250 mL/kg in the first day.
- Stool has a characteristic "rice-water" appearance: gray cloudy fluid with flecks of mucus; no blood; and a fishy, inoffensive odor.

Diagnosis

Stool cultures on selective medium (e.g., thiosulfate–citrate–bile salts–sucrose [TCBS] agar) can isolate the organism. A point-of-care antigen-detection assay is available for field use.

TREATMENT CHOLERA

Rapid fluid replacement is critical, preferably with the WHO's reduced-osmolarity oral rehydration solution (ORS), which contains (per liter of water) Na^+, 75 mmol; K^+, 20 mmol; Cl^-, 65 mmol; citrate, 10 mmol; and glucose, 75 mmol.

- If available, rice-based ORS is considered superior to standard ORS for cholera.

http://internalmedicinebook.com

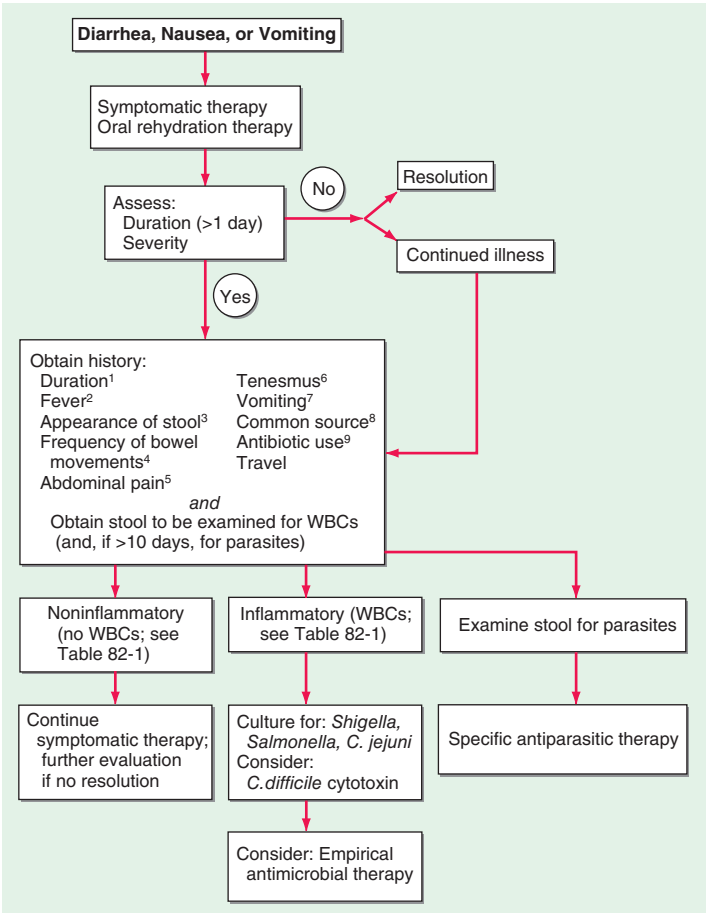


FIGURE 82-1 Clinical algorithm for the approach to pts with community-acquired infectious diarrhea or bacterial food poisoning. Key to superscripts: **1.** Diarrhea lasting >2 weeks is generally defined as chronic; in such cases, many of the causes of acute diarrhea are much less likely, and a new spectrum of causes needs to be considered. **2.** Fever often implies invasive disease, although fever and diarrhea may also result from infection outside the GI tract, as in malaria. **3.** Stools that contain blood or mucus indicate ulceration of the large bowel. Bloody stools without fecal leukocytes should alert the laboratory to the possibility of infection with Shiga toxin–producing enterohemorrhagic *Escherichia coli*. Bulky white stools suggest a small-intestinal process that is causing malabsorption. Profuse "rice-water" stools suggest cholera or a similar toxigenic process. **4.** Frequent stools over a given period can provide the first warning of impending dehydration. **5.** Abdominal pain may be most severe in inflammatory processes like those due to *Shigella, Campylobacter*, and necrotizing toxins. Painful abdominal muscle cramps, caused by electrolyte loss, can develop in severe cases of cholera. Bloating is common in giardiasis. An appendicitis-like syndrome should prompt a culture for *Yersinia enterocolitica* with cold enrichment. **6.** Tenesmus (painful rectal spasms with a strong urge to defecate but little passage of stool) may be a feature of cases with proctitis, as in shigellosis or amebiasis. **7.** Vomiting implies

http://internalmedicinebook.com

- If ORS is not available, a substitute can be made by adding 0.5 teaspoon of table salt (NaCl; 3.5 g) and 6 teaspoons of table sugar (sucrose) to 1 L of safe water, with potassium provided separately (e.g., in orange juice or coconut water).
- Severely dehydrated pts should be managed initially with IV hydration (preferably with Ringer's lactate), with the total fluid deficit replaced in the first 3–4 h (half within the first hour).
- Antibiotic therapy (azithromycin, a single 1-g dose; erythromycin, 250 mg PO qid for 3 days; tetracycline, 500 mg PO qid for 3 days; or ciprofloxacin, 500 mg PO bid for 3 days) diminishes the duration and volume of stool.

VIBRIO PARAHAEMOLYTICUS AND NON-01 *V. CHOLERAE*

These infections are linked to ingestion of contaminated seawater or undercooked seafood. After an incubation period of 4 h to 4 days, watery diarrhea, abdominal cramps, nausea, vomiting, and occasionally fever and chills develop. The disease lasts <7 days. Dysentery is a less common presentation. Pts with comorbid disease (e.g., liver disease) sometimes have extraintestinal infections that require antibiotic treatment.

NOROVIRUSES AND RELATED HUMAN CALICIVIRUSES

Microbiology and Epidemiology

These single-stranded RNA viruses are common causes of traveler's diarrhea and of viral gastroenteritis in pts of all ages as well as of epidemics worldwide, with a higher prevalence in cold-weather months. In the United States, >90% of outbreaks of nonbacterial gastroenteritis are caused by noroviruses. Very small inocula are required for infection. Thus, although the fecal-oral route is the primary mode of transmission, aerosolization, fomite contact, and person-to-person contact can also result in infection.

Clinical Manifestations

After a 24-h incubation period (range, 12–72 h), pts experience the sudden onset of nausea, vomiting, diarrhea, and/or abdominal cramps with constitutional symptoms (e.g., fever, headache, chills). Stools are loose, watery, and without blood, mucus, or leukocytes. Disease lasts 12–60 h.

Diagnosis

PCR assays have been developed to detect these viruses in stool and other body fluids. Because of poor sensitivity, enzyme immunoassays (EIAs) have limited clinical utility outside of outbreaks.

---

an acute infection (e.g., a toxin-mediated illness or food poisoning) but can also be prominent in a variety of systemic illnesses (e.g., malaria) and in intestinal obstruction. **8.** Asking pts whether anyone else they know is sick is a more efficient means of identifying a common source than is constructing a list of recently eaten foods. If a common source seems likely, specific foods can be investigated. **9.** Current antibiotic therapy or a recent history of treatment suggests *Clostridium difficile* diarrhea. Stop antibiotic treatment if possible and consider tests for *C. difficile* toxins. Antibiotic use may increase the risk of chronic intestinal carriage after salmonellosis. *(After Steiner TS, Guerrant RL: Principles and syndromes of enteric infection, in Mandell, Douglas, and Bennett's* Principles and Practice of Infectious Diseases, *7th ed, GL Mandell et al [eds]. Philadelphia, Churchill Livingstone, 2010, pp 1335–1351; RL Guerrant, DA Bobak: N Engl J Med 325:327, 1991; with permission.)*

http://internalmedicinebook.com

TREATMENT INFECTIONS WITH NOROVIRUSES AND RELATED HUMAN CALICIVIRUSES

Only supportive measures are required.

ROTAVIRUSES

Microbiology and Epidemiology

Rotavirus is a segmented, double-stranded RNA virus that infects nearly all children worldwide by 3–5 years of age; adults can become infected if exposed.

- Reinfections are progressively less severe.
- Large quantities of virus are shed in the stool during the first week of infection, and transmission takes place both via the fecal-oral route and from person to person.
- Disease incidence peaks in the cooler fall and winter months.

Clinical Manifestations

After an incubation period of 1–3 days, disease onset is abrupt. Vomiting often precedes diarrhea (loose, watery stools without blood or fecal leukocytes), and about one-third of pts have temperatures >39°C (102.2°F). Symptoms resolve within 3–7 days.

Diagnosis

EIAs or viral RNA detection techniques, such as PCR, can identify rotavirus in stool samples.

TREATMENT ROTAVIRUS INFECTIONS

Only supportive treatment is needed. Dehydration can be severe, and IV hydration may be needed in pts with frequent vomiting. Avoid antibiotics and antimotility agents.

Prevention

Rotavirus vaccines, two of which are available, are included in the routine vaccination schedule for U.S. infants. Vaccination has led to a >70% decline in hospital visits due to rotavirus illness. Notably, the efficacy of rotavirus vaccines is lower (50–65%) in low-resource settings.

GIARDIASIS

Microbiology and Epidemiology

Giardia lamblia (also known as *G. intestinalis* or *G. duodenalis*) is a protozoal parasite that inhabits the small intestines of humans and other mammals.

- Cysts are ingested from the environment, excyst in the small intestine, and release flagellated trophozoites that remain in the proximal small intestine. Some trophozoites encyst, with the resulting cysts excreted in feces.
- Transmission occurs via the fecal-oral route, by ingestion of contaminated food and water, or from person to person in settings with poor fecal hygiene (e.g., day-care centers, institutional settings). Infection results from as few as 10 cysts.
- Viable cysts can be eradicated from water by either boiling or filtration. Standard chlorination techniques used to control bacteria do not destroy cysts.
- Young pts, newly exposed pts, and pts with hypogammaglobulinemia are at increased risk—a pattern suggesting a role for humoral immunity in resistance.

http://internalmedicinebook.com

Clinical Manifestations

After an incubation period of 5 days to 3 weeks, the manifestations of infection range from asymptomatic carriage (most common) to fulminant diarrhea and malabsorption.

- Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting and usually last >1 week. Fever is rare, as is blood or mucus in stool.
- Chronic giardiasis can be continual or episodic; diarrhea may not be prominent, but increased flatulence, sulfurous belching, and weight loss can occur.
- In some cases, disease can be severe, with malabsorption, growth retardation, dehydration, and/or extraintestinal manifestations (e.g., anterior uveitis, arthritis).

Diagnosis

Giardiasis can be diagnosed by parasite antigen detection in feces, by identification of cysts (oval, with four nuclei) or trophozoites (pear-shaped, flattened parasites with two nuclei and four pairs of flagella) in stool specimens, or by nucleic acid amplification tests. Given variability in cyst excretion, multiple samples may need to be examined.

TREATMENT GIARDIASIS

- Cure rates with metronidazole (250 mg tid for 5 days) and albendazole (400 mg/d for 5–10 days) are >90%; tinidazole (2 g PO once) may be more effective. Nitazoxanide (500 mg bid for 3 days) is an alternative agent.
- If symptoms persist, continued infection should be documented before retreatment, and possible sources of reinfection should be sought. Prolonged therapy with metronidazole (750 mg tid for 21 days) has been successful.

CRYPTOSPORIDIOSIS

Microbiology and Epidemiology

Cryptosporidial infections are caused by *Cryptosporidium hominis* and *C. parvum*.

- Oocysts are ingested and subsequently excyst, enter intestinal cells, and generate oocysts that are excreted in feces. The 50% infectious dose in immunocompetent individuals is ~132 oocysts.
- Person-to-person transmission of infectious oocysts can occur among close contacts and in day-care settings. Waterborne transmission is common. Oocysts are not killed by routine chlorination.

Clinical Manifestations

After an incubation period of ~1 week, pts may remain asymptomatic or develop watery, nonbloody diarrhea, occasionally with abdominal pain, nausea, anorexia, fever, and/or weight loss lasting 1–2 weeks. In immunocompromised hosts (particularly those with $CD4^+$ T cell counts <100/μL), diarrhea can be profuse and chronic, resulting in severe dehydration, weight loss, and wasting; the biliary tract can be involved.

Diagnosis

On multiple days, fecal samples should be examined for oocysts (4–5 μm in diameter, smaller than most parasites). Although conventional stool examination for ova and parasites does not detect *Cryptosporidium*, modified acid-fast staining, direct immunofluorescent techniques, and EIAs can facilitate diagnosis.

http://internalmedicinebook.com

TREATMENT CRYPTOSPORIDIOSIS

- Nitazoxanide (500 mg bid for 3 days) is effective for immunocompetent pts but not for HIV-infected pts; improved immune status due to antiretroviral therapy can alleviate symptoms in the latter pts.
- In addition to antiprotozoal agents, supportive measures include replacement of fluid and electrolytes and use of antidiarrheal agents.

CYSTOISOSPORIASIS

Cystoisospora belli (formerly *Isospora belli*) infection is acquired by oocyst ingestion and is most common in tropical and subtropical countries. Acute infection can begin suddenly with fever, abdominal pain, and watery, nonbloody diarrhea and can last for weeks or months. Eosinophilia may occur. Compromised (e.g., HIV-infected) pts may have chronic disease that resembles cryptosporidiosis. Detection of large oocysts (~25 μm) in stool by modified acid-fast staining confirms the diagnosis.

TREATMENT CYSTOISOSPORIASIS

- Trimethoprim-sulfamethoxazole (TMP-SMX; 160/800 mg qid for 10 days) is effective in immunocompetent pts.
  - HIV-infected pts should receive prolonged therapy with TMP-SMX (160/800 mg qid for 10 days, followed by 160/800 mg tid for 3 weeks).
  - Pyrimethamine (50–75 mg/d) can be given to pts intolerant of TMP-SMX.
  - Pts with AIDS may need suppressive maintenance therapy (TMP-SMX, 160/800 mg 3 times per week) to prevent relapses.

CYCLOSPORIASIS

Cyclospora cayetanensis can be transmitted through water or food (e.g., basil, raspberries). Clinical manifestations include diarrhea, flulike symptoms, flatulence, and burping. Disease can be self-limited or can persist for >1 month. Diagnosis is made by detection of oocysts (spherical, 8–10 μm) in stool; targeted diagnostic studies must be specifically requested.

TREATMENT CYCLOSPORIASIS

TMP-SMX (160/800 mg bid for 7–10 days) is effective. Pts with AIDS may need suppressive maintenance therapy to prevent relapses.

INFLAMMATORY DIARRHEA

SALMONELLOSIS

Microbiology and Pathogenesis

Salmonellae are facultatively anaerobic gram-negative bacilli that cause infection when between 200 and 10^6 organisms are ingested.

- Conditions that reduce gastric acidity or intestinal integrity increase susceptibility to infection.
- Organisms penetrate the small-intestinal mucus layer and traverse the intestinal epithelium through M cells overlying Peyer's patches.
  - *S. typhi* and *S. paratyphi* survive within macrophages, then disseminate throughout the body via lymphatics, and ultimately colonize reticuloendothelial tissues.

http://internalmedicinebook.com

– Nontyphoidal salmonellae most commonly cause gastroenteritis, invading the large- and small-intestinal mucosa and resulting in massive PMN infiltration (as opposed to the mononuclear-cell infiltration seen with typhoid fever).

Epidemiology and Clinical Manifestations

Depending on the specific species, salmonellosis results in typhoid fever or gastroenteritis.

- *Typhoid (enteric) fever:* Typhoid fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S. typhi* or *S. paratyphi*, for which humans are the only hosts.
  - Disease results from ingestion of food or water contaminated by chronic carriers and is rare in developed nations. Worldwide, there are ~27 million cases, with 200,000–600,000 deaths annually.
  - After an incubation period of 5–21 days, prolonged fever (>75% of cases), headache (80%), chills (35–45%), anorexia (55%), and abdominal pain (30–40%) are common. Other signs and symptoms may include sweating, cough, malaise, arthralgias, nausea, vomiting, and diarrhea—or, less often, constipation.
  - Physical findings include *rose spots* (a faint, salmon-colored, blanching, maculopapular rash), hepatosplenomegaly, epistaxis, and relative bradycardia.
  - Intestinal perforation and/or GI hemorrhage can occur in the third and fourth weeks of illness; neurologic manifestations (e.g., meningitis, Guillain-Barré syndrome) occur in 2–40% of pts.
  - Long-term *Salmonella* carriage (i.e., for >1 year) in urine or stool develops in 1–5% of pts.
- *Nontyphoidal salmonellosis (NTS)*: Most commonly caused by *S. typhimurium* or *S. enteritidis*, NTS typically presents within 6–48 h of exposure as gastroenteritis (nausea, vomiting, nonbloody diarrhea, abdominal cramping, and fever) that lasts 3–7 days.
  - In the United States, NTS causes ~12 million illnesses annually.
  - Disease is acquired from multiple animal reservoirs. The main mode of transmission is via contaminated food products, such as eggs (*S. enteritidis*), poultry, undercooked meat, dairy products, manufactured or processed foods, and fresh produce. Infection is also acquired during exposure to pets, especially reptiles.
  - Stool cultures remain positive for 4–5 weeks and—in rare cases of chronic carriage—for >1 year.
  - Bacteremia, usually due to *S. choleraesuis* and *S. dublin*, develops in 8% of pts; of these pts, 5–10% develop localized infections (e.g., hepatosplenic abscesses, meningitis, pneumonia, osteomyelitis).
  - Reactive arthritis can follow *Salmonella* gastroenteritis, particularly in persons with the HLA-B27 histocompatibility antigen.

Diagnosis

Positive cultures of blood, stool, or other specimens are required for diagnosis.

TREATMENT SALMONELLOSIS

- *Typhoid fever*: A fluoroquinolone (e.g., ciprofloxacin, 500 mg PO bid for 5–7 days) is most effective against susceptible organisms.
  - Pts infected with nalidixic acid–resistant strains (whose susceptibility to ciprofloxacin is reduced) should be treated with ceftriaxone (2 g/d IV for 10–14 days), azithromycin (1 g/d PO for 5 days), or high-dose ciprofloxacin (750 mg PO bid or 400 mg IV q8h for 10–14 days).
  - Dexamethasone may be of benefit in severe cases.

http://internalmedicinebook.com

- *NTS*: Antibiotic treatment is not recommended in most cases as it does not shorten the duration of symptoms and is associated with increased rates of relapse, a prolonged carrier state, and adverse drug reactions.
  - Antibiotic treatment may be required for infants ≤3 months of age; pts >50 years of age with suspected atherosclerosis; pts with immunosuppression; pts with cardiac, valvular, or endovascular abnormalities; and pts with significant joint disease.
  - Fluoroquinolones or third-generation cephalosporins are given for 3–7 days or until defervescence (if the pt is immunocompetent) or for 1–2 weeks (if the pt is immunocompromised).
  - HIV-infected pts are at high risk for *Salmonella* bacteremia and should receive 4 weeks of oral fluoroquinolone therapy after 1–2 weeks of IV treatment. In cases of relapse, long-term suppression with a fluoroquinolone or TMP-SMX should be considered.
  - Pts with endovascular infections or endocarditis should receive 6 weeks of treatment with a third-generation cephalosporin.

CAMPYLOBACTERIOSIS

Microbiology

Campylobacters are motile, curved gram-negative rods that are a common bacterial cause of gastroenteritis in the United States. Most cases are caused by *C. jejuni*.

Epidemiology

Campylobacters are common commensals in the GI tract of many food animals and household pets. In developed countries, ingestion of contaminated poultry accounts for 30–70% of cases. Transmission to humans occurs via contact with or ingestion of raw or undercooked food products or direct contact with infected animals.

Clinical Manifestations

An incubation period of 2–4 days (range, 1–7 days) is followed by a prodrome of fever, headache, myalgia, and/or malaise. Within the next 12–48 h, diarrhea (with stools containing blood, mucus, and leukocytes), cramping abdominal pain, and fever develop.

- Most cases are self-limited, but illness persists for >1 week in 10–20% of pts and may be confused with inflammatory bowel disease.
- Species other than *C. jejuni* (e.g., *C. fetus*) can cause a similar illness in normal hosts or prolonged relapsing systemic disease without a primary focus in immunocompromised pts.
  - The course may be fulminant, with bacterial seeding of many organs, particularly vascular sites.
  - Fetal death can result from infection in a pregnant pt.
- Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host; and (3) sustained bacteremia or focal infection in a compromised host.
- Complications include reactive arthritis (particularly in persons with the HLA-B27 phenotype) and Guillain-Barré syndrome (in which campylobacters are associated with 20–40% of cases).

Diagnosis

The diagnosis is confirmed by cultures of stool, blood, or other specimens on special media and/or with selective techniques.

http://internalmedicinebook.com

TREATMENT **CAMPYLOBACTERIOSIS**

- Fluid and electrolyte replacement is the mainstay of therapy.
- Use of antimotility agents is not recommended, as they are associated with toxic megacolon.
- Antibiotic treatment (erythromycin, 250 mg PO qid for 5–7 days) should be reserved for pts with high fever, bloody or severe diarrhea, persistence for >1 week, and worsening of symptoms. Azithromycin and fluoroquinolones are alternative regimens, although resistance to fluoroquinolones is increasing.

SHIGELLOSIS AND INFECTION WITH SHIGA TOXIN–PRODUCING/ ENTEROHEMORRHAGIC/SHIGA TOXIN–PRODUCING ENTEROAGGREGATIVE *E. COLI* (STEC/EHEC/STEAEC)

Microbiology and Epidemiology

Shigellae are small, gram-negative, nonmotile bacilli that are very closely related to *E. coli*. The four most common *Shigella* serotypes are *S. dysenteriae* type 1, *S. flexneri*, *S. boydii*, and *S. sonnei* (which is more prevalent in the industrialized world). Humans are the major reservoir, but *Shigella* can be found in other higher primates and STEC/EHEC in cows.

- Person-to-person spread via the fecal-oral route is most common for *Shigella* (and occasionally STEC/EHEC/STEAEC); ingestion of contaminated food and water is the more common route of transmission of STEC/EHEC/STEAEC (and occasionally *Shigella*).
- The ability of as few as 100 organisms to cause infection helps explain the high rate of secondary household transmission.
- Shiga toxin and Shiga-like toxins produced by some strains of *E. coli* (including O157:H7) are important factors in disease severity. The toxins target endothelial cells and play a significant role in the microangiopathic complications of *Shigella* and *E. coli* infections, such as hemolytic-uremic syndrome (HUS; i.e., Coombs-negative hemolytic anemia, thrombocytopenia, and acute renal failure) and thrombotic thrombocytopenic purpura.
- An analysis of *Shigella* cases occurring in 1966–1997 revealed an annual incidence of 165 million cases (of which 69% affected children <5 years of age) with 0.5–1.1 million deaths; these numbers have likely decreased since then, but multidrug-resistant strains have emerged.

Clinical Manifestations

After an incubation period of 1–4 days, shigellosis evolves through three phases: watery diarrhea, dysentery (bloody mucopurulent stools), and the postinfectious phase.

- Most episodes resolve in 1 week without treatment; with appropriate treatment, recovery takes place within a few days, with no sequelae.
- Complications are largely intestinal (e.g., toxic megacolon, intestinal perforation, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia). Shiga toxin produced by *S. dysenteriae* type 1 is linked to HUS in developing countries but is rare in industrialized countries, where *E. coli* O157:H7 is a more common cause.

Diagnosis

Shigellosis is diagnosed directly by stool culture. STEC/EHEC infection is diagnosed by simultaneous culture (assaying for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping for O157) and assay for the detection of Shiga toxin (which can rapidly detect non-O157 STEC/EHEC and sorbitol-fermenting strains of O157:H7).

http://internalmedicinebook.com

TREATMENT SHIGELLOSIS AND INFECTION WITH STEC/EHEC

- In the United States, because of the ready transmissibility of *Shigella*, antibiotics are recommended. Fluoroquinolones (e.g., ciprofloxacin, 500 mg bid) are effective, as are ceftriaxone, azithromycin, pivmecillinam, and some fifth-generation quinolones.
  - *S. dysenteriae* infection should be treated for 5 days and non-*dysenteriae Shigella* infection for 3 days.
  - Immunocompromised pts should receive 7–10 days of treatment.
- Antibiotic treatment for STEC/EHEC infections should be avoided, since antibiotics may increase the incidence of HUS.
- Rehydration usually is not needed; *Shigella* infection rarely causes significant dehydration. If required, rehydration should be oral, and nutrition should be started as soon as possible. Use of antimotility agents may prolong fever and increase the risk of HUS and toxic megacolon.

YERSINIOSIS

Microbiology and Clinical Manifestations

Y. enterocolitica and *Y. pseudotuberculosis* are nonmotile gram-negative rods that cause enteritis or enterocolitis with self-limited diarrhea that lasts an average of 2 weeks as well as mesenteric adenitis (especially common with *Y. pseudotuberculosis*) and terminal ileitis (especially common with *Y. enterocolitica*), either of which can resemble acute appendicitis. Septicemia can occur in pts with chronic liver disease, malignancy, diabetes mellitus, and other underlying illnesses. Infection has been linked to reactive arthritis in HLA-B27-positive pts.

Diagnosis

Stool culture studies for *Yersinia* must be specifically requested and require the use of special media.

TREATMENT YERSINIOSIS

Antibiotics are not indicated for diarrhea caused by yersiniae; supportive measures suffice.

AMEBIASIS

Microbiology and Epidemiology

Entamoeba histolytica, the cause of amebiasis, infects ~10% of the world's population and is the third most common cause of death from parasitic disease (after schistosomiasis and malaria). Infection follows ingestion of cysts from fecally contaminated water, food, or hands. Motile trophozoites are released from cysts in the small intestine and then cause infection in the large bowel. Trophozoites may be shed in stool (in active dysentery) or encyst. Excreted cysts survive for weeks in a moist environment.

Clinical Manifestations

Most pts harboring *Entamoeba* species are asymptomatic, but some pts develop inflammatory colitis 2–6 weeks after ingestion of amebic cysts.

- Dysentery may develop, with daily passage of 10–12 small stools consisting mostly of blood and mucus. Fewer than 40% of pts have fever.
- Fulminant amebic colitis—characterized by more profuse diarrhea, severe abdominal pain with peritoneal signs, and fever—is more common among children.
- Liver abscess is the most common type of extraintestinal infection and can arise months after exposure to *E. histolytica*. Pts present with RUQ pain, fever, right-sided pleural

http://internalmedicinebook.com

effusion, and hepatic tenderness and typically do not have active colitis. The abscess can rupture through the diaphragm and metastasize elsewhere (e.g., lung, heart).

Diagnosis

Microscopic examination of three stool samples, often combined with serologic testing, remains the standard diagnostic approach.

- Up to 10% of pts with acute amebic liver abscess may have negative serologies; testing should be repeated in 1 week if clinical suspicion remains high.

TREATMENT **AMEBIASIS**

- Tinidazole (2 g/d PO for 3 days) or metronidazole (750 mg PO or IV tid for 5–10 days) is recommended for amebic colitis and amebic liver abscess.
  - Within 3 days of treatment initiation, >90% of pts respond clinically.
  - Drainage of liver abscesses is rarely needed. Indications for aspiration include the need to rule out pyogenic abscess, a lack of response to treatment in 3–5 days, an imminent threat of liver-abscess rupture, or the need to prevent left-lobe abscess rupture into the pericardium.
- Pts with either colitis or liver abscesses should also receive a luminal agent to ensure eradication of the infection. Paromomycin (500 mg PO tid for 10 days) is the preferred agent; iodoquinol (650 mg PO tid for 20 days) is an alternative.

CLOSTRIDIUM DIFFICILE INFECTION (CDI)

Microbiology and Epidemiology

C. difficile is an obligately anaerobic, gram-positive, spore-forming bacillus and causes diarrheal illness that is most commonly acquired in the hospital. The disease is acquired almost exclusively in association with antimicrobial treatment; virtually all antibiotics carry a risk of CDI.

- After *C. difficile* colonizes the gut, its spores vegetate, multiply, and secrete toxin A (an enterotoxin) and toxin B (a cytotoxin), causing diarrhea and pseudomembranous colitis. The rate of fecal colonization is often ≥20% among adult pts hospitalized for >1 week; in contrast, the rate is 1–3% among community residents.
- Spores can persist on environmental surfaces in the hospital for months and on the hands of hospital personnel who do not practice adequate hand hygiene.
- Rates and severity of CDI in the United States, Canada, and Europe have increased markedly in the past decade. The epidemic NAP1/BI/027 strain accounts for much of the increase and is characterized by production of 16–23 times as much toxin A and toxin B as is documented for control strains, by the presence of a third toxin (binary toxin), and by high-level resistance to fluoroquinolones.

Clinical Manifestations

Most commonly, pts develop diarrhea, with stools that are not grossly bloody and are soft to watery, with a characteristic odor. Pts may have up to 20 bowel movements per day. Fever, abdominal pain, and leukocytosis are common.

- Constipation due to an adynamic ileus can occur. Unexplained leukocytosis (≥15,000 WBCs/μL) in this setting should prompt evaluation for CDI. These pts are at high risk for complications such as toxic megacolon and sepsis.
- *C. difficile* diarrhea recurs after treatment in ~15–30% of cases.

Diagnosis

CDI is diagnosed in a pt with diarrhea (≥3 unformed stools per 24 h for ≥2 days) by detection of the organism, toxin A, or toxin B in stool or identification of pseudomembranes in the colon.

http://internalmedicinebook.com

- Most laboratory tests for toxin (e.g., ELISAs) lack sensitivity, but repeat testing is not recommended. PCR assays are rapid, sensitive, and highly specific.
- Testing of asymptomatic pts (including a test of cure for those who have completed therapy) is not recommended.

TREATMENT *C. DIFFICILE* INFECTION

- *Primary CDI:* When feasible, discontinuation of ongoing antimicrobial treatment is an effective cure in 15–23% of cases. Prompt initiation of specific therapy is recommended.
  - For mild to moderate disease, metronidazole (500 mg tid for 10 days) is recommended, with extension of therapy if the clinical response is slow.
  - For severe disease (e.g., >15,000 WBCs/μL, serum creatinine levels ≥1.5 times baseline), vancomycin (125 mg qid PO for 10–14 d) is the agent of choice. Fidaxomicin is an alternative and results in lower rates of recurrent disease.
- *Recurrent CDI:* The first recurrence should be treated the same as the initial episode.
  - For the second recurrence, an extended, tapered vancomycin regimen (125 mg qid for 10–14 d, then bid for 1 week, then daily for 1 week, then q2–3d for 2–8 weeks) should be used.
  - For multiple recurrences, there is no standard treatment course. Consider repetition of the tapered vancomycin regimen, administration of vancomycin (500 mg qid for 10 days) with *Saccharomyces boulardii* (500 mg bid for 28 d), administration of sequential therapy with vancomycin (125 mg qid for 10–14 d) followed by rifaximin (400 mg bid for 2 weeks), treatment with nitazoxanide (500 mg bid for 10 d), or treatment with IV immunoglobulin (400 mg/kg). On the basis of recent successful clinical trials, fecal transplantation is increasingly being used for recurrent CDI.
- *Fulminant CDI:* Medical management is complicated by ineffective delivery of oral antibiotics to the intestinal lumen in the setting of ileus. Vancomycin (given via nasogastric tube and by retention enema) combined with IV metronidazole has been used with some success, as has IV tigecycline. Surgical colectomy can be life-saving.



For a more detailed discussion, see LaRocque RC, Ryan ET, Calderwood SB: Acute Infectious Diarrheal Diseases and Bacterial Food Poisoning, Chap. 160, p. 852; Gerding DN, Johnson S: *Clostridium difficile* Infection, Including Pseudomembranous Colitis, Chap. 161, p. 857; Russo TA, Johnson JR: Diseases Caused by Gram-Negative Enteric Bacilli, Chap. 186, p. 1025; Pegues DA, Miller SI: Salmonellosis, Chap. 190, p. 1049; Sansonetti PJ, Bergounioux J: Shigellosis, Chap. 191, p. 1055; Blaser MJ: Infections Due to *Campylobacter* and Related Organisms, Chap. 192, p. 1058; Waldor MK, Ryan ET: Cholera and Other Vibrioses, Chap. 193, p. 1061; Prentice MB: Plague and Other *Yersinia* Infections, Chap. 196, p. 1070; Parashar UD, Glass RI: Viral Gastroenteritis, Chap. 227, p. 1285; Andrade M, Reed SL: Amebiasis and Infection with Free-Living Amebas, Chap. 247, p. 1363; and Weller PF: Protozoal Intestinal Infections and Trichomoniasis, Chap. 254, p. 1405, in HPIM-19.

http://internalmedicinebook.com

83 Sexually Transmitted and Reproductive Tract Infections

GENERAL PRINCIPLES

- Worldwide, most adults acquire at least one sexually transmitted infection (STI).
- Three factors determine the initial rate of spread of any STI within a population: rate of sexual exposure of susceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected.
- STI care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, syndrome-based treatment to cover the most likely causes, and prevention and control. The "4 C's" of control are *c*ontact tracing, ensuring *c*ompliance with treatment, and *c*ounseling on risk reduction, including *c*ondom promotion and provision.

SPECIFIC SYNDROMES

URETHRITIS IN MEN

Microbiology and Epidemiology

Most cases are caused by either *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Other causative organisms include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and HSV. *Chlamydia* causes 30–40% of nongonococcal urethritis (NGU) cases. *M. genitalium* is the probable cause in many *Chlamydia*-negative cases of NGU.

Clinical Manifestations

Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination.

Diagnosis

Pts present with a mucopurulent urethral discharge that can usually be expressed by milking of the urethra; alternatively, a Gram's-stained smear of an anterior urethral specimen containing ≥5 PMNs/1000× field confirms the diagnosis.

- Centrifuged sediment of the day's first 20–30 mL of voided urine can be examined instead.
- *N. gonorrhoeae* can be presumptively identified if intracellular gram-negative diplococci are present in Gram's-stained samples.
- Early-morning, first-voided urine should be used in "multiplex" nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* and *C. trachomatis*.

TREATMENT URETHRITIS IN MEN

- Treatment should be given promptly, while test results are pending.
  - Unless these diseases have been excluded, gonorrhea is treated with a single dose of ceftriaxone (250 mg IM) plus azithromycin (1 g PO once), and *Chlamydia* infection is treated with azithromycin (1 g PO once) or doxycycline (100 mg bid for 7 days); azithromycin may be more effective for *M. genitalium*.
  - Sexual partners of the index case should receive the same treatment.
- For recurrent symptoms: With re-exposure, both pt and partner are re-treated. Without re-exposure, infection with *T. vaginalis* (with culture or NAATs of a

http://internalmedicinebook.com

urethral swab and early-morning, first-voided urine) or doxycycline-resistant *M. genitalium* or *Ureaplasma* should be considered; treatment with metronidazole or tinidazole (a single PO dose of 2 g) plus azithromycin (1 g PO once) is recommended, and the azithromycin component is especially important if this drug was not used for the primary episode.

EPIDIDYMITIS

Microbiology

In sexually active men <35 years old, epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae*.

- In older men or after urinary tract instrumentation, urinary pathogens are most common.
- In men who practice insertive rectal intercourse, Enterobacteriaceae may be responsible.

Clinical Manifestations

Acute epididymitis—almost always unilateral—produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. Epididymitis must be differentiated from testicular torsion, tumor, and trauma. If symptoms persist after treatment, a testicular tumor or a chronic granulomatous disease (e.g., tuberculosis) should be considered.

TREATMENT EPIDIDYMITIS

- Ceftriaxone (250 mg IM once) followed by doxycycline (100 mg PO bid for 10 days) is effective for epididymitis due to *C. trachomatis* or *N. gonorrhoeae.*
- Oral cephalosporins and fluoroquinolones are no longer recommended because of increasing resistance in *N. gonorrhoeae.*
- If Enterobacteriaceae are suspected as the cause and such organisms are detected in a urine culture, levofloxacin (500 mg PO daily for 10 days) can be used.

URETHRITIS (THE URETHRAL SYNDROME) IN WOMEN

Microbiology and Clinical Manifestations

C. trachomatis, *N. gonorrhoeae*, and occasionally HSV cause symptomatic urethritis—known as *the urethral syndrome* in women—that is characterized by "internal" dysuria (usually without urinary urgency or frequency), pyuria, and an absence of *Escherichia coli* and other uropathogens at counts $\geq 10^2$/mL in urine.

Diagnosis

Specific tests (e.g., NAATs of vaginal secretions collected with a swab) are used to evaluate for infection with *N. gonorrhoeae* or *C. trachomatis*.

TREATMENT URETHRITIS (THE URETHRAL SYNDROME) IN WOMEN

See "Urethritis in Men," above.

VULVOVAGINAL INFECTIONS

Microbiology

A variety of organisms are associated with vulvovaginal infections, including *N. gonorrhoeae* and *C. trachomatis* (particularly when they cause cervicitis), *T. vaginalis*, *Candida albicans*, *Gardnerella vaginalis*, and HSV.

http://internalmedicinebook.com

Clinical Manifestations

Vulvovaginal infections encompass a wide array of specific conditions, each of which has different presenting symptoms.

- Unsolicited reporting of abnormal vaginal discharge suggests trichomoniasis or bacterial vaginosis (BV).
  - *Trichomoniasis* is characterized by vulvar irritation and a profuse white or yellow, homogeneous vaginal discharge with a pH that is typically ≥5.
  - *BV* is characterized by vaginal malodor and a slight to moderate increase in white or gray, homogeneous vaginal discharge that uniformly coats the vaginal walls and typically has a pH >4.5.
  - Vaginal trichomoniasis and BV early in pregnancy are associated with premature onset of labor.
- Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia.

Diagnosis

Evaluation of vulvovaginal symptoms includes a pelvic examination (with a speculum examination) and simple rapid diagnostic tests.

- Abnormal vaginal discharge is assessed for pH, a fishy odor after mixing with 10% KOH (BV), evidence on microscopy of motile trichomonads and/or clue cells of BV (vaginal epithelial cells coated with coccobacillary organisms) when the specimen is mixed with saline, or hyphae or pseudohyphae on microscopy when 10% KOH is added (vaginal candidiasis).
- A DNA probe test (the Affirm test) can detect *T. vaginalis*, *C. albicans*, and increased concentrations of *G. vaginalis*. A NAAT for *T. vaginalis* is available.

TREATMENT VULVOVAGINAL INFECTIONS

- *Vulvovaginal candidiasis:* Miconazole (a single 1200-mg vaginal suppository), clotrimazole (two 100-mg vaginal tablets daily for 3 days), or fluconazole (150 mg PO once) are all effective.
- *Trichomoniasis:* Metronidazole (2 g PO once) or tinidazole is effective. Treatment of sexual partners with the same regimen reduces the risk of reinfection and is the standard of care.
- *BV:* Metronidazole (500 mg PO bid for 7 days), 2% clindamycin cream (one full applicator vaginally each night for 7 days), or 0.75% metronidazole gel (one full applicator vaginally bid for 5 days) is effective, but recurrence is common regardless of the regimen used.

MUCOPURULENT CERVICITIS

Microbiology

N. gonorrhoeae, *C. trachomatis*, and *M. genitalium* are the primary causes of mucopurulent cervicitis. Of note, NAATs for these pathogens, HSV, and *T. vaginalis* have been negative in nearly half of cases.

Clinical Manifestations

Mucopurulent cervicitis represents the "silent partner" of urethritis in men and results from inflammation of the columnar epithelium and subepithelium of the endocervix.

Diagnosis

Yellow mucopurulent discharge from the cervical os, with ≥20 PMNs/1000× field on Gram's stain of cervical mucus, indicates endocervicitis. The presence of intracellular

http://internalmedicinebook.com

gram-negative diplococci on Gram's stain of cervical mucus is specific but <50% sensitive for gonorrhea; thus NAATs for *N. gonorrhoeae* and *C. trachomatis* are always indicated.

TREATMENT MUCOPURULENT CERVICITIS

See "Urethritis in Men," above.

PELVIC INFLAMMATORY DISEASE (PID)

Microbiology

The agents most often implicated in acute PID—infection that ascends from the cervix or vagina to the endometrium and/or fallopian tubes—include the primary causes of endocervicitis (e.g., *N. gonorrhoeae* and *C. trachomatis*); other organisms (e.g., *M. genitalium*, *Prevotella* spp., peptostreptococci, *E. coli, Haemophilus influenzae*, and group B streptococci) account for 25–33% of cases.

Epidemiology

In 2011, there were 90,000 visits to physicians' offices for PID in the United States; there are ~70,000–100,000 hospitalizations related to PID annually.

- Risk factors for PID include cervicitis, BV, a history of salpingitis or recent vaginal douching, menstruation, and recent insertion of an intrauterine contraceptive device (IUD).
- Oral contraceptive pills decrease risk.

Clinical Manifestations

The presenting symptoms depend on the extent to which the infection has spread.

- *Endometritis:* Pts present with midline abdominal pain and abnormal vaginal bleeding. Lower-quadrant, adnexal, or cervical motion or abdominal rebound tenderness is less severe in women with endometritis alone than in women who also have salpingitis.
- *Salpingitis:* Symptoms evolve from mucopurulent cervicitis to endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis. Nausea, vomiting, and increased abdominal tenderness may occur if peritonitis develops.
- *Perihepatitis* (Fitz-Hugh–Curtis syndrome): 3–10% of women present with pleuritic upper abdominal pain and tenderness in the RUQ due to perihepatic inflammation. Most cases are due to chlamydial salpingitis.
- *Periappendicitis:* ~5% of pts can have appendiceal serositis without involvement of the intestinal mucosa as a result of gonococcal or chlamydial salpingitis.

Diagnosis

Speculum examination shows evidence of mucopurulent cervicitis in the majority of pts with gonococcal or chlamydial PID; cervical motion tenderness, uterine fundal tenderness, and/or abnormal adnexal tenderness also is usually present. Vaginal or endocervical swab specimens should be examined by NAATs for *N. gonorrhoeae* and *C. trachomatis*.

TREATMENT PELVIC INFLAMMATORY DISEASE

- Empirical treatment for PID should be initiated in sexually active young women and in other women who are at risk for PID and who have pelvic or lower abdominal pain with no other explanation as well as cervical motion, uterine, or adnexal tenderness.
- Hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies cannot be excluded, (2) the pt is pregnant, (3) pelvic

http://internalmedicinebook.com

abscess is suspected, (4) severe illness precludes outpatient management, (5) the pt has HIV infection, (6) the pt is unable to follow or tolerate an outpatient regimen, or (7) the pt has failed to respond to outpatient therapy.

- *Outpatient regimen*: Ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO bid for 14 days) plus metronidazole (500 mg PO bid for 14 days) is effective. Women treated as outpatients should be clinically reevaluated within 72 h.
- *Parenteral regimens*: Parenteral treatment with the two regimens listed below should be given for ≥48 h after clinical improvement. A 14-day course should be completed with doxycycline (100 mg PO bid); if the clindamycin-containing regimen is used, this drug can be given by the oral route (450 mg PO qid).
  - Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h) plus doxycycline (100 mg IV/PO q12h)
  - Clindamycin (900 mg IV q8h) plus gentamicin (loading dose of 2.0 mg/kg IV/IM followed by 1.5 mg/kg q8h)
- Male sex partners should be evaluated and treated empirically for gonorrhea and chlamydial infection.

Prognosis

Late sequelae include infertility (11% after one episode of PID, 23% after two, and 54% after three or more); ectopic pregnancy (sevenfold increase in risk); chronic pelvic pain; and recurrent salpingitis.

ULCERATIVE GENITAL LESIONS

The most common etiologies for ulcerative genital lesions in the United States are genital herpes, syphilis, and chancroid. See Table 83-1 and the sections on individual pathogens below for specific clinical manifestations. Pts with persistent genital ulcers that do not resolve with syndrome-based antimicrobial therapy should have their HIV serologic status assessed if such testing has not previously been performed. Immediate treatment (before all test results are available) is often appropriate to improve response, reduce transmission, and cover pts who might not return for follow-up visits.

PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

Microbiology and Epidemiology

Acquisition of HSV, *N. gonorrhoeae*, or *C. trachomatis* (including lymphogranuloma venereum [LGV] strains of *C. trachomatis*) during receptive anorectal intercourse causes most cases of infectious proctitis in women and in men who have sex with men (MSM). Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* spp. In MSM without HIV infection, enteritis is often attributable to *Giardia lamblia*.

Clinical Manifestations

Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or proctocolitis. Proctitis is more likely to cause tenesmus and constipation, whereas proctocolitis and enteritis more often cause diarrhea.

- HSV proctitis and LGV proctocolitis can cause severe pain, fever, and systemic manifestations.
- Sacral nerve root radiculopathy, with urinary retention or anal sphincter dysfunction, is associated with primary HSV infection.

Diagnosis

Pts should undergo anoscopy to examine the rectal mucosa and exudates and to obtain specimens for diagnosis.

http://internalmedicinebook.com

TABLE 83-1 CLINICAL FEATURES OF GENITAL ULCERS

Feature	Syphilis	Herpes	Chancroid	Lymphogranuloma Venereum	Donovanosis
Incubation period	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 months)
Early primary lesions	Papule	Vesicle	Pustule	Papule, pustule, or vesicle	Papule
No. of lesions	Usually one	Multiple	Usually multiple, may coalesce	Usually one; often not detected, despite lymphadenopathy	Variable
Diameter	5–15 mm	1–2 mm	Variable	2–10 mm	Variable
Edges	Sharply demarcated, elevated, round, or oval	Erythematous	Undermined, ragged, irregular	Elevated, round, or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth, nonpurulent, relatively nonvascular	Serous, erythematous, nonvascular	Purulent, bleeds easily	Variable, nonvascular	Red and velvety, bleeds readily
Induration	Firm	None	Soft	Occasionally firm	Firm
Pain	Uncommon	Frequently tender	Usually very tender	Variable	Uncommon
Lymphadenopathy	Firm, nontender, bilateral	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral	Tender, may suppurate, loculated, usually unilateral	None; pseudobuboes

Source: From RM Ballard, in KK Holmes et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

http://internalmedicinebook.com

TREATMENT PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, ENTERITIS

- Pending test results, pts should receive empirical treatment for gonorrhea and chlamydial infection with ceftriaxone (250 mg IM once) followed by doxycycline (100 mg bid for 7 days); therapy for syphilis or herpes should be given as indicated.
- If LGV proctitis is proven or suspected, doxycycline (100 mg PO bid for 21 days) should be given.

INDIVIDUAL PATHOGENS

GONORRHEA

Microbiology

N. gonorrhoeae, the causative agent of gonorrhea, is a gram-negative, nonmotile, non-spore-forming organism that grows singly and in pairs (i.e., as diplococci).

Epidemiology

The ~311,000 cases reported in the United States in 2012 probably represent only half the true number of cases because of underreporting, self-treatment, and nonspecific treatment without a laboratory diagnosis.

- 60% of reported cases in the United States occur in 15- to 19-year-old women and 20- to 24-year-old men.
- Gonorrhea is transmitted from males to females more efficiently than in the opposite direction, with 50–70% of women acquiring gonorrhea during a single unprotected sexual encounter with an infected man. Roughly two-thirds of all infected men are asymptomatic.
- Drug-resistant strains are widespread. Penicillin, ampicillin, and tetracycline are no longer reliable therapeutic agents, and oral cephalosporins and fluoroquinolones are no longer routinely recommended. In addition, strains highly resistant to ceftriaxone have been isolated in Japan and some European countries.

Clinical Manifestations

Except in disseminated disease, the sites of infection typically reflect areas involved in sexual contact.

- *Urethritis* and *cervicitis* have an incubation period of 2–7 days and ~10 days, respectively. See above for details.
- *Anorectal gonorrhea* can cause acute proctitis in women (due to the spread of cervical exudate to the rectum) and MSM.
- *Pharyngeal gonorrhea* is usually mild or asymptomatic and results from oral–genital sexual exposure (typically fellatio). Pharyngeal infection almost always coexists with genital infection, resolves spontaneously, and is rarely transmitted to sexual contacts.
- *Ocular gonorrhea* is typically caused by autoinoculation and presents as a markedly swollen eyelid, hyperemia, chemosis, and profuse purulent discharge.
- *Gonorrhea in pregnancy* can have serious consequences for both the mother and the infant.
  - Salpingitis and PID are associated with fetal loss.
  - Third-trimester disease can cause prolonged rupture of membranes, premature delivery, chorioamnionitis, funisitis, and neonatal sepsis.
  - *Ophthalmia neonatorum*, the most common form of gonorrhea among neonates, is preventable by prophylactic ophthalmic ointments (e.g., containing erythromycin or tetracycline), but treatment requires systemic antibiotics.
- *Gonococcal arthritis* results from dissemination of organisms due to gonococcal bacteremia. Pts present during a bacteremic phase (relatively uncommon) or with

http://internalmedicinebook.com

suppurative arthritis involving one or two joints (most commonly the knees, wrists, ankles, and elbows), with tenosynovitis and skin lesions. Menstruation and complement deficiencies of the membrane attack complex (C5–C9) are risk factors for disseminated disease.

Diagnosis

NAATs, culture, and microscopic examination (for intracellular diplococci) of urogenital samples are used to diagnose gonorrhea; NAAT of urine samples is most sensitive. A single culture of endocervical discharge has a sensitivity of 80–90%.

TREATMENT GONORRHEA

See Table 83-2.

TABLE 83-2 RECOMMENDED TREATMENT FOR GONOCOCCAL INFECTIONS: ADAPTED FROM THE 2010 GUIDELINES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION

Diagnosis	Treatment of Choice[a]
Uncomplicated gonococcal infection of the cervix, urethra, pharynx[b], or rectum	
First-line regimen	Ceftriaxone (250 mg IM, single dose) *plus* Treatment for *Chlamydia* if chlamydial infection is not ruled out: Azithromycin (1 g PO, single dose) *or* Doxycycline (100 mg PO bid for 7 days)
Alternative regimens[c]	Cefixime (400 mg PO, single dose) *or* Ceftizoxime (500 mg IM, single dose) *or* Cefotaxime (500 mg IM, single dose) *or* Spectinomycin (2 g IM, single dose)[d, e] *or* Cefotetan (1 g IM, single dose) *plus* probenecid (1 g PO, single dose)[d] *or* Cefoxitin (2 g IM, single dose) *plus* probenecid (1 g PO, single dose)[d]
Epididymitis	Ceftriaxone (250 mg IM once) *followed by* doxycycline (100 mg PO bid for 10 days) is effective for epididymitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*
Pelvic inflammatory disease	See **Chap. 163 in HPIM-19**
Outpatient	Ceftriaxone (250 mg IM once) *plus* Doxycycline (100 mg PO bid for 14 days) *plus* Metronidazole (500 mg PO bid for 14 days)

(*Continued*)

http://internalmedicinebook.com

TABLE 83-2 RECOMMENDED TREATMENT FOR GONOCOCCAL INFECTIONS: ADAPTED FROM THE 2010 GUIDELINES OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION (*CONTINUED*)

Diagnosis	Treatment of Choice[a]
Inpatient	Cefotetan (2 g IV q12h) or cefoxitin (2 g IV q6h) *plus* doxycycline (100 mg IV/PO q12h) *or* Clindamycin (900 mg IV q8h) *plus* gentamicin (loading dose of 2.0 mg/kg IV/IM followed by 1.5 mg/kg q8h)
Gonococcal conjunctivitis in an adult	Ceftriaxone (1 g IM, single dose)[f]
Ophthalmia neonatorum[g]	Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg)
Disseminated gonococcal infection[h]	
Initial therapy[i]	
Pt tolerant of β-lactam drugs	Ceftriaxone (1 g IM or IV q24h; recommended) *or* Cefotaxime (1 g IV q8h) *or* Ceftizoxime (1 g IV q8h)
Pts allergic to β-lactam drugs	Spectinomycin (2 g IM q12h)[d]
Continuation therapy[i]	Cefixime (400 mg PO bid)
Meningitis or endocarditis	Ceftriaxone (1–2 g IV bid) for 10–14 days (meningitis) or ≥4 weeks (endocarditis)[j]

[a]True failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis.
[b]Ceftriaxone is the only agent recommended for treatment of pharyngeal infection.
[c]Persons given an alternative regimen should return for a test of cure targeting the infected anatomic site, with a culture strongly preferred over a NAAT. All positive cultures for test of cure should undergo antimicrobial susceptibility testing.
[d]Spectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States.
[e]Spectinomycin may be ineffective for the treatment of pharyngeal gonorrhea.
[f]Plus lavage of the infected eye with saline solution (once).
[g]Ocular neonatal instillation of a prophylactic agent (e.g., 1% silver nitrate eye drops or ophthalmic preparations containing erythromycin or tetracycline) prevents ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics.
[h]Hospitalization is indicated if the diagnosis is uncertain, if the pt has frank arthritis with an effusion, or if the pt cannot be relied on to adhere to treatment.
[i]All initial regimens should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime or a quinolone) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week. Treatment for chlamydial infection (as above) should be given if this infection has not been ruled out.
[j]Hospitalization is indicated to exclude suspected meningitis or endocarditis.

http://internalmedicinebook.com

INFECTIONS WITH *CHLAMYDIA TRACHOMATIS*

Microbiology

C. trachomatis organisms are obligate intracellular bacteria that are divided into two biovars: trachoma and LGV. The trachoma biovar causes ocular trachoma and urogenital infections; the LGV biovar causes lymphogranuloma venereum.

Epidemiology

The World Health Organization (WHO) estimates that >106.4 million cases of *C. trachomatis* infection occur annually worldwide; it is the most prevalent of all bacterial STIs. The estimated 2–3 million cases per year that occur in the United States make *C. trachomatis* infection the most commonly reported infectious disease in this country.

Clinical Manifestations

80–90% of women and >50% of men with *C. trachomatis* genital infections lack symptoms; other pts have very mild symptoms.

- Urethritis, epididymitis, cervicitis, salpingitis, PID, and proctitis are all discussed above.
- Reactive arthritis (conjunctivitis, urethritis or cervicitis, arthritis, and mucocutaneous lesions) occurs in 1–2% of NGU cases, many of which are due to *C. trachomatis*. More than 80% of pts have the HLA-B27 phenotype.
- LGV is an invasive, systemic STI that—in heterosexual individuals—presents most commonly as painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure. Progressive periadenitis results in fluctuant, suppurative nodes with development of multiple draining fistulas. Spontaneous resolution occurs after several months. See Table 83-1 for additional clinical details.

Diagnosis

NAATs of urine or urogenital swabs are the diagnostic tests of choice. Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by *C. trachomatis*, but it is not useful in diagnosing uncomplicated urogenital infections.

TREATMENT **INFECTIONS WITH *CHLAMYDIA TRACHOMATIS***

- See "Specific Syndromes," above.
- LGV should be treated with doxycycline (100 mg PO bid) or erythromycin base (500 mg PO qid) for at least 3 weeks.

INFECTIONS DUE TO MYCOPLASMAS

Microbiology and Epidemiology

Mycoplasmas are the smallest free-living organisms known and lack a cell wall. *M. hominis*, *M. genitalium*, *Ureaplasma parvum*, and *U. urealyticum* cause urogenital tract disease. These organisms are commonly present in the vagina of asymptomatic women.

Clinical Manifestations

Ureaplasmas are a common cause of *Chlamydia*-negative NGU. *M. hominis* and *M. genitalium* are associated with PID; *M. hominis* is implicated in 5–10% of cases of postpartum or postabortal fever.

Diagnosis

PCR is most commonly used for detection of urogenital mycoplasmas; culture is possible but can be done primarily at reference laboratories. Serologic testing is not helpful.

http://internalmedicinebook.com

TREATMENT INFECTIONS DUE TO MYCOPLASMAS

Recommendations for treatment of NGU and PID listed above are appropriate for genital mycoplasmas.

SYPHILIS

Microbiology and Epidemiology

Treponema pallidum subspecies *pallidum*—the cause of syphilis—is a thin, spiral organism with a cell body surrounded by a trilaminar cytoplasmic membrane. Humans are the only natural host, and the organism cannot be cultured in vitro.

- Cases are acquired by sexual contact with infectious lesions (chancre, mucous patch, skin rash, condyloma latum); nonsexual acquisition through close personal contact, infection in utero, blood transfusion, and organ transplantation is less common.
- There are ~12 million new infections per year worldwide.
  - In the United States, 31,575 cases were reported in 2000.
  - The reported cases of primary and secondary syphilis combined (which better indicate disease activity) increased from <6000 in 2000 to >14,000 in 2012, primarily affecting MSM, 20–70% of whom were co-infected with HIV.
- One-third to one-half of sexual contacts of persons with infectious syphilis become infected—a figure that underscores the importance of treating all recently exposed sexual contacts.

Pathogenesis

T. pallidum penetrates intact mucous membranes or microscopic abrasions and, within hours, enters lymphatics and blood to produce systemic infection and metastatic foci. After a median incubation period of ~21 days (range, 2–6 weeks), the primary lesion (chancre) appears at the site of inoculation, persists for 4–6 weeks, and then heals spontaneously. Generalized parenchymal, constitutional, and mucocutaneous manifestations of secondary syphilis appear 6–8 weeks later despite high antibody titers, subsiding in 2–6 weeks. After a latent period, one-third of untreated pts eventually develop tertiary disease (syphilitic gummas, cardiovascular disease, neurologic disease).

Clinical Manifestations

Syphilis progresses through three phases with distinct clinical presentations.

- *Primary syphilis:* A chancre at the site of inoculation (penis, rectum or anal canal, mouth, cervix, labia) is characteristic but often goes unnoticed. See Table 83-1 for clinical details. Regional adenopathy can persist long after the chancre heals.
- *Secondary syphilis:* The protean manifestations of the secondary stage usually include mucocutaneous lesions and generalized nontender lymphadenopathy.
  - Skin lesions can be subtle but are often pale red or pink, nonpruritic macules that are widely distributed over the trunk and extremities, including the palms and soles.
  - In moist intertriginous areas, papules can enlarge and erode to produce broad, highly infectious lesions called *condylomata lata*.
  - Superficial mucosal erosions (*mucous patches*) and constitutional symptoms (e.g., sore throat, fever, malaise) can occur.
  - Less common findings include hepatitis, nephropathy, arthritis, and ocular findings (e.g., optic neuritis, anterior uveitis, iritis).
- *Latent syphilis:* Pts without clinical manifestations but with positive syphilis serology have latent disease. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥1 year's (or unknown) duration.

http://internalmedicinebook.com

- *Tertiary syphilis:* The classic forms of tertiary syphilis include neurosyphilis, cardiovascular syphilis, and gummas.
  - *Neurosyphilis* represents a continuum, with asymptomatic disease occurring early after infection and potentially progressing to general paresis and tabes dorsalis. Symptomatic disease has three main presentations, all of which are now rare (except in pts with advanced HIV infection). *Meningeal* syphilis presents as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status within 1 year of infection. *Meningovascular* syphilis presents up to 10 years after infection as a subacute encephalitic prodrome followed by a gradually progressive vascular syndrome. *Parenchymatous* involvement presents at 20 years for general paresis and 25–30 years for tabes dorsalis. A general mnemonic for paresis is *p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (Argyll Robertson pupils, which react to accommodation but not to light), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (decrease in recent memory and orientation, judgment, calculations, insight), and *s*peech. Tabes dorsalis is a demyelination of posterior columns, dorsal roots, and dorsal root ganglia, with ataxic, wide-based gait and footslap; paresthesia; bladder disturbances; impotence; areflexia; and loss of position, deep pain, and temperature sensations.
  - *Cardiovascular syphilis* develops in ~10% of untreated pts 10–40 years after infection. Endarteritis obliterans of the vasa vasorum providing the blood supply to large vessels results in aortitis, aortic regurgitation, saccular aneurysm, and coronary ostial stenosis.
  - *Gummas* are usually solitary lesions showing granulomatous inflammation with central necrosis. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved.
- *Congenital syphilis:* Syphilis can be transmitted throughout pregnancy, but fetal disease does not become manifest until after the fourth month of gestation. All pregnant women should be tested for syphilis early in pregnancy.

Diagnosis

Serologic tests—both nontreponemal and treponemal—are the mainstays of diagnosis; changes in antibody titers can also be used to monitor response to therapy.

- Nontreponemal serologic tests that measure IgG and IgM antibodies to a cardiolipin–lecithin–cholesterol antigen complex (e.g., rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) are recommended for screening or for quantitation of serum antibody. After therapy for early syphilis, a persistent fall in titer by ≥4-fold is considered an adequate response.
- Treponemal tests, including the agglutination assay (e.g., the Serodia TP-PA test), the fluorescent treponemal antibody–absorbed (FTA-ABS) test, and treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), are used to confirm results from nontreponemal tests and should not be used as a screening test because of high false-positive rates. Results remain positive even after successful treatment.
- LP is recommended for pts with syphilis and neurologic signs or symptoms, an RPR or VDRL titer ≥1:32, or suspected treatment failure and for HIV-infected pts with a $CD4^+$ T cell count <350/μL.
  - CSF exam demonstrates pleocytosis (>5 WBCs/μL) and increased protein levels (>45 mg/dL). A positive CSF VDRL test is specific but not sensitive; an unabsorbed FTA test is sensitive but not specific. A negative unabsorbed FTA test excludes neurosyphilis.
- Pts with syphilis should be evaluated for HIV disease.

TREATMENT SYPHILIS

- See **Table 83-3** for treatment recommendations.
- The Jarisch-Herxheimer reaction is a dramatic reaction to treatment that is most common with initiation of therapy for primary (~50% of pts) or secondary

http://internalmedicinebook.com

TABLE 83-3 RECOMMENDATIONS FOR THE TREATMENT OF SYPHILIS[a]

Stage of Syphilis	Patients without Penicillin Allergy	Patients with Confirmed Penicillin Allergy[b]
Primary, secondary, or early latent	*CSF normal or not examined:* Penicillin G benzathine (single dose of 2.4 mU IM) *CSF abnormal:* Treat as neurosyphilis	*CSF normal or not examined:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks *CSF abnormal:* Treat as neurosyphilis
Late latent (or latent of uncertain duration), cardiovascular, or benign tertiary	*CSF normal or not examined:* Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) *CSF abnormal:* Treat as neurosyphilis	*CSF normal and pt not infected with HIV:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks *CSF normal and pt infected with HIV:* Desensitization and treatment with penicillin if compliance cannot be ensured *CSF abnormal:* Treat as neurosyphilis
Neurosyphilis (asymptomatic or symptomatic)	Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days *or* Aqueous procaine penicillin G (2.4 mU/d IM) *plus* oral probenecid (500 mg qid), both for 10–14 days	Desensitization and treatment with penicillin[c]
Syphilis in pregnancy	According to stage	Desensitization and treatment with penicillin

[a]See text for indications for CSF examination.
[b]Because of the documented presence of macrolide resistance in many *T. pallidum* strains in North America, Europe, and China, azithromycin or other macrolides should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used for men who have sex with men or for pregnant women.
[c]Limited data suggest that ceftriaxone (2 g/d either IM or IV for 10–14 days) can be used; however, cross-reactivity between penicillin and ceftriaxone is possible.
Abbreviations: mU, million units.
Source: Adapted from the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

(~90%) syphilis. The reaction is associated with fever, chills, myalgias, tachycardia, headache, tachypnea, and vasodilation. Symptoms subside within 12–24 h without treatment.

- Response to treatment should be monitored by determination of RPR or VDRL titers at 6 and 12 months in primary and secondary syphilis and at 6, 12, and 24 months in tertiary or latent syphilis.

http://internalmedicinebook.com

– HIV-infected pts should undergo repeat serologic testing at 3, 6, 9, 12, and 24 months, irrespective of the stage of syphilis.
– Re-treatment should be considered if serologic responses are not adequate (a persistent antibody fall by ≥4-fold) or if clinical signs persist or recur. For these pts, CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal.
– In treated neurosyphilis, CSF cell counts should be monitored every 6 months until normal. In adequately treated HIV-uninfected pts, an elevated CSF cell count falls to normal in 3–12 months.

HERPES SIMPLEX VIRUS INFECTIONS

Microbiology and Epidemiology

HSV is a linear, double-strand DNA virus, with two subtypes (HSV-1 and HSV-2).

- Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry into cells of the epidermis and dermis, viral replication, entry into neuronal cells, and centrifugal spread throughout the body.
- More than 90% of adults have antibodies to HSV-1 by age 40; 15–20% of the U.S. population has antibodies to HSV-2, with a higher prevalence in low-income countries.
- Unrecognized carriage of HSV-2 and frequent asymptomatic reactivations of virus from the genital tract foster the continued spread of HSV disease.
- Genital lesions caused by HSV-1 have lower recurrence rates in the first year (~55%) than those caused by HSV-2 (~90%).

Clinical Manifestations

See Table 83-1 for clinical details. First episodes of genital herpes due to HSV-1 and HSV-2 present similarly and can be associated with fever, headache, malaise, and myalgias. More than 80% of women with primary genital herpes have cervical or urethral involvement. Local symptoms include pain, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy.

Diagnosis

Isolation of HSV in tissue culture or demonstration of HSV antigens or DNA in scrapings from lesions is the most accurate diagnostic method. PCR is increasingly being used for detection of HSV DNA and is more sensitive than culture at mucosal sites. Staining of scrapings from the base of the lesion with Wright's, Giemsa's (Tzanck preparation), or Papanicolaou's stain to detect giant cells or intranuclear inclusions is well described, but most clinicians are not skilled in these techniques, which furthermore do not differentiate between HSV and VZV.

TREATMENT HSV GENITAL INFECTIONS

- *First episodes*: Oral acyclovir (400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective.
- *Symptomatic recurrent episodes*: Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, 1500 mg once, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration.
- *Suppression of recurrent episodes*: Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg qd) is given. Pts with >9 episodes per year should take valacyclovir (1 g qd or 500 mg bid) or famciclovir (250–500 mg bid). Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir.

http://internalmedicinebook.com

CHANCROID (*HAEMOPHILUS DUCREYI* INFECTION)

H. ducreyi is the etiologic agent of chancroid, an STI characterized by genital ulceration and inguinal adenitis. In addition to being a cause of morbidity in itself, chancroid increases the efficiency of transmission of and degree of susceptibility to HIV infection. See Table 83-1 for clinical details. Culture of *H. ducreyi* from the lesion confirms the diagnosis; PCR is starting to become available. In the setting of a compatible clinical presentation (including one or more painful genital ulcers) and negative tests for syphilis and HSV infection, a probable diagnosis of chancroid can be made.

TREATMENT CHANCROID (*HAEMOPHILUS DUCREYI* INFECTION)

- Regimens recommended by the Centers for Disease Control and Prevention (CDC) include azithromycin (1 g PO once), ciprofloxacin (500 mg PO bid for 3 days), ceftriaxone (250 mg IM once), and erythromycin base (500 mg tid for 1 week).
- Sexual partners within 10 days preceding the pt's onset of symptoms should be identified and treated, regardless of symptoms.

DONOVANOSIS (*KLEBSIELLA GRANULOMATIS* INFECTION)

Microbiology and Epidemiology

Also known as *granuloma inguinale*, donovanosis is caused by *K. granulomatis*. The infection is endemic in Papua New Guinea, parts of southern Africa, India, the Caribbean, French Guyana, Brazil, and Aboriginal communities in Australia; few cases are reported in the United States.

Clinical Manifestations

See Table 83-1 for clinical details. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue. The genitals are affected in 90% of pts and the inguinal region in 10%.

Diagnosis and Treatment

Diagnosis is often based on identification of typical Donovan bodies (gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance) within large mononuclear cells in smears from lesions or biopsy specimens. PCR is also available.

TREATMENT DONOVANOSIS (*KLEBSIELLA GRANULOMATIS* INFECTION)

Pts should be treated with azithromycin (1 g on day 1, then 500 mg qd for 7 days or 1 g weekly for 4 weeks); alternative therapy consists of a 14-day course of doxycycline (100 mg bid), trimethoprim-sulfamethoxazole (960 mg bid), erythromycin (500 mg qid), or tetracycline (500 mg qid). If any of the 14-day treatment regimens are chosen, the pt should be monitored until lesions have healed completely.

HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

Microbiology

Papillomaviruses are nonenveloped, double-strand DNA viruses. More than 125 HPV types are recognized, and individual types are associated with specific clinical manifestations. For example, HPV types 16 and 18 have been most strongly associated with cervical and anal cancers, causing 70–85% and ~90% of cases, respectively; HPV types 6 and 11 cause genital warts (*condylomata acuminata*).

http://internalmedicinebook.com

Epidemiology and Clinical Manifestations

- HPV is transmitted by sexual intercourse, by oral sex, and possibly by touching of a partner's genitalia.
- The interval between initial infection and the diagnosis of HPV-associated cancer may be >20 years, with HIV infection accelerating this progression.
- The physical appearance of warts varies with their anatomic location, ranging from soft, whitish papules on the vulva to raised, keratotic, pigmented plaques on the penis.
- Although subclinical cervical HPV infections are common, pts with cervical cancer present early on with eroded carcinomas that bleed easily; more advanced carcinomas present as ulcerated lesions or as an exophytic lesion.
- Anal cancer typically presents as rectal bleeding and pain or a mass sensation, although 20% of pts are asymptomatic.

Diagnosis

Most visible warts are diagnosed correctly by history and physical examination alone. The primary method used for cervical cancer screening is cytology via Pap smear every 3 years beginning at age 21; for women ≥30 years of age, the testing interval can be lengthened to 5 years if co-testing for HPV DNA is negative. There is no clear consensus regarding screening for anal cancer.

TREATMENT HUMAN PAPILLOMAVIRUS INFECTIONS

- Many lesions resolve spontaneously. Current treatment is not completely effective, and some agents have significant side effects.
- Provider-administered therapy can include cryotherapy, surgical excision, intralesionally administered interferon, or laser surgery.
- Pt-administered therapy consists of podophyllotoxin (0.05% solution or gel or 0.15% cream applied bid for 3 days; can be repeated up to 4 times with 4 days between treatment courses); imiquimod (5% or 3.75% cream applied 3 times per week for up to 16 weeks); and sinecatechins (15% ointment applied tid for up to 4 months).

Prevention

- A quadrivalent vaccine (Gardasil, Merck) containing HPV types 6, 11, 16, and 18 and a bivalent vaccine (Cervarix, GlaxoSmithKline) containing HPV types 16 and 18 are available. The CDC recommends administration of the quadrivalent vaccine to all boys and girls at 11–12 years of age as well as to young men and women 13–26 years of age who have not previously completed the full series.



For a more detailed discussion, see Marrazzo JM, Holmes KK: Sexually Transmitted Infections: Overview and Clinical Approach, Chap. 163, p. 869; Ram S, Rice PA: Gonococcal Infections, Chap. 181, p. 1003; Murphy TF: *Haemophilus* and *Moraxella* Infections, Chap. 182, p. 1010; O'Farrell N: Donovanosis, Chap. 198e; Lukehart SA: Syphilis, Chap. 206, p. 1132; Hardy RD: Infections Due to Mycoplasmas, Chap. 212, p. 1163; Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165; Corey L: Herpes Simplex Virus Infections, Chap. 216, p. 1175; and Ermel AC, Brown DR: Human Papillomavirus Infections, Chap. 222, p. 1197, in HPIM-19.

http://internalmedicinebook.com

84 Infections of the Skin, Soft Tissues, Joints, and Bones

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections are diagnosed principally by a careful history (e.g., temporal progression, travel, animal exposure, bites, trauma, underlying medical conditions) and physical examination (appearance of lesions and distribution). Treatment of common skin infections is summarized in Table 84-1; parenteral treatment is

TABLE 84-1 TREATMENT OF COMMON INFECTIONS OF THE SKIN

Diagnosis/ Condition	Primary Treatment	Alternative Treatment	See Also Chap(s).
Animal bite (prophylaxis or early infection)[a]	Amoxicillin/ clavulanate, 875/ 125 mg PO bid	Doxycycline, 100 mg PO bid	27
Animal bite[a] (established infection)	Ampicillin/sulbactam, 1.5–3 g IV q6h	Clindamycin, 600–900 mg IV q8h, *plus* Ciprofloxacin, 400 mg IV q12h, *or* cefoxitin, 2 g IV q6h	27
Bacillary angiomatosis	Erythromycin, 500 mg PO qid	Doxycycline, 100 mg PO bid	91
Herpes simplex (primary genital)	Acyclovir, 400 mg PO tid for 10 days	Famciclovir, 250 mg PO tid for 5–10 days, *or* Valacyclovir, 1000 mg PO bid for 10 days	99
Herpes zoster (immunocompetent host >50 years of age)	Acyclovir, 800 mg PO 5 times daily for 7–10 days	Famciclovir, 500 mg PO tid for 7–10 days, *or* Valacyclovir, 1000 mg PO tid for 7 days	99
Cellulitis (staphylococcal or streptococcal[b,c])	Nafcillin or oxacillin, 2 g IV q4–6h	Cefazolin, 1–2 g q8h, *or* Ampicillin/sulbactam, 1.5–3 g IV q6h, *or* Erythromycin, 0.5–1 g IV q6h, *or* Clindamycin, 600–900 mg IV q8h	86, 87

(*Continued*)

http://internalmedicinebook.com

TABLE 84-1 TREATMENT OF COMMON INFECTIONS OF THE SKIN (*CONTINUED*)

Diagnosis/ Condition	Primary Treatment	Alternative Treatment	See Also Chap(s).
MRSA skin infection[d]	Vancomycin, 1 g IV q12h	Linezolid, 600 mg IV q12h	86
Necrotizing fasciitis (group A streptococcal[b])	Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4h	Clindamycin, 600–900 mg IV q6–8h, *plus* Cephalosporin (first- or second-generation)	87
Necrotizing fasciitis (mixed aerobes and anaerobes)	Ampicillin, 2 g IV q4h, *plus* Clindamycin, 600–900 mg IV q6–8h, *plus* Ciprofloxacin, 400 mg IV q6–8h	Vancomycin, 1 g IV q6h, *plus* Metronidazole, 500 mg IV q6h, *plus* Ciprofloxacin, 400 mg IV q6–8h	92
Gas gangrene	Clindamycin, 600–900 mg IV q6–8h, *plus* Penicillin G, 4 million units IV q4–6h	Clindamycin, 600–900 mg IV q6–8h, *plus* Cefoxitin, 2 g IV q6h	92

[a]*Pasteurella multocida*, a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones.
[b]The frequency of erythromycin resistance in group A *Streptococcus* is currently ~5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin. Approximately 90% of *Staphylococcus aureus* strains are sensitive to clindamycin, but resistance—both intrinsic and inducible—is increasing.
[c]Severe hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the β-lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring a switch to vancomycin, daptomycin, or linezolid.
[d]Some strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) is an alternative treatment for MRSA.

usually given until systemic signs and symptoms have improved. Types of skin lesions include the following:

1. *Vesicles:* due to proliferation of organisms, usually viruses, within the epidermis (e.g., VZV, HSV, coxsackievirus, poxviruses, *Rickettsia akari*)
2. *Bullae:* caused by toxin-producing organisms. Different entities affect different skin levels. For example, staphylococcal scalded-skin syndrome and toxic epidermal necrolysis cause cleavage of the stratum corneum and the stratum

http://internalmedicinebook.com

germinativum, respectively. Bullae are also seen in necrotizing fasciitis, gas gangrene, and *Vibrio vulnificus* infections.

3. *Crusted lesions:* Impetigo caused by either *Streptococcus pyogenes* (impetigo contagiosa) or *Staphylococcus aureus* (bullous impetigo) usually starts with a bullous phase before development of a golden-brown crust. Crusted lesions are also seen in some systemic fungal infections, dermatophytic infections, and cutaneous mycobacterial infections. It is important to recognize impetigo contagiosa because of its relation to poststreptococcal glomerulonephritis.
4. *Folliculitis:* Localized infection of hair follicles is usually due to *S. aureus*. "Hot-tub folliculitis" is a diffuse condition caused by *Pseudomonas aeruginosa*. Freshwater avian schistosomes cause an allergic reaction after penetrating hair follicles, resulting in "swimmer's itch."
5. *Papular and nodular lesions:* Raised lesions of the skin occur in many different forms and can be caused by *Bartonella henselae* (cat-scratch disease and bacillary angiomatosis), *Treponema pallidum*, human papillomavirus, mycobacteria, and helminths.
6. *Ulcers, with or without eschars:* can be caused by cutaneous anthrax, ulceroglandular tularemia, plague, and mycobacterial infection. Ulcerated lesions on the genitals can be caused by chancroid (painful) or syphilis (painless).
7. *Erysipelas*: abrupt onset of fiery red swelling of the face or extremities, with well-defined indurated margins, intense pain, and rapid progression. *S. pyogenes* is the exclusive cause.

CELLULITIS

- *Pathogenesis:* Bacteria gain access to the epidermis through breaks in the skin, whether accidental (e.g., cuts, scratches, burns) or iatrogenic (e.g., surgical incisions, IV catheters). The expanding area of erythema may be due to extracellular toxins and/or the host immune response rather than to increasing bacterial numbers.
- *Microbiology:* Etiologic causes include commensal flora (e.g., *S. aureus*, *S. pyogenes*) or a wide variety of exogenous flora. With the latter, a thorough history and epidemiologic data may help identify the cause.
  - Examples of exogenous bacteria causing cellulitis include the following: *Pasteurella multocida* after a cat or dog bite; *Capnocytophaga canimorsus* after a dog bite; *Eikenella corrodens* after a human bite; *P. aeruginosa* in association with ecthyma gangrenosum in neutropenic pts, a penetrating injury (stepping on a nail), or hot-tub folliculitis; *Aeromonas hydrophila* after a laceration sustained in fresh water; or *Erysipelothrix rhusiopathiae* after contact with domestic swine and fish.
- *Clinical manifestations:* This acute inflammatory condition of the skin is characterized by localized pain, erythema, swelling, and heat.
  - Cellulitis due to *S. aureus* often spreads from a central site of localized infection, such as an abscess or an infected foreign body, and is referred to as "purulent cellulitis."
  - *S. pyogenes* can cause nonpurulent cellulitis, a rapidly spreading, diffuse process that often occurs with fever and lymphangitis.
- *Diagnosis:* If there is drainage, an open wound, or an obvious portal of entry, Gram's staining and culture may identify the etiology. Aspiration or biopsy of the leading edge of the cellulitic tissue yields a diagnosis in only 20% of cases.
- *Treatment:* See Table 84-1.

NECROTIZING FASCIITIS

- *Pathogenesis:* Infection, either apparent or inapparent, results from a breach in integrity of the skin or mucous membrane barriers and can be associated with malignancy, a diverticulum, hemorrhoids, or an anal fissure.

http://internalmedicinebook.com

  - In the case of infections with no obvious portal of entry, transient bacteremia is thought to seed sites of nonpenetrating trauma (e.g., bruise, muscle strain).
  - Infection spreads to the deep fascia and along fascial planes through venous channels and lymphatics.
- *Microbiology:* Necrotizing fasciitis is caused by *S. pyogenes*, mixed aerobic and anaerobic bacteria, or *Clostridium perfringens*; methicillin-resistant *S. aureus* (MRSA) strains that produce the Panton-Valentine leukocidin have also been reported as an occasional cause.
- *Clinical manifestations:* The timing of cutaneous manifestations (e.g., violaceous bullae; friable, necrotic skin; induration; brawny edema) depends on whether the infection began superficially (rapid onset) or in deeper structures (slower onset).
  - Early in the disease course, severe pain and unexplained fever may be the only findings.
  - Thrombosis of blood vessels in dermal papillae leads to ischemia of peripheral nerves and anesthesia of the affected area.
  - In later stages, pts appear toxic and often develop shock and multiorgan failure.
- *Diagnosis:* Diagnosis is based on clinical presentation. Other findings may include gas detected in deep tissues by imaging studies (particularly with clostridial species but rarely with *S. pyogenes*) and markedly elevated serum CPK levels (in the case of concomitant myositis).
- *Treatment:* Emergent surgical exploration to deep fascia and muscle, with removal of necrotic tissue, is essential. Table 84-1 provides recommendations for adjunctive antibiotic therapy.

MYOSITIS/MYONECROSIS

- *Clinical manifestations and microbiology:* Infections involving the muscle have differing manifestations, depending on the etiology.
  - *Myositis:* can be caused by bacteria (clostridia, streptococci), viruses (influenza virus, dengue virus, coxsackievirus), or parasites (*Trichinella*, *Taenia solium*, *Toxoplasma*). This condition usually manifests with myalgias, but pain can be severe in coxsackievirus, *Trichinella*, and bacterial infections.
  - *Pyomyositis:* a localized muscle infection usually due to *S. aureus*, common in tropical areas, and typically with no known portal of entry
  - *Myonecrosis:* can be caused by clostridial species (*C. perfringens*, *C. septicum*, *C. histolyticum*, *C. sordellii*) or by mixed aerobic and anaerobic bacteria. Myonecrosis is usually related to trauma; however, spontaneous gangrene—usually due to *C. septicum*—can occur in pts with neutropenia, GI malignancy, or diverticulosis. Myonecrosis of the uterus, typically due to *C. sordellii*, occurs in women after spontaneous or medically induced abortion and in healthy postpartum women; infection is rapidly and almost uniformly fatal as there are few or no localizing clinical findings.
- *Diagnosis and Treatment:* Emergent surgical intervention to visualize deep structures, obtain materials for culture and sensitivity testing, remove necrotic tissue, and reduce compartment pressure is both diagnostic and therapeutic.
  - Empirical antibiotic treatment should target likely etiologies—e.g., vancomycin (1 g IV q12h) for pyomyositis and ampicillin/sulbactam (2–3 g IV q6h) for mixed aerobic–anaerobic infections.
  - For treatment of clostridial myonecrosis (gas gangrene), see Table 84-1.

INFECTIOUS ARTHRITIS

- *Pathogenesis:* Joints become infected by hematogenous seeding (the most common route), by spread from a contiguous site of infection, or by direct inoculation (e.g., during trauma or surgery). Acute bacterial infection can rapidly destroy articular cartilage as a result of increased intraarticular pressure and the elicited host immune response.

http://internalmedicinebook.com

- *Microbiology:* The predominant etiologic agents differ with the pt's age; *S. aureus* is the most common nongonococcal isolate in adults of all ages.
  - In children <5 years old, *S. aureus*, *S. pyogenes*, and *Kingella kingae* predominate.
  - In young adults, *Neisseria gonorrhoeae* is the most common etiology.
  - In adults, *S. aureus* predominates, but gram-negative bacilli, pneumococci, and β-hemolytic streptococci are involved in one-third of cases in older adults.
  - Other causes of septic arthritis include *Borrelia burgdorferi* (Lyme disease), tuberculosis and other mycobacterial infections, fungal infections (e.g., coccidioidomycosis, histoplasmosis), and viral infections (e.g., rubella, mumps, hepatitis B, parvovirus infection).
- *Epidemiology and clinical manifestations:* The risk factors and presentation differ depending on whether *N. gonorrhoeae* is the cause.
  - *Nongonococcal bacterial arthritis:* Risk is increased in pts with rheumatoid arthritis, diabetes mellitus, glucocorticoid therapy, hemodialysis, malignancy, and IV drug use.
    - In 90% of pts, one joint is involved—most often the knee, which is followed in frequency by the hip, shoulder, wrist, and elbow; IV drug users often have spinal, sacroiliac, or sternoclavicular joint involvement.
    - Pts have moderate to severe pain, effusion, decreased range of motion, and fever.
  - *Gonococcal arthritis:* Women are 2–3 times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis, particularly during menses and during pregnancy (see Chap. 83).
    - DGI presents as fever, chills, rash, and articular symptoms (migratory arthritis). The cutaneous and articular findings result from an immune reaction to circulating gonococci and immune-complex deposition; thus synovial fluid cultures are consistently negative.
    - In true gonococcal arthritis (which always follows DGI), a single joint (hip, knee, ankle, or wrist) is usually involved.
  - *Prosthetic joint infections:* complicate 1–4% of joint replacements and are usually acquired intra- or perioperatively
    - Acute presentations are seen in infections caused by *S. aureus*, pyogenic streptococci, and enteric bacilli.
    - Indolent presentations are seen in infections caused by coagulase-negative staphylococci and diphtheroids.
  - *Reactive arthritis:* follows ~1% of cases of nongonococcal urethritis and 2% of enteric infections (e.g., *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, *Salmonella* spp.). Only a minority of pts have the other classic findings associated with reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash.
- *Diagnosis:* If there is concern about joint infection, examination of synovial fluid from the affected joint is essential. There is considerable overlap in the cell counts due to different etiologies, but synovial fluid culture and examination for crystals (to rule out gout and pseudogout) can help narrow the diagnosis.
  - *Normal* synovial fluid contains <180 cells (mostly mononuclear)/μL. *Acute bacterial infection* of joints results in synovial fluid cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% PMNs. Synovial fluid in *gonococcal arthritis* contains >50,000 cells/μL, but results of Gram's staining are usually negative, and cultures of synovial fluid are positive in <40% of cases. Other mucosal sites should be cultured to diagnose gonorrhea. Pts with septic arthritis due to *mycobacteria* or *fungi* can have 10,000–30,000 cells/μL in synovial fluid, with 50–70% PMNs. Synovial fluid cell counts in *noninfectious inflammatory arthritides* are typically <30,000–50,000/μL.
  - Gram's staining of synovial fluid should be performed. Injection directly into blood culture bottles can increase the yield of synovial fluid cultures.
  - Blood cultures are positive in 50–70% of cases due to *S. aureus* but are less commonly positive with other organisms.

http://internalmedicinebook.com

– Plain radiographs show soft tissue swelling, joint space widening, and displacement of tissue planes by distended capsule. Narrowing of the joint space and bony erosions suggest advanced disease.

TREATMENT INFECTIOUS ARTHRITIS

- Drainage of pus and necrotic debris is needed to cure infection and to prevent destruction of cartilage, postinfectious degenerative arthritis, and joint deformity or instability.
- A third-generation cephalosporin (cefotaxime, 1 g IV q8h; or ceftriaxone, 1–2 g IV q24h) provides adequate empirical coverage for most community-acquired infections in adults when smears demonstrate no organisms. Vancomycin (1 g IV q12h) should be used to cover the possibility of MRSA when there are gram-positive cocci on the smear.
  – In IV drug users and other susceptible pts, treatment for gram-negative organisms such as *P. aeruginosa* should be considered.
  – If a pathogen is identified by culture, treatment should be adjusted according to the specific bacterial organism and its antibiotic susceptibility.
- Treatment for *S. aureus* should be given for 4 weeks, that for enteric gram-negative bacilli for 3–4 weeks, and that for pneumococci or streptococci for 2 weeks. Treatment for gonococcal arthritis should commence with ceftriaxone (1 g/d) until improvement; depending on the susceptibilities of the isolate, the 7-day course can be completed with an oral fluoroquinolone (e.g., ciprofloxacin, 500 mg bid) or amoxicillin (500 mg tid).
- Prosthetic joint infections should be treated with surgery and high-dose IV antibiotics for 4–6 weeks. The prosthesis often has to be removed; to avoid joint removal, antibiotic suppression of infection may be tried. A 3- to 6-month course of ciprofloxacin and rifampin has been successful in *S. aureus* prosthetic-joint infections of relatively short duration, although prospective trials confirming the efficacy of this regimen are still needed.

OSTEOMYELITIS

- *Pathogenesis and epidemiology:* Osteomyelitis cases can be classified by pathogenesis, duration of infection, location of infection, and whether prosthetic material is present. Osteomyelitis is typically caused by hematogenous spread, spread from a contiguous site following surgery, and/or secondary infection in the setting of vascular insufficiency or concomitant neuropathy (e.g., in diabetes). The most common primary foci of infection are the urinary tract, skin and soft tissues, intravascular catheterization sites, and the endocardium. Hematogenous osteomyelitis in adults most commonly results in vertebral infection, with 6.5 cases/100,000 at ages >70 years.
- *Microbiology:* Irrespective of the anatomic location involved, *S. aureus* is the most common cause, accounting for ~40–50% of cases.
  – Gram-negative bacilli account for 10–20% of cases.
- *Clinical manifestations:* Pts generally have a febrile illness, with localized pain and tenderness. A history of surgery or trauma in the affected region—even in the remote past—should raise suspicion.
- *Diagnosis:* Radiographic studies and occasionally invasive sampling of lesions are needed to confirm the diagnosis.
  – Blood cultures are positive in 30–78% of cases, with lower rates if the pt has previously received antibiotics.
  – CT and especially MRI scans offer increased sensitivity in detecting osteomyelitis.
- *Treatment:* Table 84-2 lists antibiotics for the treatment of osteomyelitis in the absence of implants.

http://internalmedicinebook.com

TABLE 84-2 ANTIBIOTIC THERAPY FOR OSTEOMYELITIS IN ADULTS WITHOUT IMPLANTS[a]

Microorganism	Antimicrobial Agent (Dose,[b] Route)
Staphylococcus spp.	
Methicillin-susceptible	Nafcillin *or* oxacillin[c] (2 g IV q6h) ***followed by*** Rifampin (300–450 mg PO q12h) *plus* levofloxacin (750 mg PO q24h or 500 mg PO q12h)
Methicillin-resistant	Vancomycin[d] (15 mg/kg IV q12h) *or* daptomycin (>6–8 mg/kg IV q24h) ***followed by*** Rifampin (300–450 mg PO q12h) ***plus*** Levofloxacin (750 mg PO q24h or 500 mg PO q12h) *or* TMP-SMX[e] (1 double-strength tablet PO q8h) *or* fusidic acid (500 mg PO q8h)
Streptococcus spp.	Penicillin G[c] (5 million units IV q6h) *or* ceftriaxone (2 g IV q24h)
Enterobacteriaceae	
Quinolone-susceptible	Ciprofloxacin (750 mg PO q24h)
Quinolone-resistant[f]	Imipenem (500 mg IV q6h)
Pseudomonas aeruginosa	Cefepime *or* ceftazidime (2 g IV q8h) *plus* an aminoglycoside[g] ***or*** Piperacillin-tazobactam (4.5 g IV q8h) *plus* an aminoglycoside[g] for 2–4 weeks ***followed by*** Ciprofloxacin[h] (750 mg PO q12h)
Anaerobes	Clindamycin (600 mg IV q6–8h) for 2–4 weeks ***followed by*** Clindamycin[i] (300 mg PO q6h)

[a]Unless otherwise indicated, the total duration of antimicrobial treatment is generally 6 weeks.
[b]All dosages are for adults with normal renal function.
[c]When the pt has delayed-type penicillin hypersensitivity, cefuroxime (1.5 g IV q6–8h) can be administered. When the pt has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h).
[d]Target vancomycin trough level: 15–20 μg/mL.
[e]Trimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole.
[f]Including isolates producing extended-spectrum β-lactamase.
[g]The need for addition of an aminoglycoside has not yet been proven. However, this addition may decrease the risk of emergence of resistance to the β-lactam.
[h]The rationale for starting ciprofloxacin treatment only after pretreatment with a β-lactam is the increased risk of emergence of quinolone resistance in the presence of a heavy bacterial load.
[i]Alternatively, penicillin G (5 million units IV q6h) or ceftriaxone (2 g IV q24h) can be used against gram-positive anaerobes (e.g., *Propionibacterium acnes*), and metronidazole (500 mg IV/PO q8h) can be used against gram-negative anaerobes (e.g., *Bacteroides* spp.).
Source: From W Zimmerli: *N Engl J Med* 362:1022, 2010. © Massachusetts Medical Society. Reprinted with permission.

http://internalmedicinebook.com

– The optimal route and duration of therapy remain controversial, but a 6-week course of IV therapy is usually recommended for acute osteomyelitis. If evidence indicates clinical efficacy of an oral antibiotic to which the organism is susceptible and if the pt has normal intestinal function (without vomiting), a transition from IV to PO therapy can be considered.
– Serial measurements of inflammatory markers (ESR, C-reactive protein) can serve as surrogates for response to treatment in some infections (particularly those due to *S. aureus*).
– Surgical intervention is usually required in chronic osteomyelitis and cases involving prosthetic implants.



For a more detailed discussion, see Stevens DL: Infections of the Skin, Muscles, and Soft Tissues, Chap. 156, p. 827; Madoff LC: Infectious Arthritis, Chap. 157, p. 833; and Zimmerli W: Osteomyelitis, Chap. 158, p. 838, in HPIM-19.

85 Pneumococcal Infections

MICROBIOLOGY

- *Streptococcus pneumoniae* (the pneumococcus) is a gram-positive coccus that grows in chains, causes α-hemolysis on blood agar, is bile soluble, and is sensitive to optochin.
- Nearly every clinical isolate has a polysaccharide capsule that protects the bacteria from phagocytosis in the absence of type-specific antibody; 93 distinct capsules have been identified.

EPIDEMIOLOGY

- In industrialized countries, children serve as the major vectors of pneumococcal transmission: 20–50% of children <5 years old have asymptomatic nasopharyngeal colonization with *S. pneumoniae* (compared with 5–15% of young and middle-aged adults). Colonization rates for all age groups are even higher in low-income countries.
- Rates of pneumococcal disease vary by season (higher in winter), gender (higher for males), and underlying medical condition (e.g., higher with splenic dysfunction; chronic respiratory, heart, liver, and kidney disease; immunosuppression).
- The introduction and widespread use (in industrialized countries) of pneumococcal conjugate vaccines have led to dramatic changes in the epidemiology of invasive pneumococcal disease; rates have fallen by >75% among infants and children in the United States.

PATHOGENESIS

- Nasopharyngeal colonization can persist for many months, resulting in the development of type-specific serum IgG that ultimately leads to pneumococcal clearance

http://internalmedicinebook.com

from the nasopharynx. Accordingly, pneumococcal disease is usually associated with recent acquisition of a new colonizing serotype.
- Once the nasopharynx has been colonized, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones) or locally to contiguous areas (e.g., middle ear, lungs).
- Local cytokine production, particularly after intercurrent viral infections, facilitates pneumococcal adherence. Bacterial factors such as peptidoglycan and teichoic acid induce inflammation, result in characteristic pathology, and permit bacterial invasion.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness.

Pneumonia

Pneumococcal pneumonia—the most common serious pneumococcal syndrome—is difficult to distinguish from pneumonia of other etiologies on the basis of clinical findings.

- Pts often present with fever, abrupt-onset cough and dyspnea, and sputum production.
  - Pts may also have pleuritic chest pain, shaking chills, or myalgias.
  - Among the elderly, presenting signs and symptoms may be less specific, with confusion and malaise but without fever or cough.
- On physical examination, adults may have tachypnea (>30 breaths/min) and tachycardia, crackles on chest auscultation, and dullness to percussion of the chest in areas of consolidation.
  - In some cases, hypotension, bronchial breathing, a pleural rub, or cyanosis may be present.
  - Upper abdominal pain may be present if the diaphragmatic pleura is involved.
- Pneumococcal pneumonia is generally diagnosed by Gram's staining and culture of sputum.
  - While culture results are awaited, chest x-rays—which classically demonstrate lobar or segmental consolidation—may provide some adjunctive evidence, although they may be normal early in the course of illness or with dehydration.
  - Blood cultures are positive for pneumococci in <30% of cases.
  - Leukocytosis (>15,000/μL) is common; leukopenia is documented in <10% of cases and is associated with a fatal outcome.
  - A positive pneumococcal urinary antigen test has a high predictive value among adults, in whom the prevalence of nasopharyngeal colonization is low.
- Empyema occurs in <5% of cases and should be considered when a pleural effusion is accompanied by fever and leukocytosis after 4–5 days of appropriate antibiotic therapy. Pleural fluid with frank pus, bacteria, or a pH of ≤7.1 indicates empyema and requires aggressive drainage.

Meningitis

S. pneumoniae is among the most common causes of meningitis in both adults and children. Pneumococcal meningitis can present as a primary syndrome or as a complication of other pneumococcal conditions (e.g., otitis media, infected skull fracture, bacteremia). Pneumococcal meningitis is clinically indistinguishable from pyogenic meningitis of other etiologies.

- Pts have fever, headache, neck stiffness, photophobia, and occasionally seizures and confusion.
- On examination, pts have a toxic appearance, altered consciousness, bradycardia, and hypertension (indicative of increased intracranial pressure). Kernig's or Brudzinski's sign or cranial nerve palsies (particularly of the third and sixth cranial nerves) are noted in a small fraction of adult pts.

http://internalmedicinebook.com

- Diagnosis of pneumococcal meningitis relies on examination of CSF, which reveals an elevated protein level, elevated WBC count, and reduced glucose concentration. The etiologic agent can be specifically identified by culture, antigen testing, or PCR. A blood culture positive for *S. pneumoniae* in conjunction with clinical manifestations of meningitis is also considered confirmatory.

Other Invasive Syndromes

S. pneumoniae can affect virtually any body site and cause invasive syndromes, including bacteremia, osteomyelitis, septic arthritis, endocarditis, pericarditis, and peritonitis. The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR. Hemolytic-uremic syndrome can complicate invasive pneumococcal disease.

Noninvasive Syndromes

Sinusitis and otitis media are the two most common noninvasive syndromes caused by *S. pneumoniae*; the latter is the most common pneumococcal syndrome and most often affects young children. See Chap. 58 for more detail.

TREATMENT PNEUMOCOCCAL INFECTIONS

- Penicillin remains the cornerstone of treatment for pneumococcal disease caused by sensitive isolates, with daily doses ranging from 50,000 U/kg for minor infections to 300,000 U/kg for meningitis. Macrolides and cephalosporins are alternatives for penicillin-allergic pts but otherwise offer no advantage over penicillin.
- Strains resistant to β-lactam drugs are increasing in frequency, and antibiotic recommendations are typically based on the minimal inhibitory concentration against the isolate, particularly in cases of invasive disease.

PNEUMONIA

- *Outpatient treatment:* Amoxicillin (1 g PO q8h) is effective for virtually all cases of pneumococcal pneumonia. Fluoroquinolones (e.g., levofloxacin, 500–750 mg/d; or moxifloxacin, 400 mg/d) are also highly likely to be effective in the United States, although they are much more expensive than amoxicillin. Clindamycin and azithromycin are effective in 90% and 80% of cases, respectively.
- *Inpatient treatment:* For pts with noncritical illness, β-lactam antibiotics are recommended—e.g., penicillin (3–4 mU IV q4h) or ceftriaxone (1 g IV q12–24h). For pts with critical illness, vancomycin may be added, with its use reviewed once susceptibility data are available.
- *Treatment duration:* The optimal duration of treatment is uncertain, but continuation of antibiotics for at least 5 days after the pt becomes afebrile seems prudent.

MENINGITIS

- Because of the increased prevalence of resistant pneumococci, first-line therapy should include vancomycin (1 g IV q12h) plus a third-generation cephalosporin (ceftriaxone, 2 g IV q12h; or cefotaxime, 2 g IV q4h). Rifampin (600 mg/d) can be substituted for the third-generation cephalosporin in pts hypersensitive to β-lactam agents.
- The antibiotic regimen should be adjusted appropriately once susceptibility data are available. If the isolate is resistant to penicillin and cephalosporins, both vancomycin and the cephalosporin should be continued.
- A repeat LP should be considered after 48 h if the organism is not sensitive to penicillin and information on cephalosporin sensitivity is not yet available, if the pt's clinical condition does not improve or deteriorates, or if the pt has received dexamethasone, which may compromise clinical evaluation.

http://internalmedicinebook.com

- In adults with community-acquired bacterial meningitis, dexamethasone should be given before or in conjunction with the first dose of antibiotics, as glucocorticoids have been demonstrated to significantly reduce rates of mortality, severe hearing loss, and neurologic sequelae. The data are not clear as to whether this practice is also beneficial in children.

PREVENTION

- All persons ≥65 years old and those 2–64 years old who are at increased risk of pneumococcal disease should receive the 23-valent pneumococcal polysaccharide vaccine (PPSV23), which contains capsular polysaccharide from the 23 most prevalent serotypes of *S. pneumoniae*.
  - Persons >2 years old with continuing increased risk should be revaccinated every 5 years.
  - Persons whose only indication for vaccination is an age of ≥65 years do not need to be revaccinated.
- The efficacy of PPSV23 is controversial; it appears to be effective against invasive pneumococcal disease but less effective or ineffective against nonbacteremic pneumococcal pneumonia.
- The duration of protection conferred by PPSV23 is ~5 years.
- The poor response of infants and young children to pneumococcal polysaccharide vaccines prompted the development of pneumococcal conjugate vaccines. In the United States, the current recommendation is for infants to be routinely vaccinated with the conjugate vaccine PCV13, which contains the 13 serotypes most associated with disease.
  - All immunocompromised children and adults should receive PCV13 prior to receiving PPSV23.
  - Pneumococcal conjugate vaccines are highly effective at providing protection against vaccine-serotype invasive pneumococcal disease, pneumonia, otitis media, nasopharyngeal colonization, and all-cause mortality.
  - In the United States, there has been a >90% reduction in vaccine-serotype invasive pneumococcal disease among the whole population, including indirect protection of unvaccinated adults.

For a more detailed discussion, see Goldblatt D, O'Brien KL: Pneumococcal Infections, Chap. 171, p. 946, in HPIM-19.

86 Staphylococcal Infections

MICROBIOLOGY

Staphylococci are gram-positive cocci that form grapelike clusters on Gram's stain; they are catalase positive (unlike streptococci), nonmotile, aerobic, and facultatively anaerobic. *Staphylococcus aureus*, which is distinguished from other staphylococci by its production of coagulase, is the most virulent species.

http://internalmedicinebook.com

S. AUREUS INFECTIONS

Epidemiology

S. aureus is an important cause of community-acquired infections and a leading cause of nosocomial infections.

- *S. aureus* is a component of the normal human flora, most frequently colonizing the anterior nares and oropharynx but also colonizing the skin (particularly damaged skin), vagina, axilla, and perineum. These sites of colonization are reservoirs for future infection.
- Of healthy persons, ~30% are transiently colonized with *S. aureus*, while ~10% are persistently colonized. The rate is elevated among insulin-dependent diabetic pts, HIV-infected persons, injection drug users, hemodialysis pts, and pts with skin damage.
- Transmission of *S. aureus* most frequently results from direct personal contact, although spread via respiratory secretions has been reported. Most *S. aureus* infections are caused by a strain that is already a component of the pt's own microbiota.
- Methicillin-resistant *S. aureus* (MRSA) is common in hospitals, and its prevalence is increasing dramatically in community settings among individuals without prior medical exposure.
  - In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) causes most community-acquired MRSA (CA-MRSA) infections and can cause severe disease in immunocompetent pts.

Pathogenesis

S. aureus is a pyogenic pathogen known for its capacity to induce abscess formation.

- *Invasive disease:* For invasive *S. aureus* infection to occur, some or all of the following steps are necessary:
  - *Colonization/inoculation:* Bacteria colonize tissue surfaces or are inoculated directly into tissue—e.g., as a result of minor abrasions or via IV access catheters.
  - *Invasion:* Bacteria replicate at the site of infection and elaborate enzymes that facilitate survival and local spread. CA-MRSA isolates that produce the Panton-Valentine leukocidin toxin have been linked to more serious infections.
  - *Evasion of host defense mechanisms: S. aureus* possesses an antiphagocytic polysaccharide microcapsule that facilitates evasion of host defenses and plays a role in abscess formation. Organisms can survive intracellularly and then cause recrudescent infections when conditions are suitable.
  - *Metastatic spread: S. aureus* can survive in PMNs and may use these cells to spread to and seed other tissue sites.
- *Toxin-mediated disease: S. aureus* produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins.
  - Antitoxin antibodies are protective against toxin-mediated staphylococcal illness.
  - Enterotoxins and toxic shock syndrome toxin 1 (TSST-1) act as "superantigens" or T-cell mitogens and cause the release of large amounts of inflammatory mediators, producing multisystem disease that includes fever, rash, and hypotension.

Diagnosis

S. aureus infections are readily diagnosed by Gram's stain and microscopic examination of infected tissue.

- Routine cultures of infected material usually yield positive results, and blood cultures are sometimes positive even when infections are localized to extravascular sites.
- PCR assays have been developed for rapid testing and are increasingly being used.

Clinical Syndromes

Skin and Soft Tissue Infections *S. aureus* causes a variety of cutaneous infections characterized by pus-containing blisters, many of which can also be caused by group A

http://internalmedicinebook.com

streptococci and other streptococcal species. Predisposing factors include skin disease (e.g., eczema), skin damage (e.g., minor trauma), injections, and poor personal hygiene.

- Infections can be superficial (e.g., folliculitis, cellulitis, impetigo) or deep and painful (e.g., furuncles, carbuncles, hidradenitis suppurativa).
  - Carbuncles (often located in the lower neck) are more severe and painful than furuncles (boils that extend from hair follicles) and are due to coalesced lesions extending to deeper SC tissue.
  - Mastitis in lactating women can range from superficial cellulitis to abscess.

Musculoskeletal Infections See Chap. 84 for additional details.

- *S. aureus* is among the most common causes of *osteomyelitis* arising from either hematogenous dissemination or contiguous spread from a soft tissue site (e.g., diabetic or vascular ulcers).
  - Hematogenous osteomyelitis in adults is often vertebral and occurs in pts with endocarditis, pts undergoing hemodialysis, injection drug users, or diabetics. Intense back pain and fever can occur, but infections may also be clinically occult.
  - *Epidural abscess* is a serious complication that can present as trouble voiding or walking or as radicular pain in addition to symptoms of osteomyelitis; neurologic compromise can develop in the absence of timely treatment, which often requires surgical intervention.
  - Osteomyelitis from contiguous soft tissue infections is suggested by exposure of bone, a draining fistulous tract, failure to heal, or continued drainage.
- *S. aureus* is the most common cause of *septic arthritis* in native joints of both adults and children. *S. aureus* septic arthritis in adults may result from trauma, surgery, or hematogenous dissemination.
  - The joints most commonly affected are the knees, shoulders, hips, and phalanges.
  - Examination of synovial fluid reveals >50,000 PMNs/μL and gram-positive cocci in clusters on Gram's stain.
- *Pyomyositis*, an infection of skeletal muscles that is seen in tropical climates and in immunocompromised pts (e.g., HIV-infected pts), causes fever, swelling, and pain overlying involved muscle and is usually due to *S. aureus*.

Respiratory Tract Infections

- Newborns and infants can develop serious infections characterized by fever, dyspnea, and respiratory failure; pneumatoceles (shaggy, thin-walled cavities), pneumothorax, and empyema are known complications.
- Community-acquired pneumonia usually follows viral infections (e.g., influenza) and manifests as fever, bloody sputum production, and midlung-field pneumatoceles or multiple patchy pulmonary infiltrates.
  - Blood cultures are usually negative.
- Nosocomial pneumonia is common in intubated pts and is indistinguishable from pneumonia of other bacterial etiologies.
  - Pts produce an increased volume of purulent sputum and develop fever, new pulmonary infiltrates, and respiratory distress.

Bacteremia and Sepsis The incidence of metastatic seeding during bacteremia has been estimated to be as high as 31%, with bones, joints, kidneys, and lungs most commonly infected.

- Diabetes, HIV infection, and renal insufficiency are often seen in association with *S. aureus* bacteremia and increase the risk of complications.

Infective Endocarditis See Chap. 80 for additional details.

- *S. aureus* is the leading cause of endocarditis worldwide and accounts for 25–35% of cases.

http://internalmedicinebook.com

- The incidence is increasing as a result of injection drug use, hemodialysis, intravascular prosthetic devices, and immunosuppression.
- Mortality rates range from 20% to 40% despite the availability of effective antibiotics.
- The four clinical settings in which *S. aureus* endocarditis is encountered are (1) right-sided endocarditis in association with injection drug use, (2) left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis.

Urinary Tract Infections UTIs due to *S. aureus* are uncommon and suggest hematogenous dissemination.

Prosthetic Device–Related Infections Compared with coagulase-negative staphylococci (CoNS), *S. aureus* causes more acute disease, with localized and systemic manifestations that tend to be rapidly progressive. Successful treatment usually involves removal of the prosthetic device.

CA-MRSA Infections While the skin and soft tissues are the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and potentially life threatening (e.g., necrotizing fasciitis, necrotic pneumonia, sepsis, purpura fulminans).

Toxin-Mediated Disease Each class of toxin produced by *S. aureus* results in a characteristic syndrome.

- *Food poisoning:* results from inoculation of toxin-producing *S. aureus* into food by colonized food handlers, with subsequent toxin elaboration in growth-promoting foods (e.g., custard, potato salad, processed meat)
  - The heat-stable toxin is not destroyed even if heating kills the bacteria.
  - Because the disease is caused by preformed toxins, its onset is rapid and explosive, occurring within 1–6 h of ingestion of contaminated food.
  - The chief signs and symptoms are nausea and vomiting, but diarrhea, hypotension, and dehydration may occur. Fever is absent.
  - Symptoms resolve within 8–10 h; treatment is entirely supportive.
- *Toxic shock syndrome (TSS):* results from elaboration of an enterotoxin (many nonmenstrual TSS cases) or TSST-1 (some nonmenstrual cases and >90% of menstrual cases)
  - Although the specific toxin may differ, the clinical presentation is similar in menstrual and nonmenstrual cases.
  - Diagnosis is based on a constellation of clinical findings. Table 86-1 summarizes the case definition for staphylococcal TSS.
  - Menstrual cases occur 2–3 days after menses begin.
  - Illness occurs only in people who lack antibody to the toxin.
- *Staphylococcal scalded-skin syndrome (SSSS):* most often affects newborns and children. Fragility of the skin, with tender, thick-walled, fluid-filled bullae, can lead to exfoliation of most of the skin surface. *Nikolsky's sign* is positive when gentle pressure on bullae causes rupture of lesions and leaves denuded underlying skin.

Prevention

Hand washing and careful attention to appropriate isolation procedures prevent the spread of *S. aureus* infection. Elimination of nasal carriage of *S. aureus* (e.g., with mupirocin) has reduced the incidence of postsurgical infection.

INFECTIONS CAUSED BY COAGULASE-NEGATIVE STAPHYLOCOCCI

Microbiology

CoNS are generally less virulent than *S. aureus* but are important and common causes of prosthetic-device infections.

http://internalmedicinebook.com

TABLE 86-1 CASE DEFINITION OF *S. AUREUS* TOXIC SHOCK SYNDROME

1. Fever: temperature of ≥38.9°C (≥102°F)
2. Hypotension: systolic blood pressure of ≤90 mmHg or orthostatic hypotension (orthostatic drop in diastolic blood pressure by ≥15 mmHg, orthostatic syncope, or orthostatic dizziness)
3. Diffuse macular rash, with desquamation 1–2 weeks after onset (including the palms and soles)
4. Multisystem involvement
   a. Hepatic: bilirubin or aminotransferase levels ≥2 times normal
   b. Hematologic: platelet count ≤100,000/μL
   c. Renal: blood urea nitrogen or serum creatinine level ≥2 times the normal upper limit
   d. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
   e. Gastrointestinal: vomiting or diarrhea at onset of illness
   f. Muscular: severe myalgias or serum creatine phosphokinase level ≥2 times the normal upper limit
   g. Central nervous system: disorientation or alteration in consciousness without focal neurologic signs and in the absence of fever and hypotension
5. Negative serologic or other tests for measles, leptospirosis, and Rocky Mountain spotted fever, as well as negative blood or cerebrospinal fluid cultures for organisms other than *S. aureus*

Source: M Wharton et al: Case definitions for public health surveillance. *MMWR* 39:1, 1990; with permission.

- Of CoNS species, *S. epidermidis* most often causes disease. This organism is a normal component of the skin, oropharyngeal, and vaginal flora.
- *S. saprophyticus* is a common cause of UTIs.
- *S. lugdunensis* and *S. schleiferi* are more virulent than other CoNS species and cause serious infections, possibly because they apparently share more virulence determinants with *S. aureus* than do other CoNS species.

Pathogenesis

CoNS are uniquely adapted to cause prosthetic-device infections because they can elaborate an extracellular polysaccharide (glycocalyx or slime) that forms a biofilm on the device surface, protecting bacteria from host defenses as well as from antibiotic treatment while allowing bacterial survival.

Clinical Syndromes

CoNS cause diverse prosthetic device–related infections. Signs of localized infection are usually subtle, disease progression is slow, and systemic findings are limited. Fever and mild leukocytosis may be documented. Infections not associated with prosthetic devices are infrequent, but up to 5% of native-valve endocarditis cases have been due to CoNS in some series.

Diagnosis

CoNS are readily detected by standard methods, but distinguishing infection from colonization is often problematic because CoNS are common contaminants of cultures of blood and other sites. Only 10–25% of blood cultures positive for CoNS reflect true bacteremia.

http://internalmedicinebook.com

TREATMENT STAPHYLOCOCCAL INFECTIONS

- Suppurative collections should be surgically drained. The emergence of CA-MRSA has increased the importance of culturing material from all collections to identify the pathogen and determine its antimicrobial susceptibility.
- In most cases of prosthetic-device infection, the device should be removed, although some CoNS infections can be managed medically.
- Antibiotic therapy for *S. aureus* infection is generally prolonged (i.e., 4–8 weeks), particularly if blood cultures remain positive 96 h after initiation of therapy, if the infection was acquired in the community, if a removable focus of infection is not removed, or if cutaneous or embolic manifestations of infection occur. For immunocompetent pts in whom shorter therapy is planned, a transesophageal echocardiogram to rule out endocarditis is warranted.
- Antimicrobial therapy for serious staphylococcal infections is summarized in **Table 86-2**.
  - Penicillinase-resistant β-lactams, such as nafcillin, oxacillin, and cephalosporins, are highly effective against penicillin-resistant strains.
  - The incidence of MRSA is high in hospital settings, and strains intermediately or fully resistant to vancomycin have been described. In general, vancomycin is less reliably bactericidal than the β-lactams and should be used only when absolutely indicated.
  - Among newer antistaphylococcal agents, ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA; daptomycin is bactericidal but is not effective in pulmonary infections; quinupristin/dalfopristin is typically bactericidal but is only bacteriostatic against isolates resistant to erythromycin or clindamycin; linezolid is bacteriostatic and offers similar bioavailability after oral or parenteral administration; and telavancin—a derivative of vancomycin—is active against strains with reduced susceptibility to vancomycin (i.e., vancomycin-intermediate *S. aureus*, or VISA). Tigecycline, a broad-spectrum minocycline analogue, is bacteriostatic against MRSA.
    - Other alternatives include the quinolones, but resistance to these drugs is increasing, especially among MRSA strains.
    - Trimethoprim-sulfamethoxazole (TMP-SMX) and minocycline have been used successfully to treat MRSA infections in cases of vancomycin toxicity or intolerance.
    - Combinations of antistaphylococcal agents have been used to enhance bactericidal activity (e.g., daptomycin plus a β-lactam antibiotic) and, in selected instances (e.g., right-sided endocarditis), to shorten the duration of therapy.

Special considerations for treatment include:

- *Uncomplicated skin and soft tissue infections:* Oral agents are usually adequate.
- *Native-valve endocarditis:* A β-lactam is recommended for methicillin-sensitive *S. aureus* and vancomycin (1 g q12h) or daptomycin (6 mg/kg q24h) for MRSA. Treatment should continue for 4–6 weeks.
- *Prosthetic-valve endocarditis:* Surgery is often needed in addition to antibiotics. A β-lactam drug (or either vancomycin or daptomycin if MRSA is involved) with gentamicin and rifampin is indicated.
- *Hematogenous osteomyelitis or septic arthritis:* A 4-week treatment course is adequate for children, but adults require longer courses. Joint infections require repeated aspiration or arthroscopy to prevent damage from inflammatory cells.
- *Chronic osteomyelitis:* Surgical debridement—in addition to antibiotic therapy—is needed in most cases.
- *Prosthetic-joint infections:* Ciprofloxacin and rifampin have been used successfully in combination, particularly when the prosthesis cannot be removed.

http://internalmedicinebook.com

TABLE 86-2 ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a]

Sensitivity/ Resistance of Isolate	Drug of Choice	Alternative(s)	Comments
Parenteral Therapy for Serious Infections			
Sensitive to penicillin	Penicillin G (4 mU q4h)	Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (1 g q12h[b])	Fewer than 5% of isolates are sensitive to penicillin. The clinical microbiology laboratory must verify that the strain is not a β-lactamase producer.
Sensitive to methicillin	Nafcillin or oxacillin (2 g q4h)	Cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8–12h[b])	Pts with penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to β-lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prosthetic-valve endocarditis[c]). Type A β-lactamase may rapidly hydrolyze cefazolin and reduce its efficacy in endocarditis. Vancomycin is a less effective option.
Resistant to methicillin	Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg IV q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q12h)	Sensitivity testing is necessary before an alternative drug is selected. For some serious infections, higher doses of daptomycin have been used. Quinupristin/dalfopristin is bactericidal against methicillin-resistant isolates unless the strain is resistant to erythromycin or clindamycin. The efficacy of adjunctive therapy is not well established in many settings. Both linezolid and quinupristin/dalfopristin have had in vitro activity against most VISA and VRSA strains. See footnote for treatment of prosthetic-valve endocarditis.[c]

(*Continued*)

http://internalmedicinebook.com

TABLE 86-2 ANTIMICROBIAL THERAPY FOR STAPHYLOCOCCAL INFECTIONS[a] (*CONTINUED*)

Sensitivity/ Resistance of Isolate	Drug of Choice	Alternative(s)	Comments
Resistant to methicillin with intermediate or complete resistance to vancomycin[e]	Daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	Same as for methicillin-resistant strains; check antibiotic susceptibilities ***or*** Ceftaroline (600 mg IV q12h) Newer agents include tedizolid (200 mg administered once daily either IV or orally) or dalbavancin (two IV doses: 1000 mg followed in 1 week by 500 mg). Both drugs are approved only for the treatment of skin and soft tissue infections.	Same as for methicillin-resistant strains; check antibiotic susceptibilities. Ceftaroline is used either alone or in combination with daptomycin.
Not yet known (i.e., empirical therapy)	Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	—	Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin is recommended for suspected community- or hospital-acquired *Staphylococcus aureus* infections because of the increased frequency of methicillin-resistant strains in the community.

http://internalmedicinebook.com

Oral Therapy for Skin and Soft Tissue Infections			
Sensitive to methicillin	Dicloxacillin (500 mg qid), cephalexin (500 mg qid)	Minocycline or doxycycline (100 mg q12h[b]), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg/kg tid), linezolid (600 mg PO q12h), tedizolid (200 mg PO q24h)	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured.
Resistant to methicillin	Clindamycin (300–450 mg/kg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h[b]), linezolid (600 mg bid), or tedizolid (200 mg once daily)	Same options as under "Drug of Choice"	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All drainage should be cultured.

[a]Recommended dosages are for adults with normal renal and hepatic function.
[b]The dosage must be adjusted for pts with reduced creatinine clearance.
[c]For the treatment of prosthetic-valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced.
[d]Daptomycin cannot be used for the treatment of pneumonia.
[e]Vancomycin-resistant *S. aureus* isolates from clinical infections have been reported.
Abbreviations: ds, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus;* VRSA, vancomycin-resistant *S. aureus.*
Source: Modified with permission from FD Lowy: *N Engl J Med* 339:520, 1998 (© 1998 Massachusetts Medical Society. All rights reserved.); C Liu et al: *Clin Infect Dis* 52:285, 2011; DL Stevens et al: *Clin Infect Dis 59:148, 2014; Med Lett Drugs Ther* 56:39, 2014.

http://internalmedicinebook.com

- *TSS:* Supportive therapy and removal of tampons or other packing material or debridement of an infected site are most important. The role of antibiotics is less clear, but a clindamycin/semisynthetic penicillin combination is often recommended.
  - Clindamycin is recommended because it is a protein synthesis inhibitor and has been shown to decrease toxin synthesis in vitro; its efficacy in vivo is less clear.
  - Anecdotally, IV immunoglobulin is helpful.

For a more detailed discussion, see Lowy FD: Staphylococcal Infections, Chap. 172, p. 954, in HPIM-19.

87 Streptococcal/Enterococcal Infections, Diphtheria, and Infections Caused by Other Corynebacteria and Related Species

STREPTOCOCCAL AND ENTEROCOCCAL INFECTIONS

MICROBIOLOGY

Streptococci and enterococci are gram-positive cocci that form chains when grown in liquid media.

- Culture on blood agar reveals three hemolytic patterns:
  - α-Hemolysis results in partial hemolysis that imparts a greenish appearance to agar. This pattern is seen with *S. pneumoniae* and viridans streptococci.
  - β-Hemolysis results in complete hemolysis around a colony. This pattern is seen with streptococci of Lancefield groups A, B, C, and G. Lancefield grouping is based on cell-wall carbohydrate antigens.
  - γ-Hemolysis describes the absence of hemolytic ability. This pattern is typical of enterococci, nonenterococcal group D streptococci, and anaerobic streptococci.
- Streptococci and enterococci colonize the respiratory, GI, and genitourinary tracts as part of the normal flora. Several of these species are also important causes of human diseases.

GROUP A *STREPTOCOCCUS* (GAS)

Epidemiology and Pathogenesis

GAS (*S. pyogenes*) causes suppurative infections and is associated with postinfectious syndromes such as acute rheumatic fever (ARF) and poststreptococcal glomerulonephritis (PSGN).

http://internalmedicinebook.com

- Up to 20% of people may have asymptomatic pharyngeal colonization with GAS.
  - Pharyngitis due to GAS is one of the most common bacterial infections of childhood.
  - GAS accounts for 20–40% of all cases of exudative pharyngitis in children >3 years of age.
- The incidence of all GAS infections is ~10-fold higher in low-income than in high-income countries. Worldwide, GAS contributes to ~500,000 deaths per year.
- The major surface protein (M protein) and the hyaluronic acid polysaccharide capsule protect GAS against phagocytic ingestion and killing.
- GAS makes a large number of extracellular products that may contribute to local and systemic toxicity; these include streptolysins S and O, streptokinase, DNases, and the pyrogenic exotoxins that cause the rash of scarlet fever and contribute to the pathogenesis of toxic shock syndrome (TSS) and necrotizing fasciitis.
- Respiratory droplets provide the usual route of transmission, although other mechanisms have been described.

Clinical Manifestations

Pharyngitis After an incubation period of 1–4 days, pts develop sore throat, fever, chills, malaise, and GI manifestations.

- Examination may reveal an erythematous and swollen pharyngeal mucosa, purulent exudates over the posterior pharynx and tonsillar pillars, and tender anterior cervical adenopathy.
- Viral pharyngitis is the more likely diagnosis when pts have cough, coryza, hoarseness, conjunctivitis, or mucosal ulcers.
- Throat culture is the gold standard for diagnosis.
  - Latex agglutination or enzyme immunoassay is highly specific (>95%) and can be relied on for a rapid, definitive diagnosis.
  - Given a variable sensitivity of 55–90%, a negative rapid-assay result should be confirmed with a throat culture.

TREATMENT GAS PHARYNGITIS

- See Table 87-1 for recommended treatments.
  - The primary goal of treatment is to prevent suppurative complications (e.g., lymphadenitis, abscess, sinusitis, bacteremia, pneumonia) and ARF; therapy does not seem to significantly reduce the duration of symptoms or to prevent PSGN.
  - Follow-up cultures after completion of therapy are not routinely recommended.
- Asymptomatic pharyngeal GAS carriage usually is not treated; however, when the pt is a potential source of infection in others (e.g., health care workers), either clindamycin (300 mg PO tid for 10 days) or penicillin V (500 mg PO qid for 10 days) with rifampin (300 mg PO bid for the first 4 days) is used.

Scarlet Fever Scarlet fever is the designation for GAS infection—usually pharyngitis—associated with a characteristic rash. It is much less common now than in the past.

- The rash typically appears in the first 2 days of illness over the upper trunk and spreads to the extremities but not to the palms and soles. The skin has a sandpaper feel.
- Other findings include circumoral pallor, strawberry tongue (enlarged papillae on a coated tongue), and Pastia's lines (accentuation of rash in skin folds).
- Rash improves in 6–9 days, with desquamation on palms and soles.

Skin and Soft Tissue Infections See Chap. 84 for further discussion of clinical manifestations and treatment.

http://internalmedicinebook.com

TABLE 87-1 TREATMENT OF GROUP A STREPTOCOCCAL INFECTIONS

Infection	Treatment[a]
Pharyngitis	Benzathine penicillin G (1.2 mU IM) *or* penicillin V (250 mg PO tid or 500 mg PO bid) × 10 days (Children <27 kg: Benzathine penicillin G [600,000 units IM] *or* penicillin V [250 mg PO bid or tid] × 10 days)
Impetigo	Same as pharyngitis
Erysipelas/cellulitis	Severe: Penicillin G (1–2 mU IV q4h) Mild to moderate: Procaine penicillin (1.2 mU IM bid)
Necrotizing fasciitis/ myositis	Surgical debridement *plus* penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h)
Pneumonia/empyema	Penicillin G (2–4 mU IV q4h) *plus* drainage of empyema
Streptococcal toxic shock syndrome	Penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) *plus* IV immunoglobulin[b] (2 g/kg as a single dose)

[a]Penicillin allergy: A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents for oral therapy are erythromycin (10 mg/kg PO qid, up to a maximum of 250 mg per dose) and azithromycin (a 5-day course at a dose of 12 mg/kg once daily, up to a maximum of 500 mg/d). Vancomycin is an alternative for parenteral therapy.
[b]Efficacy unproven, but recommended by several experts. See text for discussion.

- *Impetigo:* A superficial skin infection, impetigo is most often seen in young children in warmer months or climates and under poor hygienic conditions.
  - Red papular lesions evolve into pustules that ultimately form characteristic honeycomb-like crusts, usually affecting the facial areas around the nose and mouth and the legs. Pts are usually afebrile.
  - GAS impetigo is associated with PSGN but not with ARF.
  - For treatment, see Table 87-1. Given an increasing incidence of impetigo due to *Staphylococcus aureus*, empirical antibiotic therapy should cover GAS and *S. aureus.*
    - Thus dicloxacillin or cephalexin (250 mg PO qid for 10 days) is used.
    - Topical mupirocin ointment is also effective.
- *Cellulitis:* GAS cellulitis develops at anatomic sites where normal lymphatic drainage has been disrupted (e.g., by surgery or prior cellulitis). When skin integrity is breached, organisms may enter at sites distant from the area of cellulitis.
  - GAS may cause rapidly developing postoperative wound infections with a thin exudate.
  - *Erysipelas* is a form of cellulitis characterized by pain, fever, and acute onset of bright red swelling that is sharply demarcated from normal skin.
    - It usually involves the malar facial area or the lower extremities and is caused almost exclusively by β-hemolytic streptococci, usually GAS.
    - The skin often has a *peau d'orange* texture, and blebs or bullae may form after 2 or 3 days.
  - For treatment of erysipelas or cellulitis known to be due to GAS, see Table 87-1; empirical treatment should be directed against GAS and *S. aureus*.

http://internalmedicinebook.com

- *Necrotizing fasciitis:* See Chap. 84 for details. GAS causes ~60% of cases of necrotizing fasciitis. For treatment, see Table 87-1.

Pneumonia and Empyema GAS is an occasional cause of pneumonia in previously healthy pts.

- Pts have pleuritic chest pain, fever, chills, and dyspnea; ~50% have accompanying pleural effusions that—unlike the sterile parapneumonic effusions of pneumococcal pneumonia—are almost always infected and should be drained quickly to avoid loculation.
- For treatment, see Table 87-1.

Bacteremia In most cases of GAS bacteremia, a focus is readily identifiable. Bacteremia occurs occasionally with cellulitis or pneumonia and frequently with necrotizing fasciitis.
- If no focus is immediately evident, a diagnosis of endocarditis, occult abscess, or osteomyelitis should be considered.

Toxic Shock Syndrome Unlike those with TSS due to *S. aureus*, pts with streptococcal TSS generally lack a rash, have bacteremia, and have an associated soft tissue infection (cellulitis, necrotizing fasciitis, or myositis).

- Table 87-2 presents a proposed case definition for streptococcal TSS.
- The mortality rate for streptococcal TSS is ≥30%, with most deaths due to shock and respiratory failure.
- For treatment, see Table 87-1.

Prevention

Although household contacts of individuals with invasive GAS infection are at increased risk of infection, the attack rate is low enough that antibiotic prophylaxis is not routinely recommended.

TABLE 87-2 PROPOSED CASE DEFINITION FOR THE STREPTOCOCCAL TOXIC SHOCK SYNDROME[a]

I. Isolation of group A streptococci (*Streptococcus pyogenes*)
   A. From a normally sterile site
   B. From a nonsterile site
II. Clinical signs of severity
   A. Hypotension *and*
   B. ≥2 of the following signs
      1. Renal impairment
      2. Coagulopathy
      3. Liver function impairment
      4. Adult respiratory distress syndrome
      5. A generalized erythematous macular rash that may desquamate
      6. Soft tissue necrosis, including necrotizing fasciitis or myositis; *or* gangrene

[a]An illness fulfilling criteria IA, IIA, and IIB is defined as a *definite* case. An illness fulfilling criteria IB, IIA, and IIB is defined as a *probable* case if no other etiology for the illness is identified.
Source: Modified from Working Group on Severe Streptococcal Infections: *JAMA* 269:390, 1993.

http://internalmedicinebook.com

STREPTOCOCCI OF GROUPS C AND G

- Streptococci of groups C and G cause infections similar to those caused by GAS, including cellulitis, bacteremia (particularly in elderly or chronically ill pts), pneumonia, and soft tissue infections.
- Strains that form small colonies (<0.5 mm) on blood agar are generally of the *S. milleri* group (*S. intermedius*, *S. anginosus*); large-colony groups C and G streptococci are now considered a single species (*S. dysgalactiae* subsp. *equisimilis*).
- Treatment is the same as for similar syndromes due to GAS.
  - Although it has not been shown to be superior, the addition of gentamicin (1 mg/kg IV q8h) is recommended by some experts for endocarditis or septic arthritis due to group C or G streptococci because of a poor clinical response to penicillin alone.
  - Joint infections can require repeated aspiration or open drainage for cure.

GROUP B *STREPTOCOCCUS* (GBS)

- GBS is a major cause of meningitis and sepsis in neonates and a common cause of peripartum fever in women.
  - About half of the infants delivered vaginally to mothers colonized with GBS (5–40% of women) become colonized, but only 1–2% develop infection.
  - With maternal colonization, the risk of neonatal GBS infection is high if delivery is preterm or if the mother has an early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis.
- Widespread prenatal screening for GBS has reduced the incidence of neonatal infection to 0.6 case per 1000 live births; adults now account for a larger proportion of invasive GBS infections than do newborns.

Neonatal Infections

- *Early-onset infection* occurs within the first week of life (median age, 20 h). The infection is acquired within the maternal genital tract during birth.
  - Neonates typically have respiratory distress, lethargy, and hypotension.
  - Bacteremia is noted in ~100% of cases, pneumonia in one-third to one-half, and meningitis in one-third.
- *Late-onset infection* develops in infants >1 week old and generally ≤3 months of age (mean age, 3–4 weeks). The organism is acquired during delivery or during later contact with a source.
  - Meningitis is the most common manifestation.
  - Infants present with lethargy, fever, irritability, poor feeding, and occasionally seizures.

TREATMENT **GBS INFECTIONS IN NEONATES**

- Penicillin is the agent of choice for all GBS infections.
  - Empirical therapy for suspected bacterial sepsis consists of ampicillin and gentamicin while cultures are pending.
  - Many physicians continue to give gentamicin until the pt improves clinically.

- *Prevention:* Identification of high-risk mothers and prophylactic administration of ampicillin or penicillin during delivery reduce the risk of neonatal infection.
- Maternal screening for anogenital colonization with GBS at 35–37 weeks of pregnancy is currently recommended.
- Women who have previously given birth to an infant with GBS disease, who have a history of GBS bacteriuria during pregnancy, or who have an unknown culture

http://internalmedicinebook.com

status but risk factors noted above should receive intrapartum prophylaxis (usually 5 mU of penicillin G followed by 2.5 mU q4h until delivery).
  – Cefazolin can be used for pts with a penicillin allergy who are at low risk for anaphylaxis.
  – If the mother is at risk for anaphylaxis and the GBS isolate is known to be susceptible, clindamycin can be used; otherwise, vancomycin is indicated.

Infections in Adults

Most GBS infections in adults are related to pregnancy and parturition. Other GBS infections are seen in the elderly, especially pts with underlying conditions such as diabetes mellitus or cancer.

- Cellulitis and soft tissue infection, UTI, pneumonia, endocarditis, and septic arthritis are most common.
- Penicillin (12 mU/d for localized infections and 18–24 mU/d for endocarditis or meningitis, in divided doses) is recommended. Vancomycin is an acceptable alternative for penicillin-allergic pts.
- Relapse or recurrent invasive infection occurs in ~4% of cases.

NONENTEROCOCCAL GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococci that cause human infections are *S. gallolyticus* and *S. infantarius* (previously classified together as *S. bovis*), each of which has two subspecies.

- These organisms have been associated with GI malignancies and other bowel lesions, which are found in ≥60% of pts presenting with group D streptococcal endocarditis.
- Unlike enterococcal endocarditis, group D streptococcal endocarditis can be adequately treated with penicillin alone.

VIRIDANS STREPTOCOCCI

- Many viridans streptococcal species are part of the normal oral flora, residing in close association with the teeth and gingiva. Minor trauma such as flossing or toothbrushing can cause transient bacteremia.
- Viridans streptococci have a predilection to cause endocarditis. Moreover, they are often part of a mixed flora in sinus infections and brain and liver abscesses.
- Bacteremia is common in neutropenic pts, who can develop a sepsis syndrome with high fever and shock. Risk factors in these pts include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or a fluoroquinolone, mucositis, or therapy with antacids or histamine antagonists.
- The *S. milleri* group (including *S. intermedius*, *S. anginosus*, and *S. constellatus*) differs from other viridans streptococci in both hemolytic pattern (i.e., they may be α-, β-, or γ-hemolytic) and clinical syndromes. These organisms commonly cause suppurative infections, especially abscesses of brain and viscera, as well as infections of the oral cavity and respiratory tract such as peritonsillar abscess, empyema, and lung abscess.
- Neutropenic pts should receive vancomycin pending susceptibility testing; other pts may be treated with penicillin.

ABIOTROPHIA AND *GRANULICATELLA* SPECIES (NUTRITIONALLY VARIANT STREPTOCOCCI)

- The organisms formerly known as nutritionally variant streptococci are now classified as *Abiotrophia defectiva* and three species within the genus *Granulicatella*. These fastidious organisms require media that are enriched (e.g., with vitamin B_6) for growth.

http://internalmedicinebook.com

- These organisms are more frequently associated with treatment failure and relapse in cases of endocarditis than are viridans streptococci. Thus, gentamicin (1 mg/kg q8h) must be added to the penicillin regimen.

ENTEROCOCCI

Microbiology

Enterococci are gram-positive cocci that are observed as single cells, diplococci, or short chains.

- Enterococci share many morphologic and phenotypic characteristics with streptococci and thus were previously classified as the latter.
- Enterococci are generally nonhemolytic when cultured on blood agar plates.
- Enterococci are inherently resistant to a variety of commonly used antibiotics. *E. faecium* is the most resistant species, with >80% of US isolates resistant to vancomycin (VRE) and >90% resistant to ampicillin. In contrast, only ~7% of *E. faecalis* isolates are resistant to vancomycin and ~4% to ampicillin.

Epidemiology

Although 18 enterococcal species have been isolated from human infections, *E. faecalis* and *E. faecium* cause the overwhelming majority of enterococcal infections.

- Enterococci are the second most common cause of nosocomial infection (after staphylococci), with roughly equal numbers of cases caused by *E. faecalis* and *E. faecium*.
- Colonization with VRE (as opposed to antibiotic-susceptible strains) predisposes to enterococcal infection. Risk factors for VRE colonization include prolonged hospitalization; long antibiotic courses; hospitalization in long-term care facilities, surgical units, and/or ICUs; organ transplantation; renal failure; high APACHE scores; and physical proximity to pts colonized with VRE.

Clinical Manifestations

Enterococci cause UTIs, especially in pts who have undergone instrumentation; chronic prostatitis; bacteremia related to intravascular catheters; bacterial endocarditis of both native and prosthetic valves (usually with a subacute presentation); meningitis, particularly in pts who have undergone neurosurgery; soft tissue infections, particularly involving surgical wounds; and neonatal infections. These organisms can also be a component of mixed intraabdominal infections.

TREATMENT ENTEROCOCCAL INFECTIONS

- Given low cure rates with β-lactam monotherapy, combination therapy with a β-lactam plus gentamicin or streptomycin is recommended for serious enterococcal infections. High-level resistance to aminoglycosides (i.e., minimal inhibitory concentrations of >500 and >2000 μg/mL for gentamicin and streptomycin, respectively) abolishes the synergism otherwise obtained by adding an aminoglycoside to a cell wall–active agent. This phenotype must be assessed in isolates from serious infections.
- There is burgeoning evidence that ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin in the treatment of *E. faecalis* endocarditis, with less risk of toxicity.
- For *E. faecium* isolates resistant to ampicillin:
  - Daptomycin, quinupristin/dalfopristin, or linezolid plus another active agent (doxycycline with rifampin, tigecycline, or a fluoroquinolone) may be used.
  - If daptomycin is used and if high-level resistance is not noted, an aminoglycoside should be added to the regimen.

http://internalmedicinebook.com

- If high-level aminoglycoside resistance is present, two other active agents should be used.

CORYNEBACTERIAL AND RELATED INFECTIONS

DIPHTHERIA

Microbiology

Corynebacterium diphtheriae, the causative agent of the nasopharyngeal and skin infection known as diphtheria, is a club-shaped, gram-positive, unencapsulated, nonmotile, nonsporulating rod.

- The bacteria often form clusters of parallel arrays (palisades) in culture, referred to as *Chinese characters*.
- Some strains produce diphtheria toxin, which can cause myocarditis, polyneuropathy, and other systemic toxicities and is associated with the formation of pseudomembranes in the pharynx during respiratory infection.

Epidemiology and Pathogenesis

As a result of routine immunization, fewer than five cases of diphtheria are diagnosed per year in the United States.

- Low-income countries in Africa and Asia continue to have significant outbreaks; globally, there were ~7000 cases of diphtheria in 2008 and ~5000 deaths related to diphtheria in 2004.
- *C. diphtheriae* is transmitted via the aerosol route, primarily during close contact.
- Diphtheria toxin—the primary virulence factor—irreversibly inhibits protein synthesis, thereby causing the death of the cell.

Clinical Manifestations

- *Respiratory diphtheria:* Upper respiratory tract illness due to *C. diphtheriae* typically has a 2- to 5-day incubation period and is diagnosed on the basis of a constellation of sore throat; low-grade fever; and a tonsillar, pharyngeal, or nasal pseudomembrane.
  - Unlike that of GAS pharyngitis, the pseudomembrane of diphtheria is tightly adherent; dislodging the membrane usually causes bleeding.
  - Massive swelling of the tonsils and "bull-neck" diphtheria resulting from submandibular and paratracheal edema can develop. This illness is further characterized by foul breath, thick speech, and stridorous breathing.
  - Respiratory tract obstruction due to swelling and sloughing of the pseudomembrane can be fatal.
  - Neurologic manifestations may appear during the first 2 weeks of illness, beginning with dysphagia and nasal dysarthria and progressing to cranial nerve involvement (e.g., weakness of the tongue, facial numbness, blurred vision due to ciliary paralysis).
    - Several weeks later, generalized sensorimotor polyneuropathy with prominent autonomic dysfunction (including hypotension) may occur.
    - Pts who survive the acute phase gradually improve.
- *Cutaneous diphtheria:* This variable dermatosis is generally characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation. Pts typically present to medical care because of nonhealing or enlarging ulcers; the lesions rarely exceed 5 cm in diameter.

Diagnosis

A definitive diagnosis is based on compatible clinical findings and detection of *C. diphtheriae* or toxigenic *C. ulcerans* (by isolation or histologic identification) in local lesions.

http://internalmedicinebook.com

- The laboratory should be notified that diphtheria is being considered, and appropriate selective media must be used.
- In the United States, respiratory diphtheria is a notifiable disease; cutaneous diphtheria is not.

TREATMENT DIPHTHERIA

- Diphtheria antitoxin is the most important component of treatment and should be given as soon as possible. To obtain antitoxin, contact the Emergency Operations Center at the Centers for Disease Control and Prevention (CDC) (770-488-7100). See *http://www.cdc.gov/diphtheria/dat.html* for further information.
- Antibiotic therapy is administered for 14 days to prevent transmission to contacts. The recommended options are (1) procaine penicillin G (600,000 U IM q12h in adults; 12,500–25,000 U/kg IM q12h in children) until the pt can take oral penicillin V (125–250 mg qid); or (2) erythromycin (500 mg IV q6h in adults; 40–50 mg/kg per day IV in 2–4 divided doses in children) until the pt can take oral erythromycin (500 mg qid).
  - Rifampin and clindamycin are other options for pts who cannot tolerate penicillin or erythromycin.
  - Cultures should document eradication of the organism 1 and 14 days after completion of antibiotic therapy. If the organism is not eradicated after 2 weeks of therapy, an additional 10-day course followed by repeat cultures is recommended.
- Respiratory isolation and close monitoring of cardiac and respiratory functions should be instituted.

Prognosis

Risk factors for death include a long interval between onset of local disease and antitoxin administration; bull-neck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudomembrane elongation; and laryngeal, tracheal, or bronchial involvement.

Prevention

- DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) is recommended for primary immunization of children up to age 7 years; Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) is recommended as the booster vaccine for children 11–12 years old and as the catch-up vaccine for children 7–10 and 13–18 years old.
- Td (tetanus and diphtheria toxoids) is recommended for routine booster use in adults at 10-year intervals or for tetanus-prone wounds. When >10 years have elapsed since the last Td dose, adults 19–64 years old should receive a single dose of Tdap.
- Close contacts of pts with respiratory diphtheria should have throat specimens cultured for *C. diphtheriae*, should receive a 7- to 10-day course of oral erythromycin or one dose of benzathine penicillin (1.2 mU for persons ≥6 years old; 600,000 U for children <6 years old), and should be vaccinated if immunization status is uncertain.

OTHER CORYNEBACTERIA AND RELATED ORGANISMS

Nondiphtherial *Corynebacterium* species and related organisms are common components of the normal human flora. Although frequently considered contaminants, these bacteria are associated with invasive disease in immunocompromised hosts.

http://internalmedicinebook.com

- *C. ulcerans* infection is a zoonosis that causes diphtheria-like illness and requires similar treatment.
- *C. jeikeium* infects pts with cancer or severe immunodeficiency and can cause severe sepsis, endocarditis, device-related infections, pneumonia, and soft tissue infections. Treatment consists of removal of the source of infection and administration of vancomycin.
- *C. urealyticum* is a cause of sepsis and nosocomial UTI, including *alkaline-encrusted cystitis* (a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phosphate on the surface and walls of ulcerating lesions in the bladder). Vancomycin is an effective therapeutic agent.
- *Rhodococcus* species appear as spherical to long, curved, clubbed gram-positive rods that are often acid fast. The most common presentation—nodular cavitary pneumonia of the upper lobe (similar to tuberculosis and nocardiosis) in an immunocompromised host—often occurs in conjunction with HIV infection. Vancomycin is the drug of choice, but macrolides, clindamycin, rifampin, and TMP-SMX have also been used to treat these infections.
- *Arcanobacterium haemolyticum* can cause pharyngitis and chronic skin ulcers, often in association with a scarlatiniform rash similar to that caused by GAS. The organism is susceptible to β-lactam agents, macrolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. Penicillin resistance has been reported.

For a more detailed discussion, see Wessels MR: Streptococcal Infections, Chap. 173, p. 963; Arias CA, Murray BE: Enterococcal Infections, Chap. 174, p. 971; Bishai WR, Murphy JR: Diphtheria and Other Corynebacterial Infections, Chap. 175, p. 977, in HPIM-19.

88 Meningococcal and Listerial Infections

MENINGOCOCCAL INFECTIONS

- *Etiology and microbiology: Neisseria meningitidis* is a catalase- and oxidase-positive, gram-negative aerobic diplococcus with a polysaccharide capsule that colonizes humans only.
  - Of the 13 identified serogroups, only 6—A, B, C, X, Y, and W (formerly W135)—account for the majority of cases of invasive disease.
  - Serogroups A, X, and W cause recurrent epidemics in sub-Saharan Africa. Serogroup B can cause hyperendemic disease, and serogroups C and Y cause sporadic disease and small outbreaks.
- *Epidemiology:* Up to 500,000 cases of meningococcal disease occur worldwide each year, with a mortality rate of ~10%.

http://internalmedicinebook.com

- Most commonly, meningococci asymptomatically colonize the nasopharynx; such asymptomatic nasopharyngeal carriage is detected in >25% of healthy adolescents and ~10% of adults.
- Patterns of meningococcal disease include epidemics, outbreaks (e.g., in colleges, refugee camps), hyperendemic disease, and sporadic or endemic cases.
- Although most countries have predominantly sporadic cases (0.3–5 cases per 100,000 population), epidemics in sub-Saharan Africa can have rates as high as 1000 cases per 100,000 population.
- Rates of meningococcal disease are highest among infants, with a second peak in adolescents and young adults (15–25 years of age).
- Other risk factors for meningococcal disease include complement deficiency (e.g., C5–C9, properdin, factor D), close contact with carriers, exposure to tobacco smoke, and a recent URI caused by a virus or *Mycoplasma* species.

- *Pathogenesis:* Meningococci colonizing the upper respiratory tract invade the bloodstream through the mucosa only rarely, usually within a few days after an invasive strain is acquired.
  - The capsule is an important virulence factor, providing resistance to phagocytosis and helping prevent desiccation during transmission between hosts.
  - Severity of disease is related to the degree of endotoxemia and the magnitude of the inflammatory response.
  - Endothelial injury leads to increased vascular permeability and hypovolemia, resulting in vasoconstriction and ultimately in decreased cardiac output.
  - Intravascular thrombosis caused by activation of procoagulant pathways and downregulation of anticoagulant pathways results in the characteristic purpura fulminans often seen in meningococcemia.
- *Clinical manifestations:* The most common clinical syndromes are meningitis and meningococcal septicemia, with disease usually developing within 4 days of organism acquisition.
  - A nonblanching rash (petechial or purpuric) develops in >80% of cases; early in the illness, the rash is often absent or may be indistinguishable from viral rashes.
  - Meningococcal meningitis alone (without septicemia) accounts for 30–50% of cases.
    - This meningitis is indistinguishable from other forms of bacterial meningitis unless there is an associated petechial or purpuric rash.
    - Classic signs of meningitis (e.g., headache, neck stiffness, photophobia) are often absent or difficult to discern in infants and young children.
  - Meningococcal septicemia alone accounts for ~20% of cases and initially may present as an influenza-like illness (e.g., fever, headache, myalgias, vomiting, abdominal pain).
    - May progress to shock (e.g., tachycardia, poor peripheral perfusion, oliguria), decreased level of consciousness due to decreased cerebral perfusion, spontaneous hemorrhage (pulmonary, gastric, or cerebral), and ultimately multiorgan failure and death
    - Poor prognostic factors include an absence of meningismus, hypotension, relatively low temperature (<38°C [100.4°F]), leukopenia, and thrombocytopenia.
  - Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash associated with fever, joint pain, features of arthritis, and splenomegaly that may progress to acute meningococcal septicemia if untreated.
    - This condition is occasionally associated with complement deficiencies or inadequate sulfonamide therapy.
  - Postmeningococcal reactive disease is immune complex–mediated and occurs 4–10 days after onset of meningococcal disease.
    - Manifestations can include a maculopapular or vasculitic rash (2% of cases), arthritis (≤8% of cases), iritis (1% of cases), or serositis. These features resolve spontaneously without sequelae.

http://internalmedicinebook.com

  - Less common clinical manifestations include pneumonia, pyogenic arthritis, osteomyelitis, purulent pericarditis, endophthalmitis, conjunctivitis, or primary peritonitis.
- *Diagnosis:* Although meningococcal infections are often diagnosed on clinical grounds, blood cultures are positive in ~75% of cases and should be performed to confirm the diagnosis and to facilitate public health investigations.
  - In the setting of fever and petechial rash, elevations in the WBC count and inflammatory marker levels suggest meningococcal disease.
  - With antibiotic pretreatment, blood cultures are generally negative; in contrast, PCR analysis of whole-blood samples is effective for several days after initiation of antibiotics and increases the diagnostic yield by >40%.
  - Unless contraindicated on clinical grounds, LP should be performed in cases of suspected meningococcal meningitis.
    - Gram's staining of CSF is ~80% sensitive, and CSF culture is 90% sensitive. Latex agglutination testing of CSF is insensitive and should be avoided.
    - LP should be avoided in pts with meningococcal septicemia, as positioning for the procedure may adversely affect circulatory status.

TREATMENT MENINGOCOCCAL INFECTIONS

- Initial therapy should focus on urgent clinical issues (e.g., hypovolemic shock, increased intracranial pressure, airway patency) and administration of antibiotics.
- Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per day [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to provide coverage both for meningococci and for other, potentially penicillin-resistant organisms that may produce an indistinguishable clinical syndrome.
- Meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days.
  - A single dose of ceftriaxone has been used successfully in resource-poor settings.
  - Treatment for meningococcal disease at other foci (e.g., pneumonia, arthritis) is usually continued until clinical and laboratory evidence of infection has resolved; cultures usually become sterile within 24 h of initiation of antibiotics.
- Little evidence supports other adjunctive therapies (e.g., antibody to lipopolysaccharide, recombinant bactericidal/permeability-increasing protein, activated protein C) in relevant pt populations; these therapies are not currently recommended.

- *Prognosis:* Despite the availability of antibiotics and other intensive medical interventions, ~10% of pts die.
  - Necrosis of purpuric lesions leads to scarring and the potential need for skin grafting in ~10% of cases.
  - 5% of pts have hearing loss, 7% of pts have neurologic complications, and ~25% of pts with serogroup B meningococcal disease have psychological disorders.
- *Prevention:* Polysaccharide-based and conjugate vaccines exist for primary prevention; secondary cases can be prevented with antibiotic prophylaxis.
  - Meningococcal polysaccharide vaccines are currently formulated as bivalent (serogroups A and C) or quadrivalent (serogroups A, C, Y, and W) and provide adults with immunity of 2–10 years' duration. Because the B polysaccharide is the same as a polysaccharide expressed in fetuses and is therefore recognized as self, serogroup B strains have not been targeted by polysaccharide vaccines.

http://internalmedicinebook.com

- A variety of meningococcal conjugate vaccines have been developed for administration to infants. A quadrivalent formulation (serogroups A, C, Y, and W) is most common in the United States.
- A combination vaccine that includes outer-membrane vesicles and three recombinant neisserial proteins is effective against serogroup B, is immunogenic in infancy, and has recently been licensed for use.
- Close contacts (i.e., household and kissing contacts) of pts with meningococcal disease should receive prophylaxis with ciprofloxacin, ofloxacin, or ceftriaxone to eradicate nasopharyngeal colonization by *N. meningitidis.*
  - Rifampin fails to eradicate carriage in 15–20% of cases, and emerging resistance has been reported.
  - Pts with meningococcal disease who are treated with an antibiotic that does not clear colonization (e.g., penicillin) should also be given a prophylactic agent at the end of therapy.

LISTERIAL INFECTIONS

- *Etiology and microbiology: Listeria monocytogenes* is a food-borne pathogen that can cause serious infections, particularly in pregnant women and immunocompromised individuals.
  - The organism is a facultatively anaerobic, nonsporulating, gram-positive rod that demonstrates motility when cultured at low temperatures.
  - After ingestion of food that contains a high bacterial burden, virulence factors expressed by *Listeria* allow internalization into cells, intracellular growth, and cell-to-cell spread.
- *Epidemiology*
  - *Listeria* is commonly found in processed and unprocessed foods such as soft cheeses, delicatessen meats, hot dogs, milk, and cold salads; fresh fruits and vegetables can also transmit the organism.
  - There is no human-to-human transmission (other than vertical transmission from mother to fetus) or waterborne infection.
- *Clinical manifestations: Listeria* causes several clinical syndromes, of which meningitis and septicemia are most common.
  - *Gastroenteritis:* can develop within 48 h after ingestion of contaminated foods containing a large bacterial inoculum
    - Listeriosis should be considered in outbreaks of gastroenteritis when cultures for other likely pathogens are negative.
    - Sporadic cases appear to be uncommon.
  - *Bacteremia:* Pts present with fever, chills, myalgias, and arthralgias. Endocarditis is uncommon and is associated with fatality rates of 35–50%.
  - *Meningitis: Listeria* causes ~5–10% of cases of community-acquired meningitis in adults in the United States, with case–fatality rates of 15–26%.
    - Listerial meningitis differs from meningitis of other bacterial etiologies in that its presentation is often subacute, with meningeal signs and photophobia being less common.
    - The CSF profile usually reveals <1000 WBCs/μL, with a less marked neutrophil predominance than in other meningitides. Low glucose levels and a positive Gram's stain are seen in ~30–40% of cases.
  - *Meningoencephalitis and focal CNS infection: Listeria* can directly invade the brain parenchyma and cause cerebritis or focal abscess.
    - Of CNS infections, ~10% are macroscopic abscesses, which are sometimes misdiagnosed as tumors.
    - Brainstem invasion can cause severe rhombencephalitis, with asymmetric cranial nerve defects, cerebellar signs, and hemiparetic/hemisensory defects.

http://internalmedicinebook.com

  - *Infection in pregnant women and neonates:* Listeriosis is a serious infection in pregnancy.
    - Pregnant women are usually bacteremic and present with a nonspecific febrile illness that includes myalgias/arthralgias, backache, and headache; CNS involvement is rare. Infected women usually do well after delivery.
    - Infection develops in 70–90% of fetuses from infected women; almost 50% of infected fetuses die. This risk can be reduced to ~20% with prepartum treatment.
    - Overwhelming listerial fetal infection—*granulomatosis infantiseptica*—is characterized by miliary microabscesses and granulomas, most often in the skin, liver, and spleen.
    - Late-onset neonatal disease develops ~10–30 days after delivery by mothers with asymptomatic infection.
- *Diagnosis:* Timely diagnosis requires that the illness be considered in groups at risk: pregnant women, elderly pts, neonates, immunocompromised pts, and pts with chronic underlying medical conditions (e.g., alcoholism, diabetes).
  - Listeriosis is diagnosed when the organism is cultured from a usually sterile site, such as blood, CSF, or amniotic fluid.
  - Listeriae may be confused with "diphtheroids" or pneumococci in gram-stained CSF or may be gram-variable and confused with *Haemophilus* spp.
  - Serologic tests and PCR assays are not clinically useful at present.

TREATMENT LISTERIAL INFECTIONS

- Ampicillin (2 g IV q6h) is the drug of choice for the treatment of listerial infections; penicillin is also highly active.
  - Many experts recommend the addition of gentamicin (1.0–1.7 mg/kg IV q8h) for synergy.
  - For penicillin-allergic pts, trimethoprim-sulfamethoxazole (15–20 mg of TMP/kg IV daily in divided doses q6–8h) should be given. Cephalosporins are not effective.
  - Neonates should receive ampicillin and gentamicin, dosed by weight.
- The duration of therapy depends on the syndrome: 2 weeks for bacteremia, 3 weeks for meningitis, 6–8 weeks for brain abscess/encephalitis, and 4–6 weeks for endocarditis. Early-onset neonatal disease can be severe and requires treatment for >2 weeks.

- *Prognosis:* With prompt therapy, many pts recover fully.
  - However, permanent neurologic sequelae are common in pts with brain abscess or rhombencephalitis.
  - Of live-born treated neonates in one series, 60% recovered fully, 24% died, and 13% were left with neurologic or other complications.
- *Prevention:* Pregnant women and other persons at risk for listeriosis should avoid soft cheeses and should avoid or thoroughly reheat ready-to-eat and delicatessen foods, even though the absolute risk posed by these foods is relatively low.



For a more detailed discussion, see Pollard AJ: Meningococcal Infections, Chap. 180, p. 995; Hohmann EL, Portnoy DA: *Listeria monocytogenes* Infections, Chap. 176, p. 982, in HPIM-19.

http://internalmedicinebook.com

89 Infections Caused by *Haemophilus, Bordetella, Moraxella*, and HACEK Group Organisms

HAEMOPHILUS INFLUENZAE

MICROBIOLOGY

H. influenzae is a small, gram-negative, pleomorphic coccobacillus that grows both aerobically and anaerobically.

- Six major serotypes (designated *a–f*) have been identified on the basis of antigenically distinct polysaccharide capsules.
- Unencapsulated strains are referred to as nontypable (NTHi).

EPIDEMIOLOGY

H. influenzae, an exclusively human pathogen, is spread by airborne droplets or through direct contact with secretions or fomites.

- Type b (Hib) strains are most important clinically, causing systemic invasive disease, primarily in infants and children <6 years of age.
- Widespread use of Hib conjugate vaccine in industrialized countries has dramatically decreased rates of Hib colonization and invasive disease, but the majority of children worldwide remain unimmunized.
- Both typable and nontypable strains can asymptomatically colonize the nasopharynx.

PATHOGENESIS

Hib strains cause systemic disease by invasion and systemic spread from the respiratory tract to distant sites (e.g., meninges, bones, joints). In contrast, NTHi strains cause disease by spread from the nasopharynx to contiguous sites (e.g., middle ear, lower respiratory tract).

- The polysaccharide capsule of encapsulated strains is critical for the organism's avoidance of opsonization.
- Levels of maternally derived antibodies to the capsular polysaccharide decline from birth to ~6 months of age and—in the absence of vaccination—remain low until ~2–3 years of age.

CLINICAL MANIFESTATIONS

- *Hib infection:* The most serious Hib infections are associated with meningitis or epiglottitis.
  - *Meningitis:* primarily affects children <2 years old and presents similarly to meningitis due to other bacterial pathogens
    - Mortality rates are ~5%.
    - Morbidity rates are high: 6% of pts have sensorineural hearing loss; one-fourth have some significant handicap; and one-half have some neurologic sequelae.
  - *Epiglottitis:* occurs in children 2–7 years old and occasionally in adults. It involves cellulitis of the epiglottis and supraglottic tissues that begins with a sore throat and fever and progresses rapidly to dysphagia, drooling, and airway obstruction.
  - *Other infections:* include cellulitis, pneumonia, osteomyelitis, septic arthritis, and bacteremia without an identifiable focus
- *NTHi infection:* NTHi is a common cause of lower respiratory tract disease in adults, particularly those with chronic obstructive pulmonary disease (COPD).

http://internalmedicinebook.com

- *COPD exacerbations:* characterized by increased cough, sputum production, and shortness of breath
- *Pneumonia:* presents similarly to other bacterial pneumonias, including pneumococcal pneumonia
- *Other infections:* NTHi is one of the three most common causes of childhood otitis media and is an important cause of sinusitis (in adults and children) and neonatal bacteremia. It is a less common cause of invasive infections in adults.

DIAGNOSIS

Recovery of the organism in culture is the most reliable method for diagnosis.

- The presence of gram-negative coccobacilli in gram-stained CSF provides strong evidence for meningitis due to *H. influenzae*.
- Detection of polyribitol ribose phosphate (PRP)—polymers of which form the type b capsule—in CSF allows rapid diagnosis of Hib meningitis before culture results are available.

TREATMENT *H. INFLUENZAE* INFECTIONS

- Initial therapy for Hib meningitis consists of a third-generation cephalosporin: ceftriaxone (2 g q12h) or cefotaxime (2 g q4–6h) for adults and ceftriaxone (37.5–50 mg/kg q12h) or cefotaxime (50 mg/kg q6h) for children.
  - Children >2 months of age should receive adjunctive dexamethasone (0.15 mg/kg IV q6h for 2 days) to reduce the incidence of neurologic sequelae.
  - Antibiotic therapy should continue for 7–14 days.
- Antibiotic treatment for invasive infections other than meningitis (e.g., epiglottitis) consists of the same antibiotic but at a dosage different from that given for meningitis—e.g., ceftriaxone (2 g q24h) for adults.
  - Treatment duration depends on the clinical response, but a course lasting 1–2 weeks is generally appropriate.
- Most NTHi infections can be treated with oral antibiotics, such as amoxicillin/clavulanate, extended-spectrum cephalosporins, newer macrolides (azithromycin or clarithromycin), and fluoroquinolones (in nonpregnant adults).
  - About 20–35% of NTHi strains produce β-lactamase.
  - The incidence of strains with altered penicillin-binding proteins conferring resistance to ampicillin is increasing in Europe and Japan.

PREVENTION

Hib vaccine is recommended for all children worldwide; the immunization series should be started at ~2 months of age.

- Secondary attack rates are high among household contacts of pts with Hib disease. All children and adults (except pregnant women) in households with a case of Hib disease and at least one incompletely immunized contact <4 years of age should receive prophylaxis with oral rifampin.
- A vaccine that combines NTHi and pneumococcal antigens is used in many countries outside the United States and has shown partial efficacy in preventing *H. influenzae* otitis media.

PERTUSSIS

MICROBIOLOGY AND PATHOGENESIS

Bordetella pertussis, the etiologic agent of pertussis, is a fastidious gram-negative pleomorphic aerobic bacillus that attaches to ciliated epithelial cells of the

http://internalmedicinebook.com

nasopharynx, multiplies locally, and produces a wide array of toxins and biologically active products.

- *B. parapertussis* causes a similar, though typically milder, illness. *B. holmesii* causes up to 20% of pertussis-like syndromes.
- The most important toxin in *B. pertussis* is pertussis toxin, which has ADP ribosylating activity. The absence of this toxin in *B. parapertussis* may explain the milder illness.

EPIDEMIOLOGY

Pertussis is highly communicable. In households, attack rates are 80–100% among unimmunized contacts and 20% among immunized contacts.

- Pertussis remains an important cause of infant morbidity and death in developing countries, with ~195,000 childhood deaths worldwide in 2008.
- In the United States, although the incidence of pertussis has decreased by >95% because of universal childhood vaccination, >40,000 cases were reported in 2012, with increasing rates among adolescents and adults.
- Persistent cough of >2 weeks' duration in an adult may be due to *B. pertussis* in 12–30% of cases.
- Severe morbidity and mortality are restricted to infants <6 months of age.

CLINICAL MANIFESTATIONS

After an incubation period of 7–10 days, a prolonged coughing illness begins. Symptoms are usually more severe in infants and young children.

- The initial symptoms (the *catarrhal* phase) are similar to those of the common cold (e.g., coryza, lacrimation, mild cough, low-grade fever, malaise) and last 1–2 weeks.
- The *paroxysmal* phase follows and lasts 2–4 weeks. It is characterized by a hallmark cough that occurs in spasmodic fits of 5–10 coughs each. Vomiting or a "whoop" may follow a coughing fit. Apnea and cyanosis can occur during spasms. Most complications occur during this phase.
- During the subsequent *convalescent* phase, coughing episodes resolve gradually over 1–3 months. For 6–12 months, viral infections may induce a recrudescence of paroxysmal cough.
- Disease manifestations are often atypical in adolescents and adults, with paroxysmal cough and the "whoop" being less common. Post-tussive emesis is the best predictor of pertussis as the cause of prolonged cough in adults.
- Lymphocytosis (an absolute lymphocyte count of $>10^5/\mu L$) suggests pertussis in young children, but is not common among affected adolescents and adults.

DIAGNOSIS

- Cultures of nasopharyngeal secretions—the gold standard for diagnosis—remain positive in untreated cases of pertussis for a mean of 3 weeks after illness onset. Given that the diagnosis often is not considered until the pt is in the paroxysmal phase, there is a small window of opportunity for culture-proven diagnosis.
  - Secretions must be inoculated immediately onto selective media.
  - Results become positive by day 5.
- Compared with culture, PCR of nasopharyngeal specimens is more sensitive and yields positive results longer in both treated and untreated pts.
  - Reporting of pseudo-outbreaks of pertussis based on false-positive PCR results indicates the need for greater standardization.
- Although serology can be useful in pts with symptoms lasting >4 weeks, interpretation of results is complicated by late presentation for medical care and prior immunization.

http://internalmedicinebook.com

TREATMENT **PERTUSSIS**

- Antibiotic therapy does not substantially alter the clinical course unless given early in the catarrhal phase, but is effective at eradicating the organism from the nasopharynx.
  - Macrolides (erythromycin, 1–2 g/d for 1–2 weeks; clarithromycin, 250 mg bid for 1 week; or azithromycin, 500-mg load on day 1, then 250 mg/d for 4 days) are the drugs of choice.
  - Trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet PO bid for 2 weeks) is recommended for macrolide-intolerant pts.
- Cough suppressants are ineffective and have no role in management of pertussis.
- Respiratory isolation is required for hospitalized pts until antibiotics have been given for 5 days.

PREVENTION

- Chemoprophylaxis with macrolides is recommended for household contacts of pts, especially if there are household members at high risk of severe disease (e.g., children <1 year of age, pregnant women); however, there is no evidence demonstrating that this regimen leads to a decrease in the incidence of clinical disease.
- In addition to the regular childhood immunization schedule, adolescents and adults should receive a one-time booster with an acellular vaccine.

MORAXELLA CATARRHALIS

MICROBIOLOGY AND EPIDEMIOLOGY

M. catarrhalis is an unencapsulated gram-negative diplococcus. Part of the normal flora of the upper airways, *M. catarrhalis* colonizes 33–100% of infants; the prevalence of colonization decreases steadily with age.

CLINICAL MANIFESTATIONS

- *M. catarrhalis* causes 15–20% of cases of acute otitis media in children. Acute otitis media caused by *M. catarrhalis* or NTHi is clinically milder than cases caused by *Streptococcus pneumoniae*, with less fever and a lower frequency of an erythematous, bulging tympanic membrane.
- *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults.
- In adults, *M. catarrhalis* is a common cause of exacerbations of COPD, accounting for ~10% of cases.
- *M. catarrhalis* pneumonia is uncommon, generally affecting elderly pts with underlying cardiopulmonary disease.

DIAGNOSIS

Invasive procedures are needed to definitively identify the etiology of otitis media or sinusitis and are generally not performed. Isolation of *M. catarrhalis* from sputum samples from pts with COPD is suggestive, but not diagnostic, of *M. catarrhalis* as the cause.

TREATMENT ***M. CATARRHALIS* INFECTIONS**

- Otitis media in children and exacerbations of COPD in adults are generally managed empirically with antibiotics active against *S. pneumoniae, H. influenzae,* and *M. catarrhalis*.

http://internalmedicinebook.com

- Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanate, extended-spectrum cephalosporins, newer macrolides (e.g., azithromycin, clarithromycin), TMP-SMX, and fluoroquinolones.
- More than 90% of *M. catarrhalis* strains produce a β-lactamase and are resistant to ampicillin.

THE HACEK GROUP

MICROBIOLOGY

The HACEK group consists of fastidious, slow-growing, gram-negative bacteria whose growth requires carbon dioxide. Several *Haemophilus* spp., *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* make up this group. Normal residents of the oral cavity, HACEK bacteria can cause both local oral infections and severe systemic disease, particularly endocarditis.

CLINICAL MANIFESTATIONS

- HACEK organisms caused 0.8–6% of cases of infective endocarditis; most of these cases are due to *Aggregactibacter* spp., *Haemophilus* spp., or *C. hominis*.
- Infection typically occurs in pts with underlying valvular disease, often in the setting of a recent dental procedure or nasopharyngeal infection.
- The aortic and mitral valves are most commonly affected. *Aggregatibacter* and *Haemophilus* spp. cause mitral valve vegetations most often, while *C. hominis* is associated with aortic valve vegetations.
- Embolization is common, with 28–71% of pts affected.
- *H. parainfluenzae* is the most common organism isolated in cases of HACEK endocarditis. Pts usually present within the first 2 months of illness, and 19–50% of pts develop CHF.
- *Aggregatibacter* spp. cause prosthestic valve endocarditis more often than *Haemophilus* spp. *A. actinomycetemcomitans* is isolated from soft tissue infections in association with *Actinomyces israelii*. Pts with *Aggregatibacter* endocarditis often have periodontal disease or have recently had dental work and are sick for several months before diagnosis.
- *C. hominis* typically causes endocarditis in pts with valvular heart disease or prosthetic valves. Long-standing infection with systemic manifestations usually precedes diagnosis. A second species, *C. valvarum*, has now been described in association with endocarditis.
- *E. corrodens* is usually a component of mixed infections and is common in human bite wounds, head and neck soft tissue infections, endocarditis, and infections in IV drug users.
- *K. kingae* is a common cause of skeletal infections in children <3 years old. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood-culture bottles enhances recovery of this organism. Infective endocarditis due to *K. kingae* occurs in older children and adults with preexisting valvular disease.

TREATMENT HACEK GROUP INFECTIONS

- Table 89-1 lists antibiotic regimens used to treat endocarditis and other serious infections caused by HACEK organisms.
- Native-valve endocarditis should be treated for 4 weeks and prosthetic-valve endocarditis for 6 weeks.
- Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, that due to HACEK bacteria can often be cured with antibiotics alone (i.e., without surgery).

http://internalmedicinebook.com

TABLE 89-1 TREATMENT OF INFECTIONS CAUSED BY HACEK GROUP ORGANISMS

Organisms	Preferred Therapy	Alternative Agents	Comments
Haemophilus spp. *Aggregatibacter actinomycetemcomitans, A. aphrophilus, A. paraphrophilus*, other species *Cardiobacterium hominis* *Eikenella corrodens* *Kingella kingae*	Ceftriaxone (2 g/d)	Ampicillin/sulbactam (3 g of ampicillin q6h)	Ampicillin/sulbactam resistance has been described in *Haemophilus* and *Aggregatibacter* spp.
		Levofloxacin (500–750 mg/d)	Data on use of levofloxacin for endocarditis therapy are limited. Fluoroquinolones are not recommended for treatment of pts <18 years of age.
		Penicillin (16–18 million units q4h) or ampicillin (2 g q4h)	Penicillin or ampicillin can be used if the organism is susceptible. However, because of the slow growth of HACEK bacteria, antimicrobial testing may be difficult, and β-lactamase production may not be detected.



For a more detailed discussion, see Murphy TF: *Haemophilus* and *Moraxella* Infections, Chap. 182, p. 1010; Barlam TF, Kasper DL: Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria, Chap. 183e; Top KA, Halperin SA: Pertussis and Other *Bordetella* Infections, Chap. 185, p. 1021, in HPIM-19.

90 Diseases Caused by Gram-Negative Enteric Bacteria and *Pseudomonas*

GRAM-NEGATIVE ENTERIC BACTERIA

GENERAL CONSIDERATIONS

Gram-negative bacilli (GNB) are normal components of the human colonic flora and/or a number of environmental habitats and can colonize mucosal and skin surfaces, especially in pts in long-term care facilities and hospital settings. GNB cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts; extraintestinal infections due to *Escherichia coli* and, to a lesser degree, *Klebsiella* species are most common. Isolation of GNB from any sterile site

http://internalmedicinebook.com

almost always implies infection, whereas isolation from nonsterile sites requires clinical correlation. Early appropriate antimicrobial therapy improves outcomes. Given worldwide increases in multidrug-resistant GNB (e.g., due to extended-spectrum β-lactamases [ESBLs] and AmpC β-lactamases), combination empirical antimicrobial therapy pending susceptibility results may be appropriate for critically ill pts.

EXTRAINTESTINAL PATHOGENIC *E. COLI* (EXPEC)

In contrast to intestinal pathogenic *E. coli* (see below), ExPEC strains are often found in the intestinal flora of healthy individuals but cause disease only when they enter a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs). Most ExPEC strains have virulence factor profiles distinct from those of other commensal strains and from those of pathogenic strains that cause intestinal infections.

Clinical Manifestations

The clinical presentation depends in large part on the site of the body infected by ExPEC.

- *UTI:* The urinary tract is the site most frequently infected by ExPEC; see **Chap. 144** for more details. *E. coli* causes 80–90% of ~6–8 million episodes of acute uncomplicated UTI in premenopausal women.
- *Abdominal and pelvic infection:* The abdomen and pelvis represent the second most common site of infection by ExPEC, which may be isolated in the setting of a polymicrobial infection; see **Chap. 81** for more details. Syndromes include peritonitis, intraabdominal abscesses, and cholangitis.
- *Pneumonia:* ExPEC is generally the third or fourth most commonly isolated GNB in hospital-acquired pneumonia and can be a common cause of pneumonia in pts residing in long-term-care facilities; see **Chap. 132** for more details.
- *Meningitis: E. coli* is one of the two leading causes of neonatal meningitis (the other being group B *Streptococcus).* Strains with the K1 capsular serotype are generally involved.
- *Cellulitis/musculoskeletal infection: E. coli* often contributes to infection of decubitus ulcers and diabetic lower-extremity ulcers, cellulitis, and burn-site or surgical-site infections. Hematogenously acquired osteomyelitis, particularly vertebral, is more commonly caused by *E. coli* than is generally appreciated. See **Chap. 84** for more details.
- *Bacteremia: E. coli* is one of the two most common blood isolates of clinical significance. *E. coli* bacteremia can arise from primary infection at any site, but originates most commonly from the urinary tract (50–67% of episodes) and next most commonly from the abdomen (25% of episodes). *E. coli* bacteremia is typically associated with sepsis. Endovascular infections are rare but have been described.

Diagnosis

ExPEC grows readily on standard media under either aerobic or anaerobic conditions. More than 90% of strains ferment lactose and are indole positive.

TREATMENT **EXTRAINTESTINAL INFECTIONS CAUSED BY *E. COLI***

- Rates of resistance to ampicillin, first-generation cephalosporins, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones are increasing. ESBLs are increasingly common in *E. coli*.
- Carbapenems and amikacin are the most predictably active agents overall, but carbapenemase-producing strains are on the rise.
- It is important to use the most appropriate narrower-spectrum agent whenever possible and to avoid treating colonized but uninfected pts, thus combating the increase in antibiotic resistance.

http://internalmedicinebook.com

INTESTINAL PATHOGENIC *E. COLI*

Microbiology and Clinical Manifestations

At least five distinct pathotypes of intestinal pathogenic *E. coli* exist; see Chap. 82 for more details. As mentioned above, these strains are rarely encountered as part of the commensal flora in healthy individuals.

- *Shiga toxin–producing E. coli (STEC)/enterohemorrhagic E. coli (EHEC)/Shiga toxin–producing enteroaggregegrative E. coli (STEAEC):* In addition to diarrhea, STEC/EHEC infection results in the hemolytic–uremic syndrome (HUS) in 2–8% of pts, particularly those who are very young or elderly. STEAEC results in a higher rate of HUS (~20%), with a higher incidence among adults, especially young women.
  - STEC/EHEC/STEAEC is associated with ingestion of contaminated food (e.g., undercooked ground beef, fresh produce) and water; person-to-person transmission (e.g., at day-care centers) is an important route for secondary spread.
  - Disease can be caused by $<10^2$ colony-forming units (CFUs) of STEC/EHEC/STEAEC.
  - In contrast to the other pathotypes, STEC/EHEC/STEAEC (including *E. coli* O157:H7) causes infection more frequently in industrialized countries than in developing countries.
- *Enterotoxigenic E. coli (ETEC):* These strains are a major cause of endemic diarrhea among children residing in tropical and low-income countries and are the most common agent of traveler's diarrhea; 10^6–10^{10} CFU are needed to cause disease.
- *Enteropathogenic E. coli (EPEC):* EPEC is an important cause of diarrhea among infants in developing countries.
- *Enteroinvasive E. coli (EIEC):* EIEC, an uncommon cause of diarrhea, produces inflammatory colitis (stools containing mucus, blood, and inflammatory cells) similar to that caused by *Shigella* and primarily affects children and travelers in developing countries; 10^8–10^{10} CFU are needed to cause disease.
- *Enteroaggregative and diffusely adherent E. coli (EAEC):* EAEC was initially described in young children in developing countries. More recent studies indicate that EAEC may be a common cause of prolonged, watery diarrhea in all age groups in industrialized countries.

Diagnosis

Specific diagnosis is usually unnecessary except when STEC/EHEC/STEAEC is involved. To detect the latter, simultaneous culture (screening for *E. coli* strains that do not ferment sorbitol followed by serotyping for O157) and testing for Shiga toxins or toxin genes is recommended.

TREATMENT INTESTINAL INFECTIONS CAUSED BY *E. COLI*

- See Chap. 82 for more details. Replacement of water and electrolytes and avoidance of antibiotics in STEC/EHEC/STEAEC infection (since antibiotic use may increase the incidence of HUS) are indicated.

KLEBSIELLA

Epidemiology

K. pneumoniae colonizes the colon in 5–35% of healthy individuals and, from a medical standpoint, is the most important *Klebsiella* species. *K. oxytoca* primarily causes infections in long-term care and hospital settings. *K. pneumoniae* subspecies *rhinoscleromatis*, which causes rhinoscleroma, and *K. pneumoniae* subspecies *ozaenae*, which causes chronic atrophic rhinitis, infect pts in tropical climates.

http://internalmedicinebook.com

Clinical Manifestations

As in other GNB infections, the clinical presentation depends on the infected anatomic site.

- *Pneumonia: Klebsiella* is a common cause of pneumonia among residents of long-term care facilities and hospitalized pts. In Asia and South Africa, community-acquired pneumonia due to hypervirulent strains of *K. pneumoniae* is increasingly common, particularly among younger, healthy pts.
  - The presentation is similar to that of pneumonia caused by other enteric GNB, with purulent sputum production and pulmonary infiltrates on CXR.
  - Infection can progress to pulmonary necrosis, pleural effusion, and empyema.
- *UTI: K. pneumoniae* causes 1–2% of cases of uncomplicated cystitis and 5–17% of cases of complicated UTI.
- *Abdominal infections: Klebsiella* causes a spectrum of disease similar to that of *E. coli*, but with less frequent occurrence. Hypervirulent strains have become a common cause of monomicrobial community-acquired liver abscess, spontaneous bacterial peritonitis, and splenic abscess.
- *Bacteremia:* Bacteremia can arise from a primary infection at any site; infections of the urinary tract, respiratory tract, and abdomen (especially hepatic abscess) each account for 15–30% of episodes.
- *Other infections: Klebsiella* cellulitis or soft tissue infection most frequently affects devitalized tissue and immunocompromised hosts. *Klebsiella* can also cause endophthalmitis, nosocomial sinusitis, and osteomyelitis.

Diagnosis

Klebsiellae usually ferment lactose, although the *K. pneumoniae* subspecies *rhinoscleromatis* and *ozaenae* are nonfermenters and are indole negative.

TREATMENT *KLEBSIELLA* INFECTIONS

- Klebsiellae are resistant to ampicillin and ticarcillin.
  - The increase in plasmid-encoded ESBLs has led to increasing resistance to third- and fourth-generation cephalosporins, aminoglycosides, tetracyclines, and TMP-SMX.
  - Fluoroquinolone resistance is increasing, especially among ESBL-containing strains.
- Empirical treatment of serious or health care–associated *Klebsiella* infections with amikacin or carbapenems is prudent; however, carbapenemase-producing strains are increasing in frequency. Optimal therapy for carbapenemase strains is unclear, but tigecycline and the polymyxins (e.g., colistin) are used most frequently on the basis of in vitro susceptibility profiles. When resistance to these agents is documented, combination therapy is often used.

PROTEUS

Epidemiology

P. mirabilis is part of the normal flora in 50% of healthy people and causes 90% of *Proteus* infections. *P. vulgaris* and *P. penneri* are isolated primarily from pts in hospitals and long-term care facilities.

Clinical Manifestations

Most *Proteus* infections arise from the urinary tract. *Proteus* species account for 1–2% of uncomplicated UTIs, 5% of hospital-acquired UTIs, and 10–15% of complicated UTIs (especially those associated with urinary catheters).

http://internalmedicinebook.com

- *Proteus* produces high levels of urease that result in alkalinization of urine and ultimately in formation of struvite and carbonate-apatite calculi.
- Infections at other sites are uncommon but include pneumonia, abdominal infections, soft tissue infections, and bacteremia.

Diagnosis

Proteus strains are typically lactose negative, produce H_2S, and exhibit swarming motility on agar plates. *P. mirabilis* and *P. penneri* are indole negative, whereas *P. vulgaris* is indole positive.

TREATMENT *PROTEUS* INFECTIONS

- *P. mirabilis* is susceptible to most agents except tetracycline, nitrofurantoin, polymyxins, and tigecycline. Resistance to ampicillin, first-generation cephalosporins, and fluoroquinolones is increasing.
- *P. vulgaris* and *P. penneri* are more resistant; induction of variants with stable derepression of chromosomal AmpC β-lactamase may occur with *P. vulgaris* isolates. Carbapenems, fourth-generation cephalosporins, amikacin, TMP-SMX, and fosfomycin exhibit excellent activity: 90–100% of *Proteus* isolates are susceptible.

OTHER GRAM-NEGATIVE ENTERIC PATHOGENS

- *Enterobacter* (e.g., *E. cloacae*, *E. aerogenes*), *Acinetobacter* (e.g., *A. baumannii*), *Serratia* (e.g., *S. marcescens*), and *Citrobacter* (e.g., *C. freundii*, *C. koseri*) usually cause nosocomial infections. Risk factors include immunosuppression, comorbid disease, prior antibiotic use, and ICU stays.
- Infections caused by *Morganella* (e.g., *M. morganii*) and *Providencia* (e.g., *P. stuartii*, *P. rettgeri*) resemble *Proteus* infections in terms of epidemiology, pathogenicity, and clinical manifestations but occur almost exclusively among persons in long-term care facilities and, to a lesser degree, among hospitalized pts.

Clinical Manifestations

These organisms generally cause a spectrum of disease similar to that caused by other GNB, including pneumonia (particularly ventilator-associated), UTI (especially catheter-related), intravascular device–related infection, surgical-site infection, and abdominal infections.

- *Citrobacter*, *Morganella*, and *Providencia* infections are generally associated with UTIs.
- *Acinetobacter* has caused soft tissue and bone infections among soldiers with battlefield injuries and is a well-known pathogen in burn units.

TREATMENT INFECTIONS CAUSED BY OTHER GRAM-NEGATIVE ENTERIC PATHOGENS

- Significant antibiotic resistance among these organisms makes therapy challenging.
  - Many of these organisms (e.g., *Serratia*, *Providencia*, *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Morganella*) have a derepressible AmpC β-lactamase that results in resistance to third-generation cephalosporins, monobactams, and—in many cases—β-lactam/β-lactamase inhibitor combinations.
  - *Morganella* and *Providencia* are inherently resistant to the polymyxins and tigecycline.

http://internalmedicinebook.com

- Carbapenems and amikacin are most reliably active, and fourth-generation cephalosporins are active provided the organism does not express an ESBL. Susceptibility testing is essential. Some isolates may retain susceptibility only to colistin and polymyxin B.

AEROMONAS

A. hydrophila causes >85% of *Aeromonas* infections. *Aeromonas* organisms proliferate in potable water, freshwater, and soil and are a putative cause of gastroenteritis. *Aeromonas* causes bacteremia and sepsis in infants and compromised hosts, especially those with cancer, hepatobiliary disease, trauma, or burns. The organisms can produce skin lesions similar to the ecthyma gangrenosum caused by *Pseudomonas aeruginosa*. *Aeromonas* causes nosocomial infections related to catheters, surgical incisions, and use of leeches.

TREATMENT ***AEROMONAS* INFECTIONS**

- *Aeromonas* is usually susceptible to fluoroquinolones (e.g., ciprofloxacin, 500 mg PO q12h or 400 mg IV q12h), third- and fourth-generation cephalosporins, carbapenems, and aminoglycosides.
- Susceptibility testing is critical to guide therapy since *Aeromonas* can produce various β-lactamases, including carbapenemases.

PSEUDOMONAS AERUGINOSA AND RELATED ORGANISMS

The pseudomonads make up a set of gram-negative organisms unable to ferment lactose. This group includes three medically important genera—*Pseudomonas*, *Burkholderia*, and *Stenotrophomonas*—that typically cause opportunistic disease.

P. AERUGINOSA

Microbiology

P. aeruginosa is a motile gram-negative rod that commonly produces green or bluish pigment and may have a mucoid appearance (which is particularly common in isolates from pts with cystic fibrosis). *P. aeruginosa* differs from enteric GNB in that it has a positive reaction in the oxidase test and does not ferment lactose.

Epidemiology

Because *P. aeruginosa* is found in most moist environments (e.g., in soil, in tap water, and on countertops), people routinely come into contact with the organism. The many factors that predispose to *P. aeruginosa* infection include disruption of cutaneous or mucosal barriers (e.g., due to burns or trauma), immunosuppression (e.g., due to neutropenia, AIDS, or diabetes), and disruption of the normal bacterial flora (e.g., due to broad-spectrum antibiotic therapy).

- *P. aeruginosa* is no longer a major cause of life-threatening bacteremia among pts with neutropenia or burn injury.
- *P. aeruginosa* bacteremia is currently most common among pts in the ICU.

Clinical Manifestations

P. aeruginosa can infect virtually all sites in the body but has a strong predilection for the lungs.

- *Pneumonia: P. aeruginosa* is considered a major cause of ventilator-associated pneumonia, although colonization may be difficult to distinguish from true infection.

http://internalmedicinebook.com

  - Clinically, most pts have a slowly progressive infiltrate, although progression is rapid in some cases. Infiltrates may become necrotic.
  - It is unclear whether an invasive procedure (e.g., bronchoalveolar lavage, protected-brush sampling of distal airways) is superior to tracheal aspiration in obtaining samples for culture.
  - Chronic respiratory infection with *P. aeruginosa* is associated with underlying or predisposing conditions (e.g., cystic fibrosis, bronchiectasis).
- *Bacteremia:* The presentation of *P. aeruginosa* bacteremia resembles that of sepsis in general but may be more severe, with attributable mortality rates of 28–44%.
  - Pathognomonic skin lesions (*ecthyma gangrenosum*) that at first are painful, reddish, and maculopapular and later become black and necrotic may develop in pts with marked neutropenia or HIV infection.
  - Endovascular infections occur mostly in IV drug users and pts with prosthetic valves.
- *Bone and joint infections: P. aeruginosa* is an infrequent cause of bone and joint infections.
  - Injection drug use (associated with sternoclavicular joint infections and vertebral osteomyelitis) and UTIs in the elderly (associated with vertebral osteomyelitis) are risk factors.
  - *Pseudomonas* osteomyelitis of the foot most often follows puncture wounds through sneakers and most commonly affects children.
- *CNS infections:* CNS infections due to *P. aeruginosa* are relatively rare and are almost always secondary to a surgical procedure or head trauma.
- *Eye infections:* Keratitis and corneal ulcers can occur, usually resulting from trauma or surface injury by contact lenses. These infections are rapidly progressing entities that demand immediate therapeutic intervention. *P. aeruginosa* endophthalmitis secondary to bacteremia is a fulminant disease with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis.
- *Ear infections:* In addition to mild swimmer's ear, *Pseudomonas* ear infections can result in malignant otitis externa, a life-threatening infection that presents as severe ear pain and decreased hearing.
  - Pts may develop cranial-nerve palsies or cavernous venous sinus thrombosis.
  - Most ear infections due to *P. aeruginosa* occur in elderly diabetic pts.
- *UTIs:* UTIs due to *P. aeruginosa* usually result from a foreign body in the urinary tract, an obstruction in the genitourinary system, or urinary tract instrumentation or surgery.
- *Skin and soft tissue infections: P. aeruginosa* can cause a variety of dermatitides, including pyoderma gangrenosum in neutropenic pts, folliculitis, and other papular or vesicular lesions. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools.
- *Infections in pts with fever and neutropenia: P. aeruginosa* is always targeted in empirical treatment of these pts, given high rates of infection in the past and high associated mortality rates.
- *Infections in pts with AIDS: P. aeruginosa* infections in pts with AIDS can be fatal even though the clinical presentation is not particularly severe.
  - Pneumonia is the most common type of infection, with a high frequency of cavitary disease.
  - Since the advent of antiretroviral therapy, *P. aeruginosa* infection has declined in incidence among these pts but still occurs.

TREATMENT *P. AERUGINOSA* INFECTIONS

- See **Table 90-1** for antibiotic options and schedules.
- Several observational studies indicate that a single modern antipseudomonal β-lactam agent to which the isolate is sensitive is as efficacious as combination

http://internalmedicinebook.com

TABLE 90-1 ANTIBIOTIC TREATMENT OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND RELATED SPECIES

Infection	Antibiotics and Dosages	Other Considerations
Bacteremia		
Nonneutropenic host	Monotherapy: Ceftazidime (2 g q8h IV) *or* cefepime (2 g q12h IV) Combination therapy: Piperacillin/tazobactam (3.375 g q4h IV) *or* imipenem (500 mg q6h IV) *or* meropenem (1 g q8h IV) *or* doripenem (500 mg q8h IV) ***plus*** Amikacin (7.5 mg/kg q12h *or* 15 mg/kg q24h IV)	Add an aminoglycoside for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). The duration of therapy is 7 days for nonneutropenic patients. Neutropenic patients should be treated until no longer neutropenic.
Neutropenic host	Cefepime (2 g q8h IV) *or* all other agents (except doripenem) in above dosages	
Endocarditis	Antibiotic regimens as for bacteremia for 6–8 weeks	Resistance during therapy is common. Surgery is required for relapse.
Pneumonia	Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy	IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 10–14 days.
Bone infection, malignant otitis externa	Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used	Duration of therapy varies with the drug used (e.g., 6 weeks for a β-lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks).
Central nervous system infection	Ceftazidime or cefepime (2 g q8h IV) or meropenem (1 g q8h IV)	Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks.
Eye infection		
Keratitis/ulcer	Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops	Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter.

(*Continued*)

http://internalmedicinebook.com

TABLE 90-1 ANTIBIOTIC TREATMENT OF INFECTIONS DUE TO *PSEUDOMONAS AERUGINOSA* AND RELATED SPECIES (*CONTINUED*)

Infection	Antibiotics and Dosages	Other Considerations
Endophthalmitis	Ceftazidime or cefepime as for central nervous system infection ***plus*** Topical therapy	
Urinary tract infection	Ciprofloxacin (500 mg q12h PO) *or* levofloxacin (750 mg q24h) *or* any aminoglycoside (total daily dose given once daily)	Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated UTI is 7–10 days (up to 2 weeks for pyelonephritis).
Multidrug-resistant *P. aeruginosa* infection	Colistin (100 mg q12h IV) for the shortest possible period to obtain a clinical response	Doses used have varied. Dosage adjustment is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h).
Stenotrophomonas maltophilia infection	TMP-SMX (1600/320 mg q12h IV) *plus* ticarcillin/clavulanate (3.1 g q4h IV) for 14 days	Resistance to all agents is increasing. Levofloxacin or tigecycline may be alternatives, but there is little published clinical experience with these agents.
Burkholderia cepacia infection	Meropenem (1 g q8h IV) *or* TMP-SMX (1600/320 mg q12h IV) for 14 days	Resistance to both agents is increasing. Do not use them in combination because of possible antagonism.
Melioidosis, glanders	Ceftazidime (2 g q6h) *or* meropenem (1 g q8h) *or* imipenem (500 mg q6h) for 2 weeks ***followed by*** TMP-SMX (1600/320 mg q12h PO) for 3 months	

Abbreviations: IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

therapy. However, if—in the local environment—the susceptibility rate to first-line agents is <80%, empirical combination therapy should be administered until isolate-specific susceptibility data are available.

BACTERIA RELATED TO *PSEUDOMONAS* SPECIES

Stenotrophomonas maltophilia

S. maltophilia is an opportunistic pathogen. Most infections occur in the setting of prior broad-spectrum antimicrobial therapy that has eradicated the normal flora in immunocompromised pts.

http://internalmedicinebook.com

- *S. maltophilia* causes pneumonia, especially ventilator-associated pneumonia, with or without bacteremia.
- Central venous line infection (most often in cancer pts) and ecthyma gangrenosum in neutropenic pts have been described.

Burkholderia cepacia

This organism can colonize airways during broad-spectrum antimicrobial treatment and is a cause of ventilator-associated pneumonia, catheter-associated infection, and wound infection.

- *B. cepacia* is recognized as an antibiotic-resistant nosocomial pathogen in ICU pts.
- *B. cepacia* can cause a rapidly fatal syndrome of respiratory distress and septicemia (the "cepacia syndrome") in pts with cystic fibrosis.

TREATMENT ***S. MALTOPHILIA* AND *B. CEPACIA* INFECTIONS**

- Intrinsic resistance to many antibiotics limits treatment. See Table 90-1 for recommended antibiotic regimens.

Miscellaneous Organisms

Melioidosis is endemic to Southeast Asia and northern Australia and is caused by *B. pseudomallei*. Glanders is associated with close contact with horses or other equines and is caused by *B. mallei*. These diseases present as acute or chronic pulmonary or extrapulmonary suppurative illnesses or as acute septicemia.



For a more detailed discussion, see Barlam TF, Kasper DL: Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria, Chap. 183e; Russo TA, Johnson JR: Diseases Caused by Gram-Negative Enteric Bacilli, Chap. 186, p. 1025; Paterson DL, Peleg AY: *Acinetobacter* Infections, Chap. 187, p. 1036; Ramphal R: Infections Due to *Pseudomonas* Species and Related Organisms, Chap. 189, p. 1042, in HPIM-19.

91 Infections Caused by Miscellaneous Gram-Negative Bacilli

BRUCELLOSIS

Microbiology

Brucellae are small, gram-negative, unencapsulated, nonsporulating, nonmotile rods or coccobacilli that can persist intracellularly. The genus *Brucella* includes four major clinically relevant species: *B. melitensis* (acquired by humans most commonly from

http://internalmedicinebook.com

sheep, goats, and camels), *B. suis* (from swine), *B. abortus* (from cattle or buffalo), and *B. canis* (from dogs).

Epidemiology

Brucellosis is transmitted via ingestion, inhalation, or mucosal or percutaneous exposure; the disease in humans is usually associated with exposure to infected animals or their products in either occupational settings (e.g., slaughterhouse work, farming) or domestic settings (e.g., consumption of contaminated foods, especially dairy products). The global prevalence of brucellosis is unknown because of difficulties in diagnosis and inadequacies in reporting systems.

Clinical Manifestations

Regardless of the specific infecting species, brucellosis often presents with one of three patterns: a febrile illness similar to but less severe than typhoid fever; fever and acute monoarthritis, typically of the hip or knee, in a young child (septic arthritis); or long-lasting fever, misery, and low-back or hip pain in an older man (vertebral osteomyelitis).

- An incubation period of 1 week to several months is followed by the development of undulating fever; sweats; increasing apathy and fatigue; and nonspecific symptoms such as anorexia, headache, myalgias, and chills.
- *Brucella* infection can cause lymphadenopathy, hepatosplenomegaly, epididymoorchitis, neurologic involvement, and focal abscess.
- Given the persistent fever and similar symptoms, tuberculosis is the most important differential diagnosis (Table 91-1).

Diagnosis

Laboratory personnel must be alerted to the potential diagnosis to ensure that they take precautions to prevent occupational exposure.

- The organism is successfully cultured in 50–70% of cases. Cultures using the BACTEC system usually become positive in 7–10 days and can be deemed negative at 3 weeks.
- PCR analysis of blood or tissue samples is more sensitive, faster, and safer than culture.

TABLE 91-1 RADIOLOGY OF THE SPINE: DIFFERENTIATION OF BRUCELLOSIS FROM TUBERCULOSIS

	Brucellosis	Tuberculosis
Site	Lumbar and others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Epiphysitis	Anterosuperior (Pom's sign)	General: upper and lower disk regions, central, subperiosteal
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Recovery	Sclerosis, whole-body	Variable
Paravertebral abscess	Small, well-localized	Common and discrete loss, transverse process
Psoas abscess	Rare	More likely

http://internalmedicinebook.com

- Agglutination assays for IgM are positive early in infection. Single titers of ≥1:160 and ≥1:320 are diagnostic in nonendemic and endemic areas, respectively.

TREATMENT BRUCELLOSIS

- The recommended regimen is streptomycin at a dosage of 0.75–1 g/d IM (or gentamicin at 5–6 mg/kg qd) for 14–21 days plus doxycycline at 100 mg bid for 6 weeks.
  - Rifampin (600–900 mg/d) plus doxycycline (100 mg bid) for 6 weeks constitute an alternative regimen (the current World Health Organization [WHO] recommendation).
  - Significant neurologic disease requires at least 3–6 months of treatment, with ceftriaxone supplementation of a standard regimen.
  - Endocarditis requires a four-drug regimen (an aminoglycoside, rifampin, a tetracycline, and ceftriaxone or a fluoroquinolone) for at least 6 weeks.
  - Relapse rates range from 5% to >20% and depend on the specific antibiotic regimen used; pts should be monitored for at least 2 years.

TULAREMIA

Microbiology and Epidemiology

Tularemia is the only disease caused by *Francisella tularensis*, a small, gram-negative, aerobic bacillus that is a potential agent of bioterrorism.

- Human infection occurs via interaction with biting or blood-sucking insects (especially ticks and tabanid flies in the spring and summer), wild or domestic animals (e.g., wild rabbits, squirrels), or the environment.
  - The organism gains entry into the skin or mucous membranes through bites or inapparent abrasions or is acquired via inhalation or ingestion.
  - As few as 10 organisms can result in infection when injected into the skin or inhaled; $>10^8$ organisms are required to produce infection via the oral route.
- More than half of U.S. cases occur in Arkansas, Oklahoma, and Missouri.

Clinical Manifestations

After an incubation period of 2–10 days, tularemia generally starts with an acute onset of fever, chills, headache, and myalgias. The *ulceroglandular/glandular* forms of tularemia affect 75–85% of pts, but several other syndromes involving systemic manifestations can occur.

- *Ulceroglandular/glandular tularemia:* The hallmark of ulceroglandular tularemia is an indurated, erythematous, nonhealing ulcer lasting 1–3 weeks that begins as a pruritic or tender lesion, ulcerates, has sharply demarcated edges and a yellow exudate, and develops a black base.
  - Inguinal/femoral lymphadenopathy is most common in adults; nodes can become fluctuant and drain spontaneously.
  - In glandular tularemia (5–10% of cases), no primary skin lesion is apparent.
- *Oculoglandular tularemia:* In 1% of pts, infection of the conjunctiva—usually by contact with contaminated fingers—results in purulent conjunctivitis with regional lymphadenopathy and debilitating pain. Painful preauricular lymphadenopathy distinguishes tularemia from other diseases.
- *Oropharyngeal and GI tularemia:* Acquired through oral inoculation (via contaminated foods or fingers), the infection can present as pharyngitis and cervical adenopathy, intestinal ulcerations, mesenteric lymphadenopathy, diarrhea, nausea, vomiting, and abdominal pain.

http://internalmedicinebook.com

- *Pulmonary tularemia:* Infection is acquired via inhalation or via hematogenous spread from ulceroglandular or typhoidal tularemia. Pts present with signs and symptoms similar to those of pneumonia of other etiologies (e.g., nonproductive cough, dyspnea, pleuritic chest pain, CXR with bilateral patchy or lobar infiltrates or cavitary lesions).
- *Typhoidal tularemia:* Due to pharyngeal or GI inoculation or to bacteremic disease, typhoidal tularemia consists of fever and signs of sepsis, generally without skin lesions or lymphadenopathy. This form is the result of a large inoculum or a preexisting compromising condition.

Diagnosis

The diagnosis of tularemia is most frequently confirmed by serology, although up to 30% of pts infected for 3 weeks have negative results in serologic tests.

- Cultures are positive in only 10% of cases; organisms in culture pose a significant risk to laboratory personnel.
- PCR has been used to detect *F. tularensis* DNA in clinical specimens, mainly for ulceroglandular disease.

TREATMENT TULAREMIA

- Gentamicin (2.5 mg/kg IV bid for 7–10 days) is considered the drug of choice; pts who defervesce within the first 48–72 h of treatment may receive a 5- to 7-day course.
  - Streptomycin (1 g IM q12h for 10 days) is also effective, but tobramycin is not.
  - Doxycycline is another alternative, but it must be given for at least 14 days because it is only bacteriostatic against *F. tularensis*.
  - Healing of skin lesions and lymph nodes may take 1–2 weeks. Late lymph-node suppuration can occur, with sterile necrotic tissue.

PLAGUE

Epidemiology

Yersinia pestis causes plague, a systemic zoonosis that primarily affects small rodents in rural areas of Africa (where 80% of all human cases worldwide occur), Asia, and the Americas. As the rodent population succumbs to disease, fleas (the arthropod vector) search for a new host and can transmit the bacteria to humans.

- In addition to fleabites, direct contact with infected tissues or airborne droplets can cause human infections. Given the possibility of airborne transmission, *Y. pestis* is a potential agent of bioterrorism.
- A mean of seven cases per year occur in the United States, most of them near the "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah) and further west in California, southern Oregon, and western Nevada.

Clinical Manifestations

Worldwide, bubonic plague accounts for 80–95% of all plague cases, with primary septicemic plague occurring in 10–20% of cases and primary pulmonary plague in only a small minority of cases.

- *Bubonic plague:* After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site.
  - The tender, swollen lymph node (bubo) has a boggy consistency with an underlying hard core when palpated.

http://internalmedicinebook.com

  - With treatment, fever resolves within 2–5 days, although buboes may remain enlarged for >1 week and can become fluctuant; without treatment, infection can disseminate and cause serious illness (e.g., secondary pneumonic plague, meningitis).
- *Primary septicemic plague:* Pts present with gram-negative septicemia not preceded by lymphadenopathy. Persons >40 years old are at greater risk, although this form of the disease can occur in all age groups. Diabetes and hemochromatosis are additional risk factors.
- *Pneumonic plague:* After a short incubation period averaging a few hours to 3 days, pts experience a sudden onset of fever, nonspecific signs and symptoms (e.g., headache, myalgias, vomiting), and respiratory manifestations (e.g., cough, chest pain, sputum production with hemoptysis).
  - Pneumonitis that is initially segmental can progress to lobar pneumonia and then to bilateral lung involvement.
  - The mortality rate is nearly 100% without treatment and is still >50% with effective treatment.

Diagnosis

The WHO recommends an initial presumptive diagnosis followed by confirmation in a reference laboratory.

- The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate (after injection of 1 mL of normal saline), bronchoalveolar lavage fluid or sputum, and blood, respectively. Gram's, Wayson, or Wright-Giemsa staining of these samples may reveal bipolar gram-negative rods.
- Given the potential risk to laboratory workers, culture of *Y. pestis* should be performed only at reference laboratories, which use direct immunofluorescence, PCR, and/or specific bacteriophage lysis as confirmatory tests for identification. The optimal growth temperature is 25–29°C.
- In the absence of other positive diagnostic testing, a serologic diagnosis can be made.

TREATMENT PLAGUE

- Streptomycin (1g IM q12h) or gentamicin (5 mg/kg IV q24h) is the drug of choice. Levofloxacin (500 mg PO/IV q24h), doxycycline (200 mg/d PO/IV in 1 or 2 doses), and chloramphenicol (12.5 mg/kg PO/IV q6h) are alternative agents.
- For pts who are hospitalized with pneumonic plague or in whom this disease is suspected, respiratory droplet precautions should be implemented until treatment has been given for at least 48 h.
- Postexposure antimicrobial prophylaxis lasting 7 days is recommended after household, hospital, or other close (<2 m) contact with persons with untreated pneumonic plague. Doxycycline (200 mg/d PO/IV in 1 or 2 doses), levofloxacin (500 mg PO q24h), ciprofloxacin (500 mg PO q12h), or trimethoprim-sulfamethoxazole (320 mg of the trimethoprim component PO q12h) are effective agents for prophylaxis.

BARTONELLA INFECTIONS

- *Bartonella* species are fastidious, facultative intracellular, gram-negative bacteria that cause an array of infectious disease syndromes in humans.
- Most *Bartonella* species have successfully adapted to survival in specific domestic or wild mammals, creating a reservoir for human infection. The exceptions are *B. bacilliformis* and *B. quintana*, which are not zoonotic.
- Clinical presentation generally depends on both the infecting *Bartonella* species and the immune status of the infected individual.
- Therapy for syndromes caused by *Bartonella* is summarized in **Table 91-2**.

http://internalmedicinebook.com

TABLE 91-2 ANTIMICROBIAL THERAPY FOR DISEASE CAUSED BY *BARTONELLA* SPECIES IN ADULTS

Disease	Antimicrobial Therapy
Typical cat-scratch disease	Not routinely indicated; for pts with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO qd for 4 days)
Cat-scratch disease retinitis	Doxycycline (100 mg PO bid) *plus* rifampin (300 mg PO bid) for 4–6 weeks
Other atypical cat-scratch disease manifestations[a]	As per retinitis; treatment duration should be individualized
Trench fever or chronic bacteremia with *B. quintana*	Gentamicin (3 mg/kg IV qd for 14 days) *plus* doxycycline (200 mg PO qd or 100 mg PO bid for 6 weeks)
Suspected *Bartonella* endocarditis	Gentamicin[b] (1 mg/kg IV q8h for ≥14 days) *plus* doxycycline (100 mg PO/IV bid for 6 weeks[c]) *plus* ceftriaxone (2 g IV qd for 6 weeks)
Confirmed *Bartonella* endocarditis	As for suspected *Bartonella* endocarditis *minus* ceftriaxone
Bacillary angiomatosis	Erythromycin[d] (500 mg PO qid for 3 months) *or* Doxycycline (100 mg PO bid for 3 months)
Bacillary peliosis	Erythromycin[d] (500 mg PO qid for 4 months) *or* Doxycycline (100 mg PO bid for 4 months)
Carrión's disease	
Oroya fever	Chloramphenicol (500 mg PO/IV qid for 14 days) *plus* another antibiotic (β-lactam preferred) *or* Ciprofloxacin (500 mg PO bid for 10 days)
Verruga peruana	Rifampin (10 mg/kg PO qd, to a maximum of 600 mg, for 14 days) *or* Streptomycin (15–20 mg/kg IM qd for 10 days)

[a]Data on treatment efficacy for encephalitis and hepatosplenic cat-scratch disease are lacking. Therapy similar to that given for retinitis is reasonable.
[b]Some experts recommend gentamicin at 3 mg/kg IV qd. If gentamicin is contraindicated, rifampin (300 mg PO bid) can be added to doxycycline for documented *Bartonella* endocarditis.
[c]Some experts recommend extending oral doxycycline therapy for 3–6 months.
[d]Other macrolides are probably effective and may be substituted for erythromycin or doxycycline.
Source: Recommendations are modified from JM Rolain et al: *Antimicrob Agents Chemother* 48:1921, 2004.

CAT-SCRATCH DISEASE (CSD)

Microbiology and Epidemiology

B. henselae is the principal etiologic agent of CSD, although other *Bartonella* species may rarely be involved. Consistent with the disease's name, contact (being scratched, bitten, or licked) with apparently healthy cats, and especially with kittens, is the primary source of infection. Adults are affected nearly as frequently as children. In the United States, the estimated incidence is ~10 cases per 100,000 population.

http://internalmedicinebook.com

Clinical Manifestations

Of pts with CSD, 85–90% have typical disease consisting of a localized lesion (papule, vesicle, or nodule) at the site of inoculation with subsequent painful regional lymphadenopathy ≥1–3 weeks after cat contact.

- Axillary and epitrochlear nodes are most commonly involved and suppurate in 10–15% of cases.
- Low-grade fever, malaise, and anorexia develop in ~50% of pts.
- Atypical disease involves extranodal manifestations (e.g., fever of unknown origin, ophthalmologic manifestations, neurologic involvement, osteomyelitis) and occurs in 10–15% of pts.
- In immunocompetent pts, the disease resolves spontaneously without treatment, although its resolution takes weeks or months.

Diagnosis

Serologic testing is most commonly used but is variably sensitive and specific. It is noteworthy that seroconversion may take a few weeks. *Bartonella* species are difficult to culture, but PCR analysis of lymph node tissue, pus, or the primary inoculation lesion is highly sensitive and specific.

BACILLARY ANGIOMATOSIS AND PELIOSIS

Bacillary angiomatosis is caused by *B. henselae* and *B. quintana*, while peliosis is caused only by the former species. These diseases occur most often in HIV-infected pts with CD4+ T cell counts of <100/μL.

- Pts with bacillary angiomatosis present with one or more painless skin lesions that may be tan, red, or purple in color. SC masses or nodules, ulcerated plaques, and verrucous growths also occur. Painful osseous lesions, primarily in the long bones, may develop and appear as lytic lesions on radiography.
- Peliosis is an angioproliferative disorder characterized by blood-filled cystic structures that affects primarily the liver but also the spleen and lymph nodes. Hypodense hepatic areas are usually evident on imaging.
- Both diseases are diagnosed on histologic grounds. Blood cultures may be positive.

TRENCH FEVER

- Trench fever (*5-day fever*) is caused by *B. quintana*, which is spread by the human body louse to its only animal reservoir: humans.
- Much less common today than in the trenches of World War I, the disease now primarily affects homeless people.
- After a usual incubation period of 15–25 days, disease classically ranges from a mild febrile illness to a recurrent or protracted and debilitating disease. Fever is often periodic, with episodes of 4–5 days separated by ~5-day afebrile periods.
- Diagnosis requires identification of *B. quintana* in blood cultures.
- Untreated, the disease usually lasts 4–6 weeks. Death is rare.

BARTONELLA ENDOCARDITIS

Bartonella species (typically *B quintana* or *B. henselae*) are an important cause of culture-negative endocarditis. The disease's manifestations are similar to those of subacute endocarditis of any etiology (Chap. 80). Even if incubated for prolonged periods (up to 6 weeks), blood cultures are positive in only ~25% of cases. Serologic or PCR testing for *Bartonella* in cardiac valve tissue can help establish the diagnosis in pts with negative blood cultures.

CARRIÓN'S DISEASE (OROYA FEVER AND VERRUGA PERUANA)

Carrión's disease is a biphasic disease caused by *B. bacilliformis*, which is transmitted by a sandfly vector found in the Andes valleys of Peru, Ecuador, and Colombia.

http://internalmedicinebook.com

- *Oroya fever* is the initial, bacteremic, systemic form, and *verruga peruana* is its late-onset, eruptive manifestation.
- Oroya fever may present as a nonspecific bacteremic febrile illness without anemia or as acute, severe hemolytic anemia with hepatomegaly and jaundice of rapid onset.
  - In verruga peruana, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. The lesions persist for months up to 1 year.
- In systemic illness, Giemsa-stained blood films show typical intraerythrocytic bacilli, and blood and bone marrow cultures are positive. Serologic assays may be helpful. Biopsy may be required to confirm the diagnosis of verruga peruana.



For a more detailed discussion, see Beeching NJ, Corbel MJ: Brucellosis, Chap. 194e; Jacobs RF, Schutze GE: Tularemia, Chap. 195, p. 1066; Prentice MB: Plague and Other *Yersinia* Infections, Chap. 196, p. 1070; and Giladi M, Ephros M: *Bartonella* Infections, Including Cat-Scratch Disease, Chap. 197, p. 1078, in HPIM-19.

92 Anaerobic Infections

DEFINITIONS

- *Anaerobic bacteria:* require reduced oxygen tension for growth; do not grow on the surface of solid media in 10% CO_2 in air
- *Microaerophilic bacteria:* grow in an atmosphere of 10% CO_2 in air or under anaerobic or aerobic conditions, but grow best if only a small amount of atmospheric oxygen is present
- *Facultative bacteria:* grow in the presence or absence of oxygen

TETANUS

Microbiology, Epidemiology, and Pathogenesis

Tetanus is characterized by increased muscle tone and spasms caused by tetanospasmin ("tetanus toxin"), a toxin produced by *Clostridium tetani*.

- *C. tetani* is a spore-forming, anaerobic gram-positive rod that is ubiquitous in soil and whose spores are highly resilient.
- Tetanus is a rare disease in the developed world: only 231 cases were reported in the United States between 2001 and 2008. Most cases occur in incompletely vaccinated or unvaccinated individuals.
- After spores contaminate wounds (typically puncture wounds or, in the case of neonates, the umbilical stump) and reach a suitable anaerobic environment (e.g., devitalized tissue), organisms proliferate and release toxin.

http://internalmedicinebook.com

- The toxin blocks release of inhibitory neurotransmitters (glycine and γ-aminobutyric acid) in presynaptic terminals, and rigidity results from an increased resting firing rate of the α-motor neurons.
- A toxin dose as low as 2.5 ng/kg can be fatal.

Clinical Manifestations

C. tetani can cause a usually mild local disease confined to the muscles near the wound or a more severe generalized disease (e.g., neonatal disease).

- If the cranial nerves are involved in localized cephalic tetanus, the pt may aspirate or develop airway obstruction due to pharyngeal or laryngeal muscle spasm. This situation is associated with a poor prognosis.
- The early signs and symptoms of generalized tetanus often include trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. As the disease progresses, painful muscle spasms develop and can sometimes be strong enough to cause crush fractures.
  - Without ventilatory support, respiratory failure is the most common cause of death in tetanus.
  - Autonomic disturbance (e.g., labile blood pressure; GI stasis; increased tracheal secretions; acute, high-output renal failure) is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk.

Diagnosis

The diagnosis is made on clinical grounds. Culture of *C. tetani* from a wound provides supportive evidence.

TREATMENT TETANUS

- The mainstays of early treatment are the elimination of ongoing toxin production and the neutralization of circulating toxin.
  - The entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production.
  - Metronidazole (400 mg rectally or 500 mg IV q6h for 7 days) is the preferred antibiotic. Penicillin (100,000–200,000 IU/kg qd) is an alternative but theoretically may increase spasms.
  - Antitoxin should be given as early as possible.
  - Standard treatment consists of a single IM dose of tetanus immune globulin (TIG; 3000–5000 IU) or equine antitoxin (10,000–20,000 IU). However, there is evidence that intrathecal TIG (50–1500 IU) inhibits disease progression and leads to a better outcome than IM-administered TIG.
- TIG is preferred as it is less likely to cause an anaphylactoid reaction.
- Monitoring and supportive care in a calm, quiet environment are important because light and noise can trigger spasms.
  - Spasms are controlled by heavy sedation with benzodiazepines, chlorpromazine, and/or phenobarbital; magnesium sulfate can also be used as a muscle relaxant. The doses required to control spasms also cause respiratory depression; thus, it is difficult to control spasms adequately in settings without mechanical ventilation.
  - Cardiovascular instability in severe tetanus is notoriously difficult to treat; increased sedation (e.g., with magnesium sulfate or morphine) or administration of short-acting agents that work specifically on the cardiovascular system (e.g., esmolol, calcium antagonists, inotropes) may be required.
- Recovery from tetanus may take 4–6 weeks. Because natural disease does not induce immunity, recovering pts should be immunized.

http://internalmedicinebook.com

Prevention

Vaccination effectively prevents disease.

- "Catch-up" vaccination schedules recommend a three-dose primary course followed by two further doses for unimmunized adolescents. For persons who have received a complete primary course in childhood but no further boosters, two doses at least 4 weeks apart are recommended.
- Individuals sustaining tetanus-prone wounds should be immunized if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Pts sustaining wounds not classified as clean or minor should also undergo passive immunization with TIG.

Prognosis

A shorter incubation period (time from wound to first symptom) or onset period (time from first symptom to first generalized spasm) is associated with worse outcome.

BOTULISM

Microbiology, Epidemiology, and Pathogenesis

Botulism is a paralytic disease caused by neurotoxins elaborated by *Clostridium botulinum*, an anaerobic spore-forming gram-positive bacterium, as well as a few other toxigenic *Clostridium* spp.

- Botulism is caused by the toxin's inhibition of acetylcholine release at the neuromuscular junction through an enzymatic mechanism.
  - *C. botulinum* toxin types A, B, E, and (rarely) F cause human disease, with toxin type A causing the most severe syndrome.
  - Toxin type E is associated with foods of aquatic origin.
- Transmission is usually due to consumption of foods contaminated with botulinum toxin, but contamination of wounds with spores also can result in disease.
  - Most U.S. food-borne cases (average, 23 cases per year) are associated with home-canned food.
  - Infant botulism results from toxigenic clostridial colonization of the intestine of children <1 year of age and is the most common form of the disease in the United States, with ~80–100 cases reported annually.
- Toxin is heat-labile, and spores are heat-resistant; these properties underscore the importance of properly heating foods.
- Botulinum toxin is among the most toxic substances known and thus is of concern as a potential weapon of bioterrorism.

Clinical Manifestations

Botulism occurs naturally as four syndromes: (1) food-borne illness; (2) wound infection; (3) infant botulism; and (4) adult intestinal toxemia, which is similar to infant botulism. The disease presents as symmetric cranial-nerve palsies (diplopia, dysarthria, dysphonia, ptosis, facial paralysis, and/or impaired gag reflex) followed by symmetric, descending flaccid paralysis that may progress to respiratory failure and death. Constipation due to paralytic ileus is nearly universal, and fever is usually absent.

- *Food-borne botulism* occurs 8–36 h (or up to 10 days, depending on the dose) after ingestion of food contaminated with toxin and ranges in severity from mild to fatal (within 24 h). Nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis.
- *Wound botulism* occurs when spores contaminate wounds and germinate, with an incubation period of 4–17 days.

http://internalmedicinebook.com

- In *infant botulism* and *adult intestinal toxemia*, spores germinate in the intestine and produce toxin, which is absorbed and causes illness. This form in infants has been associated with contaminated honey; thus, honey should not be fed to children <12 months of age. Adult pts typically have some anatomic or functional bowel abnormality or have a bowel flora disrupted by recent antibiotic use.

Diagnosis

The clinical symptoms suggest the diagnosis. The definitive test is the demonstration of the toxin in clinical specimens (serum, stool, gastric aspirates, wound material) and food samples.

- When results are not readily available, clinical decisions (e.g., to administer botulinum antitoxin) need to be made in their absence.
- This test may yield a negative result even if the pt has botulism, particularly if specimens are collected >7 days after symptom onset; additional tests (e.g., culture of stool or wound material for toxigenic clostridia) may be necessary.

TREATMENT BOTULISM

- The mainstays of treatment are meticulous supportive care and immediate administration of botulinum antitoxin—the only specific treatment.
  - Adults are given an equine antitoxin available through the CDC (770-488-7100); infant botulism is treated with a human-origin antitoxin (licensed as BabyBIG®) available through the California Department of Public Health (510-231-7600).
  - In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly, and antimicrobial therapy (e.g., with a penicillin) should be guided by clinical judgment, as its clinical efficacy has not been established and may result in increased circulating toxin from lysis of bacteria.

Prognosis

Botulinum antitoxin limits progression of illness by neutralizing free toxin without affecting paralysis that is already present. Toxin binding is irreversible, but nerve terminals do regenerate.

OTHER CLOSTRIDIAL INFECTIONS

Microbiology and Pathogenesis

Clostridia are pleomorphic, gram-positive, spore-forming organisms. Most species are obligate anaerobes; some (e.g., *C. septicum*, *C. tertium*) can grow—but not sporulate—in air.

- In humans, clostridia reside in the GI and female genital tracts and on the oral mucosa.
- Clostridial species produce more protein toxins than any other bacterial genus; the *C. perfringens* epsilon toxin is among the most lethal and is considered a potential agent of bioterrorism.

Epidemiology and Clinical Manifestations

Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock syndrome (TSS).

http://internalmedicinebook.com

- *Clostridial wound contamination:* Of open traumatic wounds, 30–80% are contaminated with clostridial species. Diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms, given that clostridia are isolated with equal frequency from both suppurative and well-healing wounds.
- *Polymicrobial infections involving clostridia:* Clostridial species can be involved in infection throughout the body; 66% of intraabdominal infections related to compromised mucosal integrity involve clostridia (most commonly *C. ramosum*, *C. perfringens*, and *C. bifermentans*).
- *Enteric clostridial infections:* Disease ranges from food-borne illnesses and antibiotic-associated colitis (Chap. 82) to extensive necrosis of the intestine (e.g., *enteritis necroticans* and *necrotizing enterocolitis*, which are due to toxigenic *C. perfringens* type C and type A, respectively).
- *Clostridial bacteremia: C. perfringens* causes 79% of clostridial bacteremias; when associated with myonecrosis, clostridial bacteremia has a grave prognosis.
  - *C. septicum* is also commonly associated with bacteremia (<5% of cases). More than 50% of pts with *C. septicum* bacteremia have a GI anomaly or an underlying malignancy. Neutropenia (of any origin) is also associated with *C. septicum* bacteremia.
    - Pts with clostridial bacteremia—particularly that due to *C. septicum*—require immediate treatment, as infection can metastasize and cause spontaneous myonecrosis.
- *Clostridial skin and soft-tissue infections:* Necrotizing clostridial soft-tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock. Most pts develop severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked tachycardia.
  - *C. perfringens myonecrosis (gas gangrene)* is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated.
    - If due to trauma, gas gangrene has an incubation period of 6 h to <4 days. Disease initially presents as excruciating pain at the affected site and the development of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles.
    - Spontaneous gas gangrene results from hematogenous seeding of normal muscle with toxigenic clostridia from a GI source. Confusion, extreme pain in the absence of trauma, and fever should heighten suspicion.
  - *TSS:* Endometrial clostridial infection (particularly with *C. sordellii*) is usually related to pregnancy or gynecologic procedures and proceeds rapidly to TSS and death.
    - Systemic manifestations, including edema, effusions, profound leukocytosis (50,000–200,000/μL), and hemoconcentration (Hct of 75–80%), are followed by the rapid onset of hypotension and multiple-organ failure.
    - Fever is usually absent.
  - Other clostridial skin and soft-tissue infections include crepitant cellulitis (involving SC or retroperitoneal tissues in diabetic pts), cellulitis and abscess formation due to *C. histolyticum*, and endophthalmitis due to *C. sordellii* or *C. perfringens*.

Diagnosis

Isolation of clostridia from clinical sites does not in itself indicate severe disease. Clinical findings and presentation must also be taken into account.

TREATMENT OTHER CLOSTRIDIAL INFECTIONS

- Table 92-1 lists treatment regimens for clostridial infections.

http://internalmedicinebook.com

TABLE 92-1 TREATMENT OF CLOSTRIDIAL INFECTIONS

Condition	Antibiotic Treatment	Penicillin Allergy	Adjunctive Treatment/Note
Wound contamination	None	—	Treatment should be based on clinical signs and symptoms as listed below and not solely on bacteriologic findings.
Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic)	Ampicillin (2 g IV q4h) ***plus*** Clindamycin (600–900 mg IV q6–8h) ***plus*** Ciprofloxacin (400 mg IV q6–8 h)	Vancomycin (1 g IV q12h) ***plus*** Metronidazole (500 mg IV q6h) ***plus*** Ciprofloxacin (400 mg IV q6–8h)	Empirical therapy should be initiated. Therapy should be based on Gram's stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text).
Clostridial sepsis	Penicillin, 3–4 mU IV q4–6h ***plus*** Clindamycin (600–900 mg IV q6–8h)	Clindamycin alone ***or*** Metronidazole (as above) ***or*** Vancomycin (as above)	Transient bacteremia without signs of systemic toxicity may be clinically insignificant.
Gas gangrene	Penicillin G (4 mU IV q4–6h) ***plus*** Clindamycin (600–900 mg IV q6–8h)	Cefoxitin (2 g IV q6h) ***plus*** Clindamycin (600–900 mg IV q6–8h)	Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotic initiation.

MIXED ANAEROBIC INFECTIONS

Microbiology, Epidemiology, and Pathogenesis

Nonsporulating anaerobic bacteria are important components of the normal flora of mucosal surfaces of the mouth, lower GI tract, skin, and female genital tract and contribute to physiologic, metabolic, and immunologic functions of the host.

- Most clinically relevant anaerobes are relatively aerotolerant and can survive for prolonged periods in the presence of low levels of oxygen.
  - Clinically relevant anaerobes include gram-positive cocci (e.g., *Peptostreptococcus* spp.), gram-positive rods (e.g., spore-forming clostridia and *Propionibacterium acnes*), and gram-negative bacilli (e.g., the *Bacteroides fragilis* group in the intestines, *Fusobacterium* spp. in the oral cavity and GI tract, *Prevotella* spp. in the oral cavity and female genital tract, and *Porphyromonas* spp. in the oral microbiota).

http://internalmedicinebook.com

- Infections caused by anaerobes are typically polymicrobial (including at least one anaerobic organism and sometimes involving microaerophilic and facultative bacteria) and occur when organisms penetrate a previously sterile site that has a reduced oxidation–reduction potential—e.g., from tissue ischemia, trauma, surgery, perforated viscus, shock, or aspiration. Bacterial synergy, bacterial virulence factors, and mechanisms of abscess formation are factors involved in the pathogenesis of anaerobic infections.
- Anaerobes account for 0.5–12% of all cases of bacteremia, with *B. fragilis* isolated in 60–80% of these cases.

Clinical Manifestations

The clinical presentation of anaerobic infections depends, in part, on the anatomic location affected.

- *Mouth, head, and neck infections:* Odontogenic infections (e.g., dental caries, periodontal disease, gingivitis) are common, can spread locally, and may be life-threatening.
  - Acute necrotizing ulcerative gingivitis (trench mouth, Vincent's stomatitis) is associated with bleeding tender gums, foul breath, and ulceration with gray exudates.
  - Noma (*cancrum oris*) is a necrotizing infection of the oral mucous membranes that rapidly evolves from gingival inflammation to orofacial gangrene with destruction of bone and soft tissue. Noma occurs most frequently in 1- to 4-year-old children with malnutrition or systemic disease, particularly those in sub-Saharan Africa.
  - Acute necrotizing infection of the pharynx is associated with ulcerative gingivitis. Pts have a sore throat, foul breath, fever, a choking sensation, and tonsillar pillars that are swollen, red, ulcerated, and covered with a gray membrane. Aspiration of infected material can lead to a lung abscess.
  - Peripharyngeal infections include peritonsillar abscess (*quinsy*; caused by a mixed flora including anaerobes and group A streptococci) and submandibular space infection (*Ludwig's angina*), which arises from the second and third molars in 80% of cases and is associated with swelling (sometimes leading to respiratory obstruction), pain, trismus, and displacement of the tongue.
  - Chronic sinusitis and otitis (Chap. 58) are commonly due to anaerobes.
  - Complications of anaerobic mouth, head, and neck infections include Lemierre's syndrome, osteomyelitis, CNS infections (e.g., brain abscess, epidural abscess, subdural empyema), mediastinitis, pleuropulmonary infections, and hematogenous dissemination.
    - Lemierre's syndrome, which is typically due to *Fusobacterium necrophorum*, is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent metastasis, most commonly to the lung. A typical clinical triad includes pharyngitis, a tender/swollen neck, and noncavitating pulmonary infiltrates.
    - Pleuropulmonary infections include aspiration pneumonia (which is difficult to distinguish from chemical pneumonitis due to aspiration of gastric juices), necrotizing pneumonitis, lung abscesses, and empyema. Bacterial aspiration pneumonia is associated with a depressed gag reflex, impaired swallowing, or altered mental status; anaerobic lung abscess usually arises from a dental source.
- *Intraabdominal infections:* See Chap. 81.
- *Pelvic infections:* See Chap. 83 for more details. Anaerobes, typically in combination with coliforms, are isolated from most women with genital tract infections (e.g., pelvic inflammatory disease, pelvic abscess, endometritis, tuboovarian abscess, postoperative or postpartum infections) that are not caused by a sexually transmitted pathogen. The major anaerobic pathogens are *B. fragilis*, *Prevotella* spp. (*bivia*, *disiens*, *melaninogenica*), anaerobic cocci, and *Clostridium* spp.

http://internalmedicinebook.com

- *Skin and soft tissue infections:* See Chap. 84 for more details. These infections most frequently occur at sites prone to contamination with feces or with upper airway secretions.
- *Bone and joint infections:* Anaerobic bone and joint infections usually occur adjacent to soft tissue infections. Actinomycosis is the leading cause of anaerobic bone infections worldwide; *Fusobacterium* spp. are the most common anaerobic cause of septic arthritis.

Diagnosis

The three critical steps in successfully culturing anaerobic bacteria from clinical samples are (1) proper specimen collection, with avoidance of contamination by the normal microbiota; (2) rapid specimen transport to the microbiology laboratory in anaerobic transport media; and (3) proper specimen handling. A foul odor is often indicative (and nearly pathognomonic) of an anaerobic infection.

TREATMENT MIXED ANAEROBIC INFECTIONS

- Appropriate treatment requires antibiotic administration (Table 92-2), surgical resection or debridement of devitalized tissues, and drainage.
  - Given that most infections involving anaerobes also include aerobic bacteria, therapeutic regimens should include agents active against both classes of organisms.
  - Infections above the diaphragm usually reflect the orodental microbiota, which includes many organisms that produce β-lactamase. Accordingly, the

TABLE 92-2 ANTIMICROBIAL THERAPY FOR INFECTIONS INVOLVING COMMONLY ENCOUNTERED ANAEROBIC GRAM-NEGATIVE RODS

Category 1 (Nearly Always Active)	Category 2 (Usually Active)	Category 3 (Variable Resistance)	Category 4 (Resistance)
Carbapenems (imipenem, meropenem, doripenem)	Tigecycline	Cephamycins (cefoxitin, cefotetan)	Aminoglycosides
Metronidazole[a]	High-dose antipseudomonal penicillins	Clindamycin	Monobactams
β-Lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam)		Penicillins	Trimethoprim-sulfamethoxazole
Chloramphenicol[b]		Cephalosporins	
		Tetracycline	
		Vancomycin	
		Erythromycin	
		Moxifloxacin	

[a]Usually needs to be given in combination with aerobic bacterial coverage. For infections originating below the diaphragm, aerobic gram-negative coverage is essential. For infections from an oral source, aerobic gram-positive coverage is added. Metronidazole also is not active against *Actinomyces, Propionibacterium*, or other gram-positive non-spore-forming bacilli (e.g., *Eubacterium, Bifidobacterium*) and is unreliable against peptostreptococci.

[b]Despite excellent in vitro activity against all clinically important anaerobes, this drug is less desirable than other active drugs because of documented clinical failures.

http://internalmedicinebook.com

recommended regimens include clindamycin, a β-lactam/β-lactamase inhibitor combination, or metronidazole in combination with a drug active against microaerophilic and aerobic streptococci.

– Infections below the diaphragm must be treated with agents active against *Bacteroides* spp., such as metronidazole, β-lactam/β-lactamase inhibitor combinations, or carbapenems. Treatment should also cover the aerobic gram-negative flora, including enterococci (e.g., ampicillin or vancomycin) when indicated.

- Pts with anaerobic infections that fail to respond to treatment or that relapse should be reassessed, with consideration of additional surgical drainage or debridement. Superinfection with resistant gram-negative facultative or aerobic bacteria should also be considered.



For a more detailed discussion, see Thwaites CL, Yen LM: Tetanus, Chap. 177, p. 984; Maslanka S, Rao AK: Botulism, Chap. 178, p. 987; Bryant AE, Stevens DL: Gas Gangrene and Other Clostridial Infections, Chap. 179, p. 990; and Cohen-Poradosu R, Kasper DL: Infections Due to Mixed Anaerobic Organisms, Chap. 201, p. 1094, in HPIM-19.

93 Nocardiosis, Actinomycosis, and Whipple's Disease

NOCARDIOSIS

Microbiology

Nocardiae are branching, beaded, gram-positive filaments that usually give positive results with modified acid-fast stains. These saprophytic aerobic actinomycetes are common in soil.

- Nine species or species complexes are most commonly associated with human disease.
- Speciation of nocardiae is precluded in most clinical laboratories because it is nearly impossible without molecular phylogenetic techniques.
- *Nocardia brasiliensis* is most often associated with localized skin lesions.

Epidemiology

Nocardiosis occurs worldwide and has an incidence of ~0.375 cases per 100,000 persons in Western countries. The risk of disease is greater than usual among persons who have deficient cell-mediated immunity—e.g., that associated with lymphoma, transplantation, glucocorticoid therapy, or HIV infection with <250 CD4+ T cells/μL.

http://internalmedicinebook.com

Pathogenesis

Pneumonia and disseminated disease follow inhalation of fragmented bacterial mycelia.

- Nocardiosis causes abscesses with neutrophilic infiltration and necrosis.
- Organisms have multiple mechanisms for surviving within phagocytes.

Clinical Manifestations

- *Respiratory tract disease:* Pneumonia is usually subacute, presenting over days to weeks, but can be acute in immunocompromised pts.
  - A prominent cough productive of small amounts of thick purulent sputum, fever, anorexia, weight loss, and malaise are common; dyspnea, hemoptysis, and pleuritic chest pain are less common.
  - CXR may demonstrate single or multiple nodular infiltrates of varying sizes that tend to cavitate. Empyema is noted in one-quarter of cases.
  - Extrapulmonary disease is documented in >50% of cases.
- *Extrapulmonary disease:* In 20% of cases of disseminated disease, lung disease is absent.
  - Nocardial dissemination manifests as subacute abscesses in the brain (most commonly), skin, kidney, bone, eye, and/or muscle.
  - Brain abscesses are usually supratentorial, are often multiloculated, can be single or multiple, and tend to burrow into ventricles or extend into the subarachnoid space.
  - Meningitis is uncommon, and nocardiae are difficult to recover from CSF.
- *Disease following transcutaneous inoculation:* usually presents as cellulitis, lymphocutaneous disease, or actinomycetoma
  - *Cellulitis* presents 1–3 weeks after a break in the skin (often with contamination by soil).
    - The firm, tender, erythematous, warm, and nonfluctuant lesions may involve underlying structures, but dissemination is rare.
    - *N. brasiliensis* and species in the *N. otitidiscaviarum* complex are most common in cellulitis.
  - *Lymphocutaneous* disease resembles sporotrichosis and presents as a pyodermatous nodule at the inoculation site, with central ulceration and purulent or honey-colored discharge.
    - SC nodules often appear along lymphatics that drain the primary lesion.
  - *Actinomycetoma* progresses from a nodular swelling at the site of local trauma (typically on the feet or hands, although other sites can be affected) to fistula formation; dissemination is rare.
    - The discharge is serous or purulent and can contain granules consisting of masses of mycelia.
    - Lesions, which spread slowly along fascial planes to involve adjacent skin and SC tissue and bone, can cause extensive deformity after months or years.
- *Eye disease:* Endophthalmitis can occur after eye surgery or during disseminated disease.

Diagnosis

- Sputum or pus should be examined microscopically and by culture for the presence of nocardiae. In pts with nocardial pneumonia, sputum smears are often negative, and bronchoscopy may be needed to obtain adequate specimens.
  - Cultures take 2–4 weeks to yield the organism. To maximize the likelihood of isolation, the laboratory should be alerted if nocardiosis is being considered.
  - Sputum cultures positive for nocardiae should be assumed to reflect disease in immunocompromised hosts, but may represent colonization in immunocompetent pts.

http://internalmedicinebook.com

- Discharge from lesions suspected to constitute an actinomycetoma should be examined for granules, the appearance of which can help differentiate this diagnosis from eumycetoma (cases involving fungi) and botryomycosis (cases involving cocci or bacilli).
  - Granules from actinomycetomas consist of fine filaments (0.5–1 μm wide) radiating from a central core.
  - In contrast, granules from eumycetomas have broader filaments (2–5 μm wide) encased in a matrix, and those from botryomycosis consist of loose masses of bacteria.
- Brain imaging should be considered in pts with pulmonary or disseminated disease.

TREATMENT NOCARDIOSIS

- Sulfonamides are the empirical drugs of choice, and trimethoprim-sulfamethoxazole (TMP-SMX; 10–20 mg of TMP/kg qd and 50–100 mg of SMX/kg qd initially, with later reduction to 5 and 25 mg/kg qd, respectively) may be more effective than sulfonamides alone.
  - Susceptibility testing, particularly in severe cases or cases failing to improve, can guide alternative treatments and should be performed at reference labs.
  - Alternative oral agents that are often effective include minocycline, linezolid (whose long-term use is complicated by side effects), amoxicillin/clavulanic acid (except for strains in the *N. nova* complex), and fluoroquinolones (with moxifloxacin and gemifloxacin the most active).
  - Effective parenteral agents include amikacin, ceftriaxone, cefotaxime, and imipenem.
- Pts with severe disease are initially treated with a combination of TMP-SMX, amikacin, and either ceftriaxone or imipenem. After definite clinical improvement, the regimen can usually be simplified to a single oral agent.
- Surgical management of nocardial infections is similar to that of other bacterial diseases.
  - Brain abscesses that are large or unresponsive to antibiotic treatment should be aspirated.
  - Medical therapy is generally sufficient for actinomycetomas.
- Relapse is common.
  - Long courses of therapy are required (Table 93-1).
  - Pts should be followed for at least 6 months after therapy completion.

ACTINOMYCOSIS

Microbiology

Actinomycosis is caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces* (e.g., *A. israelii, A. naeslundii*, *A. odontolyticus*), that colonize the mouth, colon, and vagina. Most infections are polymicrobial, but the role of other species in the pathogenesis of the disease is unclear.

Epidemiology

Actinomycosis is associated with poor dental hygiene, prolonged use of intrauterine contraceptive devices (IUCDs), and treatment with bisphosphonates.

Pathogenesis

After disruption of the mucosal barrier, resident *Actinomyces* can infect locally and spread contiguously in a slow progressive manner, ignoring tissue planes. The hallmark of actinomycosis is the development of single or multiple indurated lesions with fibrotic walls often described as "wooden." Central necrosis of lesions with neutrophils and sulfur granules is virtually diagnostic of the disease.

TABLE 93-1 TREATMENT DURATION FOR NOCARDIOSIS

Disease	Duration
Pulmonary or systemic	
Intact host defenses	6–12 months
Deficient host defenses	12 months[a]
CNS disease	12 months[b]
Cellulitis, lymphocutaneous syndrome	2 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Actinomycetoma	6–12 months after clinical cure
Keratitis	Topical: until apparent cure Systemic: until 2–4 months after apparent cure

[a]In some pts with AIDS and CD4+ T lymphocyte counts of <200/μL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely.
[b]If all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.

Clinical Manifestations

- *Oral-cervicofacial disease:* Infection starts as a soft-tissue swelling, abscess, or mass, often at the angle of the jaw, with occasional contiguous extension to the cranium, cervical spine, or thorax. Pain, fever, and leukocytosis are variable. Radiation therapy and particularly bisphosphonate treatment are associated with actinomycosis of the maxilla and mandible.
- *Thoracic disease:* The pulmonary parenchyma and/or pleural space is usually involved. Chest pain, fever, and weight loss are common.
  - Radiographic studies demonstrate a mass lesion or pneumonia. Cavitary disease or mediastinal or hilar adenopathy may occur, and >50% of pts have pleural thickening, effusion, or empyema.
  - Lesions cross fissures or pleura and may involve the mediastinum, contiguous bone, or the chest wall. In the absence of these findings, the disease is often mistaken for a neoplasm or for pneumonia.
- *Abdominal disease:* The diagnosis is challenging given that abdominal disease may not present clinically until months or years after the initial event (e.g., appendicitis, diverticulitis, bowel surgery) and that any abdominal organ or region can be involved.
  - The disease usually presents as an abscess, mass, or lesion fixed to underlying tissue and is often mistaken for cancer.
  - Sinus tracts to the abdominal wall, perianal region, or other organs may develop and mimic inflammatory bowel disease. Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis.
- *Pelvic disease:* Pelvic actinomycosis is often associated with IUCDs that have been in place for >1 year. The presentation is indolent and may follow removal of the device.
  - Pts have fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge. Endometritis progresses to pelvic masses or tuboovarian abscess.
  - When there are no symptoms and *Actinomyces*-like organisms are identified on Papanicolaou-stained specimens, the pt should undergo close follow-up but the IUCD does not have to be removed.
- *Miscellaneous sites:* Actinomycosis can involve musculoskeletal tissue, soft tissue, or (rarely) the CNS. Hematogenous dissemination, most commonly to the lungs and liver, can occur.

Diagnosis

Actinomycosis should be considered when a chronic progressive process with mass-like features crosses tissue boundaries, a sinus tract develops, and/or the pt has evidence of a refractory or relapsing infection despite short courses of antibiotics.

- Aspirations, biopsies, or surgical excision may be required to obtain material for diagnosis.
- Microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues helps establish the diagnosis; however, additional histopathologic and microbiologic studies are required to distinguish actinomycosis from mycetoma and botryomycosis, in both of which sulfur granules develop.
- Anaerobic cultures usually require 5–7 days to become positive but may take 2–4 weeks; even a single antibiotic dose can affect the yield of cultures.

TREATMENT ACTINOMYCOSIS

- For serious infection and bulky disease, IV therapy for 2–6 weeks (usually with penicillin, 18–24 million units IV daily) followed by oral therapy for 6–12 months (e.g., with penicillin or ampicillin) is suggested.
  - Less extensive disease, particularly that involving the oral–cervicofacial region, may be cured with a shorter course.
  - If treatment is extended beyond the point of resolution of measurable disease (as quantified by CT or MRI), relapse is minimized.
- Suitable alternative agents include the tetracyclines (e.g., doxycycline or minocycline, 100 mg PO/IV q12h) or clindamycin (900 mg IV q8h or 300–450 mg PO q6h).

WHIPPLE'S DISEASE

Microbiology and Epidemiology

Whipple's disease is a chronic multiorgan infection caused by *Tropheryma whipplei*, a weakly staining gram-positive bacillus. Seroprevalence studies indicate that ~50% of people in Western Europe and ~75% of those in rural Senegal have been exposed to *T. whipplei*. The route of transmission is unclear but probably involves fecal–oral spread and possibly droplet and/or airborne transmission.

Clinical Manifestations

Exposure to *T. whipplei* typically results in asymptomatic carriage but can lead to acute disease or chronic infection (Whipple's disease).

- *Acute infection:* Acquisition of *T. whipplei* can result in fever, acute gastroenteritis, and/or pneumonia.
- *Chronic infection:* "Classic" Whipple's disease typically begins with oligo- or polyarthralgias/seronegative arthritis. GI signs and symptoms (diarrhea, weight loss, abdominal pain) due to involvement of the duodenum and/or jejunum begin, on average, 6–8 years later. Other organ systems (e.g., the CNS and the cardiac, pulmonary, and lymphatic systems) are variably involved.

Diagnosis

The key to diagnosis is considering *T. whipplei* infection. PCR-based testing of tissue specimens rather than body fluids generally has a higher diagnostic yield. Histologic examination of intestinal biopsy samples remains an important diagnostic procedure, although it is less sensitive than PCR.

TREATMENT **WHIPPLE'S DISEASE**

Although the optimal regimen and duration are not known (and likely depend on the site of infection), ceftriaxone (2 g IV q24h) or meropenem (1 g IV q8h) for 2 weeks followed by TMP-SMX (160/800 mg PO bid) for 3–12 months appears to be efficacious. For CNS or cardiac infection, ceftriaxone (2 g IV q12h) or meropenem (2 g IV q8h) for ≥2 weeks followed by oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for ≥1 year seems prudent.

For a more detailed discussion, see Filice GA: Nocardiosis, Chap. 199, p. 1084; and Russo TA: Actinomycosis and Whipple's Disease, Chap. 200, p. 1088, in HPIM-19.

94 Tuberculosis and Other Mycobacterial Infections

TUBERCULOSIS

MICROBIOLOGY

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, the most common and important agent of human mycobacterial disease, and *M. bovis*, which (like several other mycobacterial species) is acquired via ingestion of unpasteurized milk. *M. tuberculosis* is a thin aerobic bacillus that is neutral on Gram's staining but that, once stained, is acid-fast; i.e., it cannot be decolorized by acid alcohol because of the cell wall's high content of mycolic acids and other lipids.

EPIDEMIOLOGY

An estimated 9 million new cases of TB occurred worldwide in 2013, with ~1.5 million TB-related deaths—almost entirely in low-income countries. Globally, TB rates are stable or falling.

- In the United States, TB primarily affects HIV-infected adults, immigrants, the elderly, and disadvantaged/marginalized populations.
- Isolates of *M. tuberculosis* that are multidrug-resistant (MDR; resistant to at least isoniazid and rifampin) and extensively drug-resistant (XDR; resistant to isoniazid, rifampin, and fluoroquinolones and to amikacin, kanamycin, or capreomycin) are increasing in frequency; ~480,000 cases of MDR-TB may have emerged in 2013, of which ~10% were probably XDR.
- Disease from a pt with pulmonary TB is spread by droplet nuclei that are aerosolized by coughing, sneezing, or speaking.
  - Droplets <5–10 μm in diameter may be suspended in air for several hours.
  - Transmission is determined by the intimacy and duration of contact with a pt with TB, the degree of infectiousness of the pt, and the shared environment.

  - Pts with cavitary or laryngeal disease are most infectious, with as many as 10^5–10^7 acid-fast bacilli (AFB)/mL of sputum.
- Risk factors for development of active disease after *M. tuberculosis* infection include recent acquisition (i.e., within the preceding 18 months), comorbidity (e.g., HIV disease, diabetes, silicosis, immunosuppression, gastrectomy), malnutrition, tobacco smoking, and presence of fibrotic lesions.

PATHOGENESIS

AFB that reach alveoli are ingested by macrophages. The bacilli impair phagosome maturation, multiply, lyse the macrophages, and spread to regional lymph nodes, from which they may disseminate throughout the body. These initial stages of infection are generally asymptomatic and induce cellular and humoral immunity.

- About 2–4 weeks after infection, a tissue-damaging response resulting from delayed-type hypersensitivity (the basis for tuberculin skin testing [TST]) destroys nonactivated macrophages that contain multiplying bacilli, and a macrophage-activating response activates cells capable of killing AFB. A granuloma forms at the site of the primary lesion and at sites of dissemination. The lesions can then either heal by fibrosis or undergo further evolution. Despite "healing," viable bacilli can remain dormant within macrophages or in necrotic material for years.
- Cell-mediated immunity confers partial protection against TB. Cytokines secreted by alveolar macrophages contribute to disease manifestations, granuloma formation, and mycobacterial killing.

CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Extrapulmonary TB may occur in 10–40% of pts, with even higher rates among HIV-infected pts.

Pulmonary TB

Primary disease may cause no or mild signs and symptoms (fever and occasional pleuritic chest pain) in contrast to the prolonged disease course that is common in postprimary or adult-type disease.

- Primary disease is frequently located in the middle and lower lobes. The primary lesion usually heals spontaneously, and a calcified nodule (Ghon focus) remains.
  - Transient hilar and paratracheal lymphadenopathy is common.
  - In immunosuppressed pts and children, primary disease may progress rapidly to significant clinical disease, with cavitation, pleural effusions, and hematogenous dissemination (miliary disease).
- Adult-type disease presents initially with nonspecific and insidious signs and symptoms, such as diurnal fever, night sweats, weight loss, anorexia, malaise, and weakness.
  - As the disease progresses, pts develop cough and purulent sputum production, often with blood streaking. Extensive cavitation may develop, with occasional massive hemoptysis following erosion of a vessel located in the wall of a cavity.
  - Disease is usually localized to the apical and posterior segments of the upper lobes and the superior segments of the lower lobes.

Extrapulmonary TB

Any site in the body can be involved, but the most commonly affected sites are (in order of frequency) the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. Up to two-thirds of HIV-infected pts with TB have extrapulmonary disease.

- *Lymphadenitis* occurs in 35% of extrapulmonary TB cases, especially among children and HIV-infected pts. Painless swelling of cervical and supraclavicular nodes (scrofula) is typical.

  - Nodes are discrete early on but can develop into a matted nontender mass with a fistulous tract.
  - Fine-needle aspiration or surgical-excision biopsy of the node is required for diagnosis. Cultures are positive in 70–80% of cases.
- *Pleural involvement* is common (~20% of extrapulmonary cases) and results from a hypersensitivity response to mycobacterial antigens or contiguous spread of parenchymal inflammation.
  - Pleural fluid is straw-colored and exudative, with protein levels >50% of those in serum, normal to low glucose levels, a usual pH of ~7.3 (occasionally <7.2), and pleocytosis (500–6000 cells/μL). The pleural concentration of adenosine deaminase, if low, virtually excludes TB.
  - Pleural biopsy is often required for diagnosis, with up to 80% of biopsy cultures and 75% of PCR tests positive. Direct smears, cultures, and PCR of pleural fluid are less sensitive.
  - Empyema is an uncommon complication of pulmonary TB and results from rupture of a cavity with many bacilli into the pleural space. In these cases, direct smears and cultures are often positive, and surgical drainage is usually required in addition to chemotherapy.
- In *genitourinary disease*, local symptoms predominate (e.g., urinary frequency, dysuria, hematuria, abdominal or flank pain), and up to 75% of pts have a CXR demonstrating previous or concomitant pulmonary disease. Disease is occasionally identified only after severe destructive lesions of the kidneys have developed.
  - In 90% of cases, urinalysis shows pyuria and hematuria with negative bacterial cultures.
  - Mycobacterial culture of three morning urine specimens is diagnostic in 90% of cases.
- Weight-bearing joints (spine, hips, and knees) are the most common sites of *skeletal disease*.
  - Spinal TB (Pott's disease) often involves two or more adjacent vertebral bodies; in adults, lower thoracic/upper lumbar vertebrae are usually affected. Disease spreads to adjacent vertebral bodies, later affecting the intervertebral disk and causing collapse of vertebral bodies in advanced disease (kyphosis, gibbus). Paravertebral cold abscesses may form.
- *Meningitis* occurs most often in young children and HIV-seropositive pts. Disease typically evolves over 1–2 weeks and often involves paresis of cranial nerves (particularly of ocular nerves). The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.
  - CSF can have a high lymphocyte count, an elevated protein level, and a low glucose concentration. Cultures are positive in 80% of cases. PCR is ~80% sensitive and is the preferred initial diagnostic option.
  - Neurologic sequelae are seen in ~25% of treated pts; adjunctive glucocorticoids enhance survival among pts >14 years of age but do not reduce the frequency of neurologic sequelae.
- *Gastrointestinal disease* can affect any portion of the GI tract (with the terminal ileum and cecum most commonly involved), causing abdominal pain, obstruction, hematochezia, and often a palpable mass. TB peritonitis can follow spread of the organism from ruptured lymph nodes and intraabdominal organs; peritoneal biopsy is usually required for diagnosis.
- *Pericarditis* is characterized by an acute or subacute onset of fever, dull retrosternal pain, and sometimes a friction rub. Effusion is common. Chronic constrictive pericarditis is a potentially fatal complication, even in treated pts. Adjunctive glucocorticoids remain controversial; no conclusive data demonstrate a benefit.
- *Miliary disease* arises from hematogenous spread of *M. tuberculosis* throughout the body. Symptoms are nonspecific, and small (1- to 2-mm) granulomas may develop in many organs. Hepatomegaly, splenomegaly, lymphadenopathy, and choroidal tubercles of the eye may occur.

HIV-Associated TB

The manifestations of TB vary with the stage of HIV infection. When cell-mediated immunity is only partly compromised, pulmonary TB presents as typical upper-lobe cavitary disease. In late HIV infection, a primary TB-like pattern may be evident, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy.

- Extrapulmonary disease occurs frequently; common forms include lymphadenitis, meningitis, pleuritis, pericarditis, mycobacteremia, and disseminated disease.
- Immune reconstitution inflammatory syndrome (IRIS), which may occur 1–3 months after initiation of antiretroviral therapy, may exacerbate the signs and symptoms of TB.

DIAGNOSIS

The key to diagnosis is a high index of suspicion.

- AFB microscopy of diagnostic specimens—i.e., light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes or fluorescence microscopy of samples stained with auramine-rhodamine—can provide a presumptive diagnosis. In suspected pulmonary TB, two or three sputum samples should be examined.
- Definitive diagnosis requires growth of *M. tuberculosis* in culture or identification of the organism's DNA in clinical samples.
  - Liquid media and speciation by molecular methods have decreased the time required for diagnostic confirmation to 2–3 weeks (from 4–8 weeks).
  - Nucleic acid amplification is useful not only for rapid confirmation of TB in AFB-positive specimens but also for diagnosis of AFB-negative pulmonary and extrapulmonary TB.
- Drug susceptibility can be assessed via indirect testing on solid media (which takes ≥8 weeks), direct testing in liquid media (which takes ~3 weeks), or PCR (which can provide results within hours).
- TST is of limited value in active disease because of low sensitivity and specificity but is the most widely used screening test for latent TB infection.
- Interferon γ release assays (IGRAs) measure the release of interferon γ by T cells after stimulation with TB-specific antigens and are more specific for *M. tuberculosis* than is TST.
  - In low-incidence settings, IGRAs may be more sensitive than TST.
  - In high TB- and/or HIV-burden settings, the performance of IGRAs has varied greatly, and these tests are not recommended as a replacement for the TST.

TREATMENT TUBERCULOSIS

DRUGS

First-Line Agents

- *Rifampin:* Rifampin is the most important and potent antituberculous agent. The standard dosage in adults is 600 mg/d.
  - The drug distributes well throughout body tissues, including inflamed meninges. It turns body fluids (e.g., urine, saliva, tears) red-orange and is excreted through bile and the enterohepatic circulation.
  - Rifampin is usually well tolerated; adverse events are infrequent and generally mild.
  - Of note, rifampin is a potent inducer of the hepatic cytochrome P450 system and decreases the half-life of many other drugs.
- *Isoniazid:* Isoniazid is a critical drug for active and latent TB disease. The usual adult dosage is 300 mg/d or 900 mg twice per week.
  - Isoniazid is distributed well throughout the body and infected tissues, including CSF and body cavities.

- The most important toxicities are hepatotoxicity and peripheral neuropathy.
  - Isoniazid-associated hepatitis is idiosyncratic. Its frequency increases with age and alcohol use and in the postpartum period.
  - Because peripheral neuropathy can result from interference with pyridoxine metabolism, pyridoxine (25–50 mg/d) should be given to pts with other risk factors for neuropathy, such as diabetes, alcohol abuse, or malnutrition.

- *Ethambutol:* The least potent first-line agent, ethambutol is synergistic with the other drugs in the standard first-line regimen. Ethambutol is usually given at a dosage of 15 mg/kg daily.
  - The drug is distributed throughout the body but reaches only low levels in CSF.
  - This agent can cause dose-dependent optic neuritis, producing central scotoma and impairing both visual acuity and the ability to see green.
- *Pyrazinamide:* The usual dosage is 15–30 mg/kg daily (maximum, 2 g/d). The drug distributes well throughout the body, including the CSF.
  - Hyperuricemia that can be managed conservatively is common.
  - Clinical gout is rare.

Other Effective Agents

- *Streptomycin:* The usual adult dose is 0.75–1.0 g IM daily or 5 times per week. Streptomycin causes ototoxicity (primarily vestibulotoxicity) but is less nephrotoxic than other aminoglycosides.
- *Rifabutin:* Rifabutin has fewer drug interactions than rifampin and is recommended in place of rifampin for HIV-infected pts who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Rifabutin reaches tissue concentrations 5–10 times higher than those in plasma and has a much longer half-life than rifampin. The drug is well tolerated, and its adverse effects are dose related.
- *Rifapentine:* Rifapentine is similar to rifampin but can be given once or twice weekly. This drug is not approved for treatment in HIV-infected pts because of elevated rates of relapse.

Second-Line Agents

- *Fluoroquinolones:* Levofloxacin, gatifloxacin (no longer marketed in the United States because of its severe toxicity), and moxifloxacin have solid, broad antimycobacterial activity. Ciprofloxacin and ofloxacin are no longer recommended for treatment of TB because of poor efficacy.
- Other agents (e.g., capreomycin, clofazimine, linezolid) are used uncommonly but may be needed in disease caused by resistant strains of *M. tuberculosis*.

REGIMENS

See Table 94-1.

- During the initial phase, the majority of tubercle bacilli are killed, symptoms resolve, and usually the pt becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.
- Nonadherence to the regimen is the most important impediment to cure. Directly observed treatment (especially during the initial 2 months) and fixed drug-combination products should be used if possible.
- Bacteriologic evaluation is the preferred method of monitoring response to treatment.
  - Virtually all pts should have negative sputum cultures after 3 months of treatment. If the culture remains positive, treatment failure and drug resistance should be suspected.
  - With extrapulmonary TB, bacteriologic monitoring may not be feasible. In these cases, the response to treatment must be assessed clinically and radiographically.

TABLE 94-1 RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS

	Initial Phase		Continuation Phase	
Indication	**Duration, Months**	**Drugs**	**Duration, Months**	**Drugs**
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c,d]
New culture-negative cases	2	HRZE[a]	4	HR[a]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default (pending susceptibility testing)	3	HRZES[f]	5	HRE
Failures[g]	← Tailored according to drug susceptibility testing →			
Resistance (or intolerance) to H	Throughout (6–9)	RZE[h]		
Resistance (or intolerance) to R	← Same as for MDR-TB; see below [i] →			
MDR-TB (resistance to at least H + R)	Throughout (20 months in most cases)	Q, Inj[j], Eto/Pto, Z, Cs/PAS		
XDR-TB	← Tailored according to drug susceptibility testing[k] →			
Intolerance to Z	2	HRE	7	HR

(*Continued*)

TABLE 94-1 RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS (*CONTINUED*)

	Initial Phase		Continuation Phase	
Indication	**Duration, Months**	**Drugs**	**Duration, Months**	**Drugs**

[a]All drugs can be given daily or intermittently (three times weekly throughout). A twice-weekly regimen after 2–8 weeks of daily therapy during the initial phase is sometimes used, although it is not recommended by the WHO.
[b]Streptomycin can be used in place of ethambutol but is no longer considered a first-line drug.
[c]Some experts suggest extending the continuation phase to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture–positive after the initial phase of treatment. However, treatment in such patients must be guided by drug susceptibility testing to rule out drug-resistant TB.
[d]A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase.
[e]The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months.
[f]Streptomycin should be discontinued after 2 months. Drug susceptibility results will determine the best regimen option.
[g]The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.
[h]Although normally not recommended, a fluoroquinolone may strengthen the regimen for patients with extensive disease. A later-generation agent (such as levofloxacin, moxifloxacin, or possibly gatifloxacin; see text) is preferred.
[i]Isoniazid is added if susceptibility to this agent is confirmed or presumed.
[j]Amikacin and kanamycin (aminoglycosides) or capreomycin (polypeptide). Any of these injectable agents is recommended for the first 8 months in most patients, but the duration may be modified according to the clinical response to therapy. Continuation of treatment with the injectable drug for at least 4 months after culture conversion is advised.
[k]Aggressive management of cases comprising early drug-susceptibility testing, rational combination of at least five drugs (one of which is an injectable agent), readjustment of the regimen, strict directly observed therapy, monthly bacteriologic monitoring, intensive patient support, and possible adjuvant surgery may result in cure and avert death.
Abbreviations: Cs/PAS, cycloserine or para-aminosalicylic acid; E, ethambutol; Eto/Pto, ethionamide or prothionamide; H, isoniazid; Inj, an injectable agent (the aminoglycosides amikacin and kanamycin or the polypeptide capreomycin); MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; S, streptomycin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

- Drug resistance may be either primary (i.e., present in a strain prior to therapy) or acquired (i.e., arising during treatment because of an inadequate regimen or noncompliance).
- Close monitoring for drug toxicity should take place during treatment and should include baseline LFTs and monthly questioning about possible hepatitis symptoms. High-risk pts (e.g., older pts, pts who use alcohol daily) should have LFT values monitored during treatment.
- For pts with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.
- Three important considerations are relevant to TB treatment in HIV-infected pts: an increased frequency of paradoxical reactions, interactions between antiretroviral agents and rifamycins, and development of rifampin monoresistance with widely spaced intermittent treatments.

TABLE 94-2 TUBERCULIN REACTION SIZE AND TREATMENT OF LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION

Risk Group	Tuberculin Reaction Size, mm
HIV-infected persons	≥5
Recent contacts of a patient with TB	≥5[a]
Organ transplant recipients	≥5
Persons with fibrotic lesions consistent with old TB on chest radiography	≥5
Persons who are immunosuppressed, e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors	≥5
Persons with high-risk medical conditions[b]	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c]	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons[d]	≥15

[a]Tuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat TST. Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.
[b]These conditions include silicosis and end-stage renal disease managed by hemodialysis
[c]These settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities.
[d]Except for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.
Source: Adapted from Centers for Disease Control and Prevention: TB elimination—treatment options for latent tuberculosis infection (2011). Available at *http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.pdf.*

TABLE 94-3 REGIMENS FOR THE TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) IN ADULTS[a]

Regimen	Schedule	Duration	Comments
Isoniazid	300 mg/d (5 mg/kg)	9 months (6 months acceptable)	Supplement with pyridoxine (25–50 mg daily).
	Alternative: 900 mg twice weekly (15 mg/kg)		Twice-weekly regimens require directly observed therapy.
Rifampin	600 mg/d (10 mg/kg)	4 months	Broader efficacy studies are needed.
Isoniazid plus rifapentine[b]	900 mg (15 mg/kg) weekly + 900 mg weekly	12 weeks	Directly observed therapy is recommended for the once-weekly regimen. This regimen may be supplemented with pyridoxine (25–50 mg/d).

Source: D Menzies et al: *Ann Intern Med* 149:689, 2008; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: *Am J Respir Crit Care Med* 167:603, 2003; and T Sterling et al: *N Engl J Med* 365:2155, 2011.

[a]Adapted from Table 205e-1 in HPIM-19.

[b]This regimen is not recommended for HIV-infected pts who are receiving antiretroviral therapy or for pregnant women.

PREVENTION

- *Vaccination:* An attenuated strain of *M. bovis*, bacille Calmette-Guérin (BCG), protects infants and young children from serious forms of TB (e.g., meningitis and miliary disease) and is recommended for routine use in countries with high TB prevalence.
- *Treatment of latent infection:* Candidates for chemoprophylaxis are identified by TST or IGRA. Positive skin tests are determined by reaction size and risk group (Table 94-2). Drug treatment should be considered for pts with evidence of latent infection (Table 94-3). Isoniazid should not be given to persons with active liver disease.

LEPROSY

MICROBIOLOGY AND EPIDEMIOLOGY

Leprosy is a nonfatal chronic infectious disease caused by *M. leprae*, an obligate intracellular bacterial species indistinguishable microscopically from other mycobacteria. The organism is confined to humans, armadillos (in some locales), and sphagnum moss.

- *M. leprae* cannot yet be cultured in vitro. The organism has a doubling time in mice of 2 weeks (compared with 20 min for *Escherichia coli* and 1 day for *M. tuberculosis*).
- Leprosy, which is associated with poverty and rural residence, is a disease of the developing world; its global prevalence is difficult to assess and is variously estimated at 0.6–8 million.
  - More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Nepal, Brazil, Nigeria, and Madagascar.

  - In the United States, ~4000 people have leprosy and 100–200 new cases are reported annually.
- The route of transmission is uncertain but may be via nasal droplets, contact with infected soil, or insect vectors.

CLINICAL MANIFESTATIONS

The spectrum from polar tuberculoid to polar lepromatous disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*–specific cellular immunity. Prognosis, complications, and intensity of antimicrobial therapy depend on where a pt presents on the clinical spectrum. The incubation period ranges from 2 to 40 years but is usually 5–7 years.

Tuberculoid (TT) Leprosy

At the less severe end of the disease spectrum, TT leprosy results in symptoms confined to the skin and peripheral nerves.

- One or several hypopigmented macules or plaques with sharp margins that are hypesthetic and have lost sweat glands and hair follicles are present. AFB are few or absent.
- There is asymmetric enlargement of one or several peripheral nerves—most often the ulnar, posterior auricular, peroneal, and posterior tibial nerves—associated with hypesthesia and myopathy.

Lepromatous (LL) Leprosy

Pts develop symmetrically distributed skin nodules, raised plaques, and diffuse dermal infiltration that can cause leonine facies, loss of eyebrows and lashes, pendulous earlobes, and dry scaling.

- Numerous bacilli are present in skin (up to 10^9/g), nerves, and all organs except the lungs and CNS.
- Nerve enlargement and damage are usually symmetric and are due to bacillary invasion.

COMPLICATIONS

- *Reactional states:* These common, immunologically mediated inflammatory states cause considerable morbidity. Erythema nodosum leprosum—characterized by painful erythematous papules that resolve spontaneously in ~1 week—occurs in ~50% of pts near the LL end of the disease spectrum within 2 years of initiation of therapy.
- *Extremities:* Neuropathy results in insensitivity and affects fine touch, pain, and heat receptors. The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and—in lepromatous pts—a poorly understood and sometimes profound osteolytic process.
- *Eyes:* Owing to cranial nerve palsies, lagophthalmos and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. Leprosy is a major cause of blindness in low-income countries.
- *Nerve abscesses:* Pts with leprosy can develop abscesses of nerves (most commonly the ulnar) and require urgent surgical decompression to prevent irreversible sequelae.

DIAGNOSIS

In TT leprosy, the advancing edge of a skin lesion should be biopsied. In LL leprosy, biopsy of even normal-appearing skin often yields positive results. Serology, skin testing, and PCR of the skin offer little diagnostic assistance.

TREATMENT LEPROSY

DRUGS

- Rifampin (600 mg daily or monthly) is the only agent bactericidal against *M. leprae*. See the preceding section on *M. tuberculosis* for more details on rifampin.
- Monotherapy with dapsone (50–100 mg/d) results in a resistance-related relapse rate of only 2.5%.
  - A decrease in hemoglobin levels of ~1 g/dL is a common adverse effect; the sulfone syndrome (high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture) occurs rarely.
  - G6PD deficiency must be ruled out before therapy to avoid hemolytic anemia.
- Clofazimine (50–100 mg/d, 100 mg 3 times per week, or 300 mg monthly) is a phenazine iminoquinone dye that is weakly active against *M. leprae*. Adverse effects include red-black skin discoloration.

REGIMENS Given the unreliability of skin smears and the lack of accessibility to histopathology in many countries in which leprosy is endemic, treatment regimens are based on the number of lesions present.

- *Paucibacillary disease* in adults (<6 skin lesions) is treated with dapsone (100 mg/d) and rifampin (600 mg monthly, supervised) for 6 months or with dapsone (100 mg/d) for 5 years. For a single lesion, a single dose of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) is recommended.
- *Multibacillary disease* in adults (≥6 skin lesions) is treated with dapsone (100 mg/d) plus clofazimine (50 mg/d)—unsupervised—in addition to rifampin (600 mg monthly) plus clofazimine (300 mg monthly)—supervised—for 1 year.
  - Some experts prefer rifampin (600 mg/d) for 3 years and dapsone (100 mg/d) for life.
  - Relapse can occur years later; prolonged follow-up is needed.
- *Reactional states*
  - Lesions at risk for ulceration or in cosmetically important areas can be treated with glucocorticoids (40–60 mg/d for at least 3 months).
  - If erythema nodosum leprosum is present and persists despite two short courses of steroids (40–60 mg/d for 1–2 weeks), thalidomide (100–300 mg nightly) should be given. Because of thalidomide's teratogenicity, its use is strictly regulated.

INFECTIONS WITH NONTUBERCULOUS MYCOBACTERIA (NTM)

Mycobacteria other than those of the *M. tuberculosis* complex and *M. leprae* are referred to as *nontuberculous* or *atypical* mycobacteria and are ubiquitous in soil and water.

MICROBIOLOGY

NTM are broadly differentiated into rapidly and slowly growing forms (<7 days and ≥7 days, respectively). *M. abscessus*, *M. fortuitum*, and *M. chelonae* are examples of rapid growers; species such as *M. avium* and *M. intracellulare* (the *M. avium* complex, or MAC), *M. kansasii, M. ulcerans,* and *M. marinum* are slow growers.

EPIDEMIOLOGY

Most NTM cause disease in humans only rarely unless some aspect of host defense is impaired (as in bronchiectasis) or breached (as by inoculation—e.g., during liposuction or trauma). The bulk of NTM disease in North America is due to *M. kansasii*, MAC organisms, and *M. abscessus*.

CLINICAL MANIFESTATIONS

Although there are many NTM species, the clinical presentations they cause can be broadly categorized by the organ system(s) affected.

- *Disseminated disease* is now quite rare; even pts with advanced HIV infection do not often develop disseminated NTM infection, given improved treatment of HIV infection and effective antimycobacterial prophylaxis.
  - Organisms typically spread from the bowel to the bone marrow and bloodstream, but disease is indolent, and it can take weeks or months for the pt to present for medical attention with malaise, fever, weight loss, organomegaly, and lymphadenopathy.
  - A child with involvement of ≥2 organ systems and no iatrogenic cause should be evaluated for defects in the interferon γ/interleukin 12 pathway.
- *Pulmonary disease* represents the most common NTM infection in industrialized countries. MAC organisms are most commonly involved in North America. Pts present with months or years of throat clearing, nagging cough, and slowly progressive fatigue. *M. kansasii* can cause a TB-like syndrome, with hemoptysis, chest pain, and cavitary lung disease.
- Isolated *cervical lymphadenopathy* is the most common NTM infection among young children in North America and is most frequently caused by MAC organisms. The nodes are typically firm and painless and develop in the absence of systemic symptoms.
- *Skin and soft tissue disease* usually requires a break in the skin for introduction of the organism. Different NTM species are associated with specific exposures.
  - *M. fortuitum* is linked to pedicure bath–associated infections, particularly if skin abrasion (e.g., during leg shaving) has immediately preceded the pedicure.
  - Rapidly growing NTM are associated with outbreaks of infection acquired via skin contamination from surgical instruments (especially in cosmetic surgery), injections, and other procedures. These infections are typically accompanied by painful, erythematous, draining SC nodules, usually without associated fever or systemic symptoms.
  - *M. marinum* can be acquired from fish tanks, swimming pools, barnacles, and fish scales. Pts typically develop papules or ulcers ("fish-tank granuloma") that can progress to tendonitis and tender nodules on the arm in a pattern similar to that caused by *Sporothrix schenckii*. Lesions appear days or weeks after acquisition of the organism.
  - *M. ulcerans* is a waterborne organism found primarily in tropical areas, especially in Africa. Skin lesions are typically painless, clean ulcers that slough and can cause osteomyelitis.

DIAGNOSIS

Similar to *M. tuberculosis*, NTM can be detected on acid-fast or fluorochrome smears of clinical samples and can be cultured on mycobacterial medium. Isolation of NTM from a clinical specimen may reflect colonization and requires an assessment of the organism's clinical significance.

- Isolation of NTM from blood specimens is clear evidence of disease; many NTM species require special media and will not grow in standard blood culture medium.
- The American Thoracic Society has published guidelines for the diagnosis of pulmonary NTM disease that require the growth of NTM from two of three sputum samples, a positive bronchoalveolar lavage sample, or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM in culture. Although these guidelines are specific to MAC, *M. abscessus,* and *M. kansasii*, they probably apply to other NTM as well.
- The only antibiotic susceptibility assessment indicated is testing of MAC organisms for susceptibility to clarithromycin and of *M. kansasii* for susceptibility to rifampin.

TREATMENT INFECTIONS WITH NTM

Since NTM disease evolves over a long period, it is rarely necessary to begin treatment on an emergency basis before identifying the infecting species.

- MAC infection requires multidrug therapy with a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months.
- *M. kansasii* lung disease is similar to TB in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Treatment should continue until cultures have been negative for at least 1 year.
- Extrapulmonary disease due to rapidly growing NTM is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility). Pulmonary disease due to *M. abscessus* is difficult to cure and often requires repeated courses that include a macrolide along with an IV-administered agent such as amikacin, a carbapenem, cefoxitin, or tigecycline.
- *M. marinum* infection is effectively treated with any combination of a macrolide, ethambutol, and a rifamycin for 1–2 months after clinical resolution of isolated soft-tissue disease; tendon and bone involvement may require longer courses in light of clinical evolution.
- Treatment of infections caused by other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated.

For a more detailed discussion, see Raviglione MC: Tuberculosis, Chap. 202, p. 1102; Gelber RH: Leprosy, Chap. 203, p. 1122; Holland SM: Nontuberculous Mycobacterial Infections, Chap. 204, p. 1128; and O'Donnell MR, Reddy D, Saukkonen JJ: Antimycobacterial Agents, Chap. 205e, in HPIM-19.

95 Lyme Disease and Other Nonsyphilitic Spirochetal Infections

LYME BORRELIOSIS

Microbiology and Epidemiology

Borrelia burgdorferi, the causative agent of Lyme disease, is a fastidious microaerophilic spirochete. The human infection Lyme borreliosis is caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto* (hereafter referred to as *B. burgdorferi*), *Borrelia garinii*, and *Borrelia afzelii*.

- *B. burgdorferi* is the sole cause of Lyme borreliosis in the United States; all three genospecies are found in Europe, and the latter two species occur in Asia.
- Lyme disease is the most common vector-borne illness in the United States, with ~300,000 cases each year.
  - *Ixodes* ticks transmit the disease.
  - *I. scapularis*, which also transmits babesiosis and anaplasmosis, is found in northeastern and midwestern states; *I. pacificus* is found in western states.
- The white-footed mouse is the preferred host for larval and nymphal *I. scapularis*. Adult ticks prefer the white-tailed deer as host.
- Nymphal ticks transmit the disease to humans during the early summer months after feeding for ≥24 h.

Clinical Manifestations

Lyme disease usually begins with *erythema migrans* (EM; stage 1, localized infection) before disseminating (stage 2) or causing persistent infection (stage 3).

- *Stage 1 (localized infection):* After an incubation period of 3–32 days, EM develops at the site of the tick bite (commonly the thigh, groin, or axilla) in 80% of pts.
  - The classic presentation is a red macule that expands slowly to form an annular lesion with a bright red outer border and central clearing. Central erythema, induration, necrosis, vesicular changes, or many red rings within an outer ring are also possible.
  - Most pts do not remember the preceding tick bite.
- *Stage 2 (disseminated infection):* Given that some pts do not notice EM, many pts present within days or weeks after infection with secondary annular skin lesions, nonspecific systemic signs and symptoms, neurologic deficits, or cardiac manifestations due to hematogenous spread.
  - Nonspecific signs and symptoms include severe headache, mild neck stiffness, fever, chills, migratory musculoskeletal pain, arthralgias, malaise, and fatigue. These manifestations subside within a few weeks, even in untreated pts.
  - Neurologic deficits occur in ~15% of pts and may include meningitis; encephalitis; cranial neuritis, including bilateral facial palsy; motor or sensory radiculoneuropathy; mononeuritis multiplex; ataxia; or myelitis. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations.
  - Cardiac involvement occurs in ~8% of pts. Atrioventricular (AV) block of fluctuating degree is most common, but acute myopericarditis is possible. Cardiac involvement usually lasts for only a few weeks but may recur in untreated pts.
- *Stage 3 (persistent infection):* Of untreated pts in the United States, ~60% develop frank arthritis, usually consisting of intermittent attacks of oligoarticular arthritis in large joints (especially the knees) that last for weeks or months.
  - Joint-fluid cell counts range from 500 to 110,000/μL (average, 25,000/μL); the majority of the cells are neutrophils.
  - Arthritis can persist despite eradication of spirochetes, potentially due to infection-induced autoimmunity or retained spirochetal antigens.
  - Chronic neurologic involvement (e.g., subtle encephalopathy affecting memory, mood, or sleep; peripheral neuropathy) is less common. In Europe, severe encephalomyelitis is seen with *B. garinii* infection.
  - Acrodermatitis chronica atrophicans, a late skin manifestation, is seen in Europe and Asia and is associated with *B. afzelii* infection.
- *Post-Lyme syndrome:* For months or years afterward, ~10% of pts have subjective pain, neurocognitive manifestations, or fatigue symptoms—a syndrome indistinguishable from chronic fatigue syndrome and fibromyalgia. There is no evidence that these symptoms are caused by active infection.

Diagnosis

Serologic evidence combined with a compatible clinical picture is the usual basis for diagnosis.

- Only 20–30% of pts have positive serologic results in acute-phase samples, whereas 70–80% have positive results in convalescent-phase samples obtained 2–4 weeks later. Of note, serologic tests do not discriminate between active and past disease as both IgM and IgG may persist for years after treatment.
  - Serologic analysis consisting of a two-step approach (ELISA screening with western blot confirmation for cases with positive or equivocal results) is recommended only for pts with at least an intermediate pretest likelihood of having Lyme disease.
  - IgM and IgG testing should be done in the first 2 months of illness, after which IgG testing alone is adequate.
  - CDC-adopted criteria dictate that the IgM western blot must show at least 2 of 3 defined bands and that the IgG western blot must show at least 5 of 10 defined bands to be considered positive.
- PCR is most useful for joint fluid, is less sensitive for CSF, and has little or no utility for plasma or urine.
- Although culture of the organism is possible, it is reserved primarily for research settings.

TREATMENT LYME BORRELIOSIS

- Doxycycline (100 mg bid) is the agent of choice for men and nonpregnant women with localized or disseminated infection and is also effective against anaplasmosis (Chap. 96).
  - Amoxicillin (500 mg tid), cefuroxime (500 mg bid), erythromycin (250 mg qid), and newer macrolides—preferred in that order—are alternative agents.
  - Except in cases of neurologic disease and third-degree AV block, the drug can usually be taken by mouth.
  - A 14-day course of treatment for localized infection or a 21-day course for disseminated infection is generally sufficient.
  - Approximately 15% of pts experience a Jarisch-Herxheimer-like reaction during the first 24 h of treatment.
- For pts with objective neurologic abnormalities (with the possible exception of isolated facial palsy), IV treatment with ceftriaxone for 14–28 days should be given. Cefotaxime or penicillin is an alternative.
- Pts with high-degree AV block (PR interval, >0.3 s) should receive IV treatment for at least part of the course; cardiac monitoring is recommended.
- Pts with Lyme arthritis should be treated with 30 days of oral doxycycline or amoxicillin.
  - For pts who do not respond to oral agents, re-treatment with IV ceftriaxone for 28 days is appropriate.
  - If joint inflammation persists for months after both oral and IV antibiotics, anti-inflammatory agents, disease-modifying antirheumatic drugs, or synovectomy may be successful.
- For pts diagnosed with chronic Lyme disease, no data demonstrate that additional antibiotic therapy is helpful.

Prophylaxis

The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged *I. scapularis* nymph is found or if follow-up will be difficult, a single 200-mg dose of doxycycline, given within 72 h of the tick bite, effectively prevents the disease.

Prognosis

Early treatment results in an excellent prognosis. Most pts recover with minimal or no residual deficits.

ENDEMIC TREPONEMATOSES

Microbiology and Epidemiology

The endemic treponematoses—yaws (*Treponema pallidum* subspecies *pertenue*), endemic syphilis (*T. pallidum* subspecies *endemicum*), and pinta (*T. carateum*)—are nonvenereal chronic diseases acquired during childhood and caused by organisms closely related to the agent of syphilis, *T. pallidum* subspecies *pallidum*.

- Disease is transmitted by direct contact.
- The most recent WHO estimate (1995) suggested that there are 460,000 new cases per year and a prevalence of 2.5 million infected persons.
- Disease is limited to people in rural areas of developing nations and recent émigrés from these regions.

Clinical Manifestations

The major clinical distinctions made between venereal syphilis and the nonvenereal treponematoses are the apparent lack of congenital transmission and of CNS involvement in the nonvenereal infections. However, these distinctions may not be entirely accurate.

- *Yaws* is characterized by the development of one or more primary lesions ("mother yaw") followed by multiple disseminated skin lesions.
  - At 3–4 weeks after acquisition of the organism, the pt develops a papule that ultimately enlarges, is associated with regional lymphadenopathy, and heals spontaneously within 6 months.
  - Late gummatous lesions of the skin and long bones affect 10% of untreated persons and are similar to the destructive lesions of leprosy and leishmaniasis.
- *Endemic syphilis* is initially localized to mucocutaneous and mucosal surfaces. Pts develop an intraoral papule, which is followed by mucous patches on the oral mucosa and mucocutaneous lesions resembling the condylomata lata of secondary syphilis. Destructive gummas, osteitis, and gangosa (destruction of the nose, maxilla, palate, and pharynx) are more common in endemic syphilis than in yaws.
- *Pinta* is the most benign of the treponemal infections in that it does not cause destructive lesions or involve tissues other than the skin. The disease has three stages that are characterized by marked changes in skin color.

Diagnosis

The diagnosis is based on clinical presentation, dark-field microscopy of scrapings from lesions, and serologic testing (as for venereal syphilis).

TREATMENT ENDEMIC TREPONEMATOSES

Benzathine penicillin (1.2 million units for adults, 600,000 units for children <10 years of age) is the treatment of choice. A single dose of azithromycin (30 mg/kg; maximum, 2 g) is also effective, and doxycycline is probably an effective alternative.

LEPTOSPIROSIS

Microbiology and Epidemiology

Leptospires are spirochetal organisms that cause an important zoonosis with a broad spectrum of clinical manifestations.

- Rodents, particularly rats, are the most important reservoir, but leptospirosis affects almost all mammalian species. Transmission can occur during contact with urine, blood, or tissue from infected animals or, more commonly, during exposure to contaminated environments (e.g., during recreational water activities).
- Globally, there are ~1 million severe cases each year, with a mean case–fatality rate of ~10%.

Clinical Manifestations

After an average incubation period of 1–2 weeks, infection by *Leptospira* results in a subclinical infection, an undifferentiated febrile illness, or Weil's disease (the most severe form).

- Leptospirosis is a biphasic illness. The initial *leptospiremic* phase lasts 3–10 days and is characterized by fever; organisms can be cultured from blood during this phase. After another 3–10 days (the *immune* phase), symptoms resolve, and leptospires can be cultured from urine.
  - Nonspecific physical findings may include conjunctival suffusion, nonexudative pharyngeal injection, muscle tenderness, lymphadenopathy, crackles on lung auscultation, jaundice, hepatosplenomegaly, and a transient rash.
- Severe leptospirosis, often referred to as *Weil's syndrome*, encompasses the triad of hemorrhage, jaundice, and acute renal injury. Up to 50% of pts die of septic shock with multiorgan failure and/or severe bleeding in the lungs, GI and urogenital tracts, and skin.

Diagnosis

An appropriate exposure history combined with any of the protean manifestations of leptospirosis suggests the clinical diagnosis and guides confirmatory testing.

- Definitive diagnosis rests on demonstration of the organism by culture isolation (which takes weeks or months), on a positive PCR result, or on seroconversion or a ≥4-fold rise in antibody titer.
  - Leptospires can be cultured from blood and CSF during the first 7–10 days of illness.
  - Urine cultures are positive in the second week of illness.

TREATMENT LEPTOSPIROSIS

- Prompt initiation of antibiotics probably shortens the course of severe leptospirosis and prevents the progression of mild disease.
- For mild disease, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are co-endemic, doxycycline or azithromycin is the drug of choice.
- For severe disease, parenteral treatment with penicillin, ceftriaxone, cefotaxime, or doxycycline should be given. From a pragmatic viewpoint, severe leptospiral disease frequently requires empirical initiation of broad-spectrum parenteral therapy before the diagnosis is confirmed.

RELAPSING FEVER

Microbiology

Borrelia recurrentis causes louse-borne relapsing fever (LBRF) and is transmitted from person to person by the body louse. Spirochetes are introduced not from the bite itself but from rubbing of the insect's feces into the bite site in response to

irritation. Tick-borne relapsing fever (TBRF), a zoonosis usually transmitted via the bite of various *Ornithodoros* ticks, is caused by multiple *Borrelia* species. *B. miyamotoi* can cause relapsing fever but is transmitted to humans from other mammals by hard ticks (e.g., *Ixodes scapularis*) that also transmit *B. burgdorferi* and other tick-borne illnesses.

Epidemiology

LBRF transmission is currently limited to Ethiopia and adjacent countries, with epidemics occurring during famine, natural disaster, and war. TBRF occurs worldwide, with Africa most affected. In North America, most cases are due to *B. hermsii* and *B. turicatae* and occur in the western United States and Canada.

Clinical Manifestations

- Both TBRF and LBRF present with a sudden onset of discrete febrile periods separated by afebrile periods of a few days.
  - In LBRF, the first episode of fever persists for 3–6 days and is followed by a single milder episode.
  - In TBRF, multiple febrile periods last 1–3 days each.
  - In both forms, the duration of an afebrile period ranges from 4 to 14 days.
- In addition to fever, pts commonly develop headaches, myalgias, nausea, abdominal pain (due to hepatosplenomegaly), and arthralgias.
  - Petechiae, ecchymoses, and epistaxis are common in LBRF but not in TBRF.
  - Localizing neurologic findings (e.g., Bell's palsy, deafness, visual impairment) are more common in TBRF.

Diagnosis

In pts with a compatible history (i.e., a characteristic fever pattern and exposure to body lice or soft-bodied ticks 1–2 weeks prior to illness onset), laboratory confirmation is made by the detection or isolation of spirochetes from blood during a febrile episode. Microscopic examination of Wright- or Giemsa-stained thin blood smears usually yields positive results if the concentration of spirochetes is $\geq 10^5$/mL.

- PCR techniques may reveal spirochetes between febrile episodes.
- Serologic confirmation of infection is limited by false-positive results and poor sensitivity.

TREATMENT RELAPSING FEVER

- One dose of doxycycline (200 mg PO), tetracycline (500 mg PO), or penicillin G (400,000–800,000 units IM) is effective for LBRF. A 10-day course of tetracycline (500 mg q6h) or doxycycline (100 mg bid) is preferred for TBRF; erythromycin (500 mg q6h) is an alternative when tetracyclines are contraindicated. The Jarisch-Herxheimer reaction, which has an incidence of ~80% in LBRF and ~50% in TBRF, presents as rigors, fevers, and hypotension within 2–3 h of initiation of antibiotic therapy. Given that some cases are fatal, pts should be monitored for several hours following the first dose of antibiotics.
- Little is known about treatment for *B. miyamotoi* infections, but the guidelines for Lyme disease are probably sufficient.

Prognosis

The mortality rates for untreated LBRF and TBRF are 10–70% and 4–10%, respectively. With treatment, the mortality rate is 2–5% for LBRF and <2% for TBRF.

For a more detailed discussion, see Lukehart SA: Endemic Treponematoses, Chap. 207e; Hartskeerl RA, Wagenaar JFP: Leptospirosis, Chap. 208, p. 1140; Barbour AG: Relapsing Fever, Chap. 209, p. 1146; and Steere AC: Lyme Borreliosis, Chap. 210, p. 1149, in HPIM-19. For a discussion of syphilis, see Chap. 83 in this manual.

96 Rickettsial Diseases

Microbiology

Rickettsiae are obligate intracellular gram-negative coccobacilli and short bacilli usually transmitted by tick, mite, flea, or louse vectors. Except in the case of louse-borne typhus, humans are incidental hosts.

Clinical Manifestations

The clinical manifestations of all the acute rickettsial presentations are similar during the first 5 days and consist of nonspecific signs and symptoms: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including occurrence of a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and meningoencephalitis—vary from one disease to another. (See Table 96-1 and details below.)

TICK- AND MITE-BORNE SPOTTED FEVERS

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Epidemiology

Caused by *R. rickettsii*, RMSF has the highest case–fatality rate of all rickettsial diseases.

- In the United States, the prevalence is highest in the south-central and southeastern states. Most cases occur between May and September.
- A rare presentation of fulminant RMSF is seen most often in male black pts with G6PD deficiency.
- RMSF is transmitted by different ticks in different geographic areas—e.g., the American dog tick (*Dermacentor variabilis*) transmits RMSF in the eastern two-thirds of the United States and in California, and the Rocky Mountain wood tick (*D. andersoni*) transmits RMSF in the western United States.

Pathogenesis

Rickettsiae are inoculated by the tick after ≥6 h of feeding, spread lymphohematogenously, and infect numerous foci of contiguous endothelial cells. Increased vascular permeability, with edema, hypovolemia, and ischemia, causes tissue and organ injury.

TABLE 96-1 FEATURES OF SELECTED RICKETTSIAL INFECTIONS

Disease	Organism	Transmission	Geographic Range	Incubation Period, Days	Duration, Days	Rash, %	Eschar, %	Lymphadenopathy[a]
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor andersoni*, *D. variabilis*	United States	2–14	10–20	90	<1	+
		Amblyomma cajennense, *A. aureolatum*	Central/South America					
		Rhipicephalus sanguineus	Mexico, Brazil, United States					
Mediterranean spotted fever	*R. conorii*	Tick bite: *R. sanguineus*, *Rhipicephalus pumilio*	Southern Europe, Africa, Middle East, Central Asia	5–7	7–14	97	50	+
African tick-bite fever	*R. africae*	Tick bite: *A. hebraeum*, *A. variegatum*	Sub-Saharan Africa, West Indies	4–10	4–19	50	90	++++
Maculatum disease	*R. parkeri*	Tick bite: *A. maculatum*	United States, South America	2–10	6–16	88	94	++
Rickettsialpox	*R. akari*	Mite bite: *Liponyssoides sanguineus*	United States, Ukraine, Turkey, Mexico, Croatia	10–17	3–11	100	90	+++
Tick-borne lymphadenopathy	*R. slovaca*	Tick bite: *D. marginatus*, *D. reticularis*	Europe	7–9	17–180	5	100	++++
Flea-borne spotted fever	*R. felis*	Flea (mechanism undetermined): *Ctenocephalides felis*	Worldwide	8–16	8–16	80	15	—

(Continued)

TABLE 96-1 FEATURES OF SELECTED RICKETTSIAL INFECTIONS (*CONTINUED*)

Disease	Organism	Transmission	Geographic Range	Incubation Period, Days	Duration, Days	Rash, %	Eschar, %	Lymphadenopathy[a]
Epidemic typhus	*R. prowazekii*	Louse feces: *Pediculus humanus corporis*, fleas and lice of flying squirrels, or recrudescence	Worldwide	7–14	10–18	80	None	—
Murine typhus	*R. typhi*	Flea feces: *Xenopsylla cheopis*, *C. felis*, others	Worldwide	8–16	9–18	80	None	—
Human monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *A. americanum*, *D. variabilis*	United States	1–21	3–21	26	None	++
Ewingii ehrlichiosis	*E. ewingii*	Tick bite: *A. americanum*	United States	1–21	4–21	0	None	
Unnamed ehrlichiosis	*E. muris*–like agent	Tick bite: *Ixodes scapularis*	United States	Unknown	3–14	None	None	
Human granulocytotropic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *I. scapularis*, *I. ricinus*, *I. pacificus*, *I. persulcatus*	United States, Europe, Asia	4–8	3–14	Rare	None	—
Unnamed disease	*Candidatus* Neoehrlichia mikurensis	Tick bite: *I. ricinus*, *I. persulcatus*, *Haemaphysalis concinna*	Europe, China	≥8	11–75	10	None	

Scrub typhus	*Orientia tsutsugamushi*	Mite bite: *Leptotrombidium deliense*, others	Asia, Australia, Pacific and Indian Ocean islands	9–18	6–21	50	35	+++
Q fever	*Coxiella burnetii*	Inhalation of aerosols of infected parturition material (goats, sheep, cattle, cats, others), ingestion of infected milk or milk products	Worldwide except New Zealand, Antarctica	3–30	5–57	<1	None	—

[a]++++, severe; +++, marked; ++, moderate; +, present in a small proportion of cases; —, not a noted feature.

Clinical Manifestations

The incubation period is ~1 week (range, 2–14 days). After 3 days of nonspecific symptoms, half of pts have a rash characterized by macules appearing on the wrists and ankles and subsequently spreading to the rest of the extremities and the trunk.

- Lesions ultimately become petechial in 41–59% of pts, appearing on or after day 6 of illness in ~74% of all cases that include a rash. The palms and soles become involved after day 5 in 43% of pts but do not become involved at all in 18–64%.
- Pts may develop hypovolemia, prerenal azotemia, hypotension, noncardiogenic pulmonary edema, renal failure, hepatic injury, and cardiac involvement with dysrhythmias. Bleeding is a rare but potentially life-threatening consequence of severe vascular damage.
- CNS involvement—manifesting as encephalitis, focal neurologic deficits, or meningoencephalitis—is an important determinant of outcome. In meningoencephalitis, CSF findings are notable for pleocytosis with a mononuclear cell or neutrophil predominance, increased protein levels, and normal glucose levels.
- Laboratory findings may include increased plasma levels of acute-phase reactants such as C-reactive protein, hypoalbuminemia, hyponatremia, and elevated levels of creatine kinase.

Prognosis

Without treatment, the pt usually dies in 8–15 days; fulminant RMSF can result in death within 5 days. The mortality rate is 3–5% despite the availability of effective antibiotics, mostly because of delayed diagnosis. Survivors of RMSF usually return to their previous state of health.

Diagnosis

Within the first 3 days, diagnosis is difficult, since only 3% of pts have the classic triad of fever, rash, and known history of tick exposure. When the rash appears, RMSF should be considered.

- Immunohistologic examination of a cutaneous biopsy sample from a rash lesion is the only useful diagnostic test during acute illness, with a sensitivity of 70% and a specificity of 100%.
- Serology, most commonly the indirect immunofluorescence assay (IFA), is usually positive 7–10 days after disease onset, and a diagnostic titer of ≥1:64 is usually documented.

TREATMENT ROCKY MOUNTAIN SPOTTED FEVER

- Doxycycline (100 mg bid PO or IV) is the agent of choice for both children and adults but not for pregnant women and pts allergic to this drug, who should receive chloramphenicol.
- Treatment is given until the pt is afebrile and has been improving for 2 or 3 days.

OTHER TICK-BORNE SPOTTED FEVERS

- *R. conorii* causes disease in southern Europe, Africa, and Asia. The name for *R. conorii* infection varies by region (e.g., Mediterranean spotted fever, Kenya tick typhus).
  - Disease is characterized by high fever, rash, and—in most locales—an inoculation eschar (*tâche noire*) at the site of the tick bite.
  - A severe form of disease with a mortality rate of ~50% occurs in pts with diabetes, alcoholism, or heart failure.
- *R. africae* causes African tick-bite fever, which occurs in sub-Saharan Africa and the Caribbean and is a mild illness consisting of headache, fever, eschar, and regional lymphadenopathy.

- Tick-borne spotted fever is diagnosed on the basis of clinical and epidemiologic findings; the diagnosis is confirmed by serology or detection of rickettsiae.

TREATMENT **OTHER TICK-BORNE SPOTTED FEVERS**

Doxycycline (100 mg PO bid for 1–5 days) or chloramphenicol (500 mg qid PO for 7–10 days) is effective for treatment. Pregnant pts may be treated with josamycin (3 g/d PO for 5 days).

RICKETTSIALPOX

Epidemiology

Rickettsialpox is caused by *R. akari* and is maintained by mice and their mites. Recognized principally in New York City, rickettsialpox has been reported in other urban and rural locations in the United States as well as in Ukraine, Croatia, Mexico, and Turkey.

Clinical Manifestations

A papule forms at the site of the mite bite and develops a central vesicle that becomes a painless black-crusted eschar surrounded by an erythematous halo. Lymph nodes draining the region of the eschar enlarge.

- After an incubation period of 10–17 days, malaise, chills, fever, headache, and myalgia mark disease onset.
- A macular rash appears on day 2–6 of illness and evolves sequentially into papules, vesicles, and crusts that heal without scarring.
- If untreated, fever lasts 6–10 days.

TREATMENT **RICKETTSIALPOX**

Doxycycline is the drug of choice for treatment.

FLEA- AND LOUSE-BORNE TYPHUS GROUP RICKETTSIOSES

ENDEMIC MURINE TYPHUS (FLEA-BORNE)

Etiology and Epidemiology

Caused by *R. typhi*, endemic murine typhus has a rat reservoir and is transmitted by fleas.

- Humans become infected when *Rickettsia*-laden flea feces are scratched into pruritic bite lesions; less often, the flea bite itself transmits the organisms or aerosolized rickettsiae from flea feces are inhaled.
- In the United States, endemic typhus occurs mainly in southern Texas and southern California; globally, it occurs in warm (often coastal) areas throughout the tropics and subtropics.
- Flea bites often are not recalled by pts, but exposure to animals such as cats, opossums, raccoons, skunks, and rats is reported by ~40%.
- Risk factors for severe disease include older age, underlying disease, and treatment with a sulfonamide drug.

Clinical Manifestations

Prodromal symptoms 1–3 days before the abrupt onset of chills and fever include headache, myalgia, arthralgia, nausea, and malaise; nausea and vomiting are nearly universal early in illness.

- Rash is apparent at presentation (usually ~4 days after symptom onset) in 13% of pts; 2 days later, half of the remaining pts develop a maculopapular rash that involves the trunk more than the extremities, is seldom petechial, and rarely involves the face, palms, or soles.
- Pulmonary disease is common, causing a hacking, nonproductive cough in 35% of pts. Almost one-fourth of pts who undergo CXR have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions.
- Laboratory abnormalities include anemia, leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased hepatic aminotransferase levels, and prerenal azotemia.
- Complications may include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis.
- The duration of untreated disease averages 12 days (range, 9–18 days).

Diagnosis

The diagnosis can be based on culture, PCR, serologic studies of acute- and convalescent-phase sera, or immunohistology, but most pts are treated empirically.

TREATMENT **ENDEMIC MURINE TYPHUS (FLEA-BORNE)**

Doxycycline (100 mg PO bid for 7–15 days) is effective. Ciprofloxacin provides an alternative if doxycycline is contraindicated.

EPIDEMIC TYPHUS (LOUSE-BORNE)

Etiology and Epidemiology

Epidemic typhus is caused by *R. prowazekii* and is transmitted by the human body louse. Eastern flying squirrels and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle.

- The louse lives in clothing under poor hygienic conditions, particularly in colder climates and classically at times of war or natural disaster.
- Lice feed on pts with epidemic typhus and then defecate the organism on their subsequent host during their next meal. The pt autoinoculates the organism while scratching.
- *Brill-Zinsser disease* is a recrudescent form of epidemic typhus whose occurrence years after acute illness suggests that *R. prowazekii* remains dormant in the host, with reactivation when immunity wanes.

Clinical Manifestations

Epidemic typhus presents abruptly with the onset of high fevers, prostration, severe headache, cough, and severe myalgias. Photophobia with conjunctival injection and eye pain is also common.

- A rash appears on the upper trunk around the fifth day of illness and spreads to involve all body-surface areas except the face, palms, and soles.
- Confusion and coma, skin necrosis, and gangrene of the digits are noted in severe cases.
- Untreated, the disease is fatal in 7–40% of cases. Pts develop renal failure, multiorgan involvement, and prominent neurologic manifestations.

Diagnosis

Epidemic typhus is sometimes misdiagnosed as typhoid fever. The diagnosis can be based on serology, immunohistochemistry, or detection of the organism in a louse found on a pt.

TREATMENT EPIDEMIC TYPHUS (LOUSE-BORNE)

Doxycycline (100 mg bid) is given until 2 or 3 days after the pt has defervesced, although a one-time dose of 200 mg has proved effective under epidemic conditions.

SCRUB TYPHUS

- *Orientia tsutsugamushi*, the agent of scrub typhus, is transmitted by larval mites or chiggers in environments with heavy scrub vegetation.
- Disease occurs during the wet season. It is endemic in eastern and southern Asia, northern Australia, and the Pacific islands.
- The classic case description includes signs rarely seen in indigenous pts: an eschar at the site of chigger feeding, regional lymphadenopathy, and maculopapular rash. Westerners commonly do not present with all three findings. Severe cases include encephalitis and interstitial pneumonia.
- Scrub typhus can be diagnosed by serologic assays (IFA, indirect immunoperoxidase, and enzyme immunoassays); PCR analysis of eschars and blood is also effective.

TREATMENT SCRUB TYPHUS

A 7- to 15-day course of doxycycline (100 mg bid) or chloramphenicol (500 mg qid) or a 3-day course of azithromycin (500 mg qd) is effective.

EHRLICHIOSES AND ANAPLASMOSIS

Two distinct *Ehrlichia* species and one *Anaplasma* species—all obligately intracellular organisms—are transmitted by ticks to humans and cause infections that can be severe and prevalent.

HUMAN MONOCYTOTROPIC EHRLICHIOSIS (HME)

Etiology and Epidemiology

HME is caused by *Ehrlichia chaffeensis* and, in the United States, generally occurs in southeastern, south-central, and mid-Atlantic states from May to July. The incidence can be as high as 414 cases per 100,000 population.

- *E. chaffeensis* is transmitted by the Lone Star tick (*Amblyomma americanum*), and white-tailed deer are the major reservoir.
- The median age of pts is 52 years; 60% of pts are male.
- *E. ewingii* and an *E. muris*–like agent cause an illness similar to, but less severe than, that due to *E. chaffeensis*.

Clinical Manifestations

Clinical findings are nonspecific and include fever (96%), headache (72%), myalgia (68%), and malaise (77%). Nausea, vomiting, diarrhea, cough, rash, and confusion may be noted.

- The median incubation period is 8 days.
- Disease can be severe: up to 49% of pts are hospitalized and ~2% die. Complications include a toxic shock–like syndrome, respiratory distress, cardiac failure, hepatitis, meningoencephalitis, fulminant infection, and hemorrhage.
- Leukopenia (61%), thrombocytopenia (73%), and elevated serum aminotransferase levels (84%) are common.

Diagnosis

Because HME can be fatal, empirical antibiotic therapy based on clinical diagnosis is required. PCR testing before initiation of antibiotic therapy or retrospective serodiagnosis to detect increased antibody titers can be performed. Morulae are seen in <10% of peripheral-blood smears.

TREATMENT HUMAN MONOCYTOTROPIC EHRLICHIOSIS

Doxycycline (100 mg PO/IV bid) or tetracycline (250–500 mg PO q6h) is effective and should be continued for 3–5 days after defervescence.

HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS (HGA)

Etiology and Epidemiology

HGA is caused by *Anaplasma phagocytophilum* and, in the United States, occurs mainly in northeastern and upper midwestern states.

- The geographic distribution is similar to that of Lyme disease and *Babesia microti* infection, given the shared *Ixodes scapularis* tick vector.
- HGA incidence peaks in May through July, but the disease can occur year-round.
- The epidemiology of HGA is similar to that of HME, with males (59%) and older persons (median age, 51 years) more often affected.

Clinical Manifestations

Given high seroprevalence rates in endemic areas, it appears that most people develop subclinical infections.

- After an incubation period of 4–8 days, pts develop fever (75–100%), myalgia (77%), headache (82%), and malaise (97%).
- Severe complications—respiratory distress, a toxic shock–like syndrome, and opportunistic infections—occur most often in elderly pts.
- On laboratory examination, pts are found to have leukopenia (55%), thrombocytopenia (75%), and elevated serum aminotransferase levels (83%).

Diagnosis

HGA should be considered in pts with influenza-like illness during May through December and in pts with atypical severe presentations of Lyme disease.

- Peripheral-blood films may reveal morulae in neutrophils in 20–75% of infections.
- PCR testing before antibiotic therapy or retrospective serologic testing demonstrating a ≥4-fold rise in antibody titer can confirm the diagnosis.

TREATMENT HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS

Doxycycline (100 mg PO bid) is effective, and most pts defervesce within 24–48 h. Pregnant women and children <8 years old may be treated with rifampin.

Prevention

HME and HGA are prevented by avoidance of ticks in endemic areas, use of protective clothing and tick repellents, careful tick searches after exposures, and prompt removal of attached ticks.

Q FEVER

Microbiology

Coxiella burnetii—the etiologic agent of Q fever—is a small, pleomorphic coccobacillus that has a gram-negative cell wall and is located intracellularly.

Epidemiology and Pathogenesis

A worldwide disease, Q fever is a zoonosis. Cattle, sheep, and goats are responsible for most cases of human infection; many other animals can serve as vectors of transmission or as reservoirs of disease.

- *C. burnetii* localizes to the uterus and mammary glands of infected female mammals. It is reactivated in pregnancy and is found at high concentrations in the placenta. At parturition, the organism is dispersed as an aerosol, and infection usually follows inhalation.
- Abattoir workers, veterinarians, farmers, and other persons who have contact with infected animals, particularly with newborn animals or infected products of conception, are at risk.
- In the United States, there are 28–54 cases per year; in Australia, there are 30 cases per 1 million population per year.

Clinical Manifestations

The specific presentation of acute Q fever differs geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille), potentially reflecting differences in routes of infection or infecting strains; chronic Q fever almost always implies endocarditis.

- *Acute Q fever:* After an incubation period of 3–30 days, pts may present with flu-like syndromes, prolonged fever, pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy.
  - Signs and symptoms are often nonspecific (e.g., fever, fatigue, headache, chills, sweats, nausea, vomiting, diarrhea, cough, and occasionally rash).
  - Multiple rounded opacities on CXR in pts in endemic areas are highly suggestive of Q fever pneumonia.
  - The WBC count is usually normal, but thrombocytopenia occurs. During recovery, reactive thrombocytosis can develop.
  - Prolonged fatigue, along with a constellation of nonspecific symptoms (e.g., headaches, myalgias, arthralgias), can follow Q fever (post–Q fever fatigue syndrome).
- *Chronic Q fever:* Pts with *C. burnetii* endocarditis typically have prior valvular heart disease, immunosuppression, or chronic renal failure.
  - Fever is absent or low grade; pts may be ill for >1 year before diagnosis.
  - Valvular vegetations are seen in 21–50% of cases with transesophageal echocardiography but in only 12% with transthoracic echocardiography. The vegetations differ from those in bacterial endocarditis of other etiologies and manifest as endothelium-covered nodules on the valve.
  - The disease should be suspected in all pts with culture-negative endocarditis.
  - Although *C. burnetii* can be isolated by a shell-vial technique, most laboratories are not permitted to attempt isolation because of the organism's highly contagious nature. PCR testing of tissue or biopsy specimens can be used, but serology is the most common diagnostic tool; IFA is the method of choice.

TREATMENT Q FEVER

- Acute Q fever is treated with doxycycline (100 mg bid for 14 days).
  - Quinolones are also efficacious.
  - If Q fever is diagnosed during pregnancy, trimethoprim-sulfamethoxazole should be administered up to term.

- The currently recommended treatment for chronic Q fever is doxycycline (100 mg bid) and hydroxychloroquine (200 mg tid; plasma concentrations maintained at 0.8–1.2 μg/mL) for 18 months.
  - In vitro, hydroxychloroquine renders doxycycline bactericidal against *C. burnetii*.
  - The minimal inhibitory concentration (MIC) of doxycycline for the pt's isolate should be determined and serum levels monitored, with a goal of a serum level–to–doxycycline MIC ratio of ≥1.
  - Pts should be advised about photosensitivity and retinal toxicity risks with treatment.
  - Pts who cannot receive doxycycline–hydroxychloroquine should be treated with at least two agents active against *C. burnetii*. The combination of rifampin (300 mg once daily) plus doxycycline (100 mg bid) or ciprofloxacin (750 mg bid) has been used with success.
    - This alternative regimen should be discontinued when IgG antibody levels have decreased by fourfold at 1 year, IgM antibody to phase II has disappeared, and the pt is clinically stable.

For a more detailed discussion, see Walker DH, Dumler JS, Marrie T: Rickettsial Diseases, Chap. 211, p. 1154, in HPIM-19.

97 *Mycoplasma pneumoniae*, *Legionella* Species, and *Chlamydia pneumoniae*

Mycoplasma pneumoniae, *Legionella* species, and *Chlamydia pneumoniae* are often grouped together as the most important causes of "atypical" community-acquired pneumonia. (For a discussion of urogenital mycoplasmas, see Chap. 83.)

MYCOPLASMA PNEUMONIAE

With a size of only 150–350 nm, mycoplasmas are the smallest free-living organisms. Genome sequence data from many different *Mycoplasma* species have helped define the minimal set of genes necessary for cellular life. Lacking a cell wall and bounded only by a plasma membrane, mycoplasmas colonize mucosal surfaces of the respiratory and urogenital tracts.

Epidemiology

M. pneumoniae occurs worldwide with no seasonal pattern. Infection causes upper respiratory tract disease ~20 times more frequently than pneumonia.

- Infection is acquired by inhalation of aerosols, with an incubation period of 2–4 weeks.
- *M. pneumoniae* accounts for ~23% of cases of community-acquired pneumonia in adults.

Clinical Manifestations

The clinical presentation does not help distinguish *M. pneumoniae* pneumonia from that of any other bacterial etiology.

- Acute *M. pneumoniae* infection manifests as a nonspecific upper respiratory syndrome with pharyngitis, tracheobronchitis, and/or wheezing.
- Pneumonia develops in 3–13% of infected pts. The most common presenting symptom is a nonproductive cough. Headache, malaise, chills, and fever are common.
- On physical examination, ~80% of pts have wheezes or rales.
- Symptoms usually resolve in 2–3 weeks, and appropriate antimicrobial therapy significantly shortens the duration of clinical illness.
- Infection uncommonly results in critical illness and rarely causes death.
- Extrapulmonary manifestations of *M. pneumoniae* infection are relatively uncommon but include skin eruptions (e.g., erythema multiforme major, rashes), neurologic manifestations (e.g., encephalitis, Guillain-Barré syndrome, acute demyelinating encephalomyelitis), septic arthritis (particularly in pts with hypogammaglobulinemia), and hematologic manifestations (e.g., hemolytic anemia, coagulopathies).

Diagnosis

Clinical findings, nonmicrobiologic laboratory tests, and CXR are not useful in distinguishing *M. pneumoniae* pneumonia from pneumonia of other etiologies.

- Acute *M. pneumoniae* infection can be diagnosed by PCR analysis of respiratory tract secretions, which is 65–90% sensitive and 90–100% specific.
- *M. pneumoniae* culture (which requires special medium) is not recommended for routine diagnosis because its sensitivity is ≤60% and growth of the organism can take weeks.
- Serologic testing for IgM and IgG antibodies to *M. pneumoniae* requires acute- and convalescent-phase samples and is therefore less useful for diagnosis of active infections. Moreover, IgM antibodies to *M. pneumoniae* can persist for up to 1 year after acute infection.
- Measurement of cold agglutinin titers is no longer recommended for the diagnosis of *M. pneumoniae* infection because the findings are nonspecific.

TREATMENT *M. PNEUMONIAE* INFECTIONS

- Antibiotic options include macrolides (azithromycin, 500 mg PO for 1 day followed by 250 mg for 4 days), tetracyclines (doxycycline, 100 mg PO bid for 10–14 days), and respiratory fluoroquinolones (levofloxacin, 500–750 mg PO qd for 10–14 days).
- Ciprofloxacin and ofloxacin are *not* recommended because of their high minimal inhibitory concentrations against *M. pneumoniae*.

LEGIONELLA SPECIES

Microbiology

Legionellaceae are intracellular aerobic gram-negative bacilli that grow on buffered charcoal yeast extract (BCYE) agar. *L. pneumophila* causes 80–90% of cases of human *Legionella* disease and includes 16 serogroups; serogroups 1, 4, and 6 are most common.

Epidemiology

- *Legionella* is found in fresh water and human-constructed water sources. Outbreaks have been traced to drinking water systems and rarely to cooling towers.

- The organisms are transmitted to individuals primarily via aspiration, but can also be transmitted by aerosolization and direct instillation into the lungs during respiratory tract manipulations.
- *Legionella* is the fourth most common cause of community-acquired pneumonia, accounting for 2–13% of cases. It causes 10–50% of cases of nosocomial pneumonia if the hospital's water system is colonized with the organism.
- Pts who have chronic lung disease, who smoke, and/or who are elderly, immunosuppressed, or recently discharged from the hospital are at particularly high risk for disease.

Clinical Manifestations

Legionellosis manifests as either an acute, febrile, self-limited illness (Pontiac fever) or pneumonia (Legionnaires' disease).

- Pontiac fever is a flulike illness with a 24- to 48-h incubation period. Malaise, fatigue, and myalgias occur in 97% of cases. Fever, chills, and headaches are also very common, but pneumonia does not develop. The disease is self-limited and does not require antimicrobial treatment. Recovery takes place in a few days.
- Legionnaires' disease is more severe than other atypical pneumonias and is more likely to result in ICU admission.
  - After a usual incubation period of 2–10 days, nonspecific symptoms (e.g., fever, malaise, fatigue, headache, anorexia) develop and are followed by a cough that is usually mild and only slightly productive. Chest pain and GI difficulties can be prominent.
  - Radiologic findings are nonspecific, but pleural effusions are present in 28–63% of pts on hospital admission.
  - Legionnaires' disease is not readily distinguishable from pneumonia of other etiologies based on clinical manifestations, but diarrhea, confusion, temperatures >39°C (102.2°F), hyponatremia, increased aminotransferase levels, hematuria, hypophosphatemia, and elevated creatine phosphokinase levels are documented more frequently than in other pneumonias.
  - Extrapulmonary infection results from hematogenous dissemination and most commonly affects the heart (e.g., myocarditis, pericarditis).

Diagnosis

The use of *Legionella* testing—especially the *Legionella* urinary antigen test—is recommended for all pts with community-acquired pneumonia.

- Sputum or bronchoscopy specimens can be subjected to direct fluorescent antibody (DFA) staining and culture.
  - DFA testing is rapid and specific but is less sensitive than culture.
  - Cultures on BCYE medium (with antibiotics to suppress competing flora) require 3–5 days to become positive.
- Serologic confirmation requires comparison of acute- and convalescent-phase samples. Detection of the necessary fourfold rise in titers often requires 12 weeks, but a single titer of 1:256 is presumptive evidence for Legionnaires' disease.
- Urinary antigen testing is rapid, inexpensive, easy to perform, second only to culture in terms of sensitivity, and highly specific. It is useful only for *L. pneumophila* serogroup 1, which causes 80% of disease cases.
  - Urinary antigen is detectable 3 days after disease onset and generally disappears over 2 months, although positivity can be prolonged if the pt is receiving glucocorticoid therapy.
  - The test is not affected by antibiotic administration.

TREATMENT *LEGIONELLA* INFECTIONS

- Newer macrolides (e.g., azithromycin at 500 mg/d PO, with doubling of the first dose considered; or clarithromycin at 500 mg bid IV or PO) or fluoroquinolones

(e.g., levofloxacin at 750 mg/d IV or 500 mg/d PO or moxifloxacin at 400 mg/d PO) are most effective.
  - Rifampin (300–600 mg bid) combined with either class of drug is recommended in severe cases.
  - Tetracyclines (doxycycline at 100 mg bid IV or PO) are alternatives.
- Immunocompetent hosts should receive 10–14 days of therapy, but immunocompromised hosts and pts with advanced disease should receive a 3-week course.
  - A 5- to 10-day course of azithromycin is adequate because of this drug's long half-life.
  - A clinical response usually occurs within 3–5 days after the initiation of parenteral therapy, at which point oral therapy can be substituted.

Prognosis

Mortality rates approach 80% among immunocompromised pts who do not receive timely therapy. Among immunocompetent hosts, mortality can approach 31% without treatment but ranges from 0 to 11% with appropriate and timely therapy. Fatigue, weakness, and neurologic symptoms can persist for >1 year.

CHLAMYDIA PNEUMONIAE

Epidemiology

C. pneumoniae is a common cause of human respiratory diseases, primarily in young adults.

- Seroprevalence rates of 40–70% demonstrate that *C. pneumoniae* is widespread worldwide. Seropositivity is first detected at school age and then increases by ~10% per decade.
- The role of *C. pneumoniae* in atherosclerotic disease has long been discussed, but large-scale treatment studies have cast doubts on the etiologic role of this organism in this disease.

Clinical Manifestations

The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonia.

- Pneumonia due to *C. pneumoniae* resembles that due to *M. pneumoniae*. Pts have antecedent upper respiratory tract symptoms, fever, nonproductive cough, minimal findings on auscultation, small segmental infiltrates on CXR, and no leukocytosis.
  - Primary infection is more severe than reinfection.
  - Elderly pts can have severe disease.

Diagnosis

Serology is the most clinically useful means for diagnosing *C. pneumoniae* infection.

- The diagnosis of acute *C. pneumoniae* infection requires demonstration of a fourfold rise in titer between acute- and convalescent-phase serum samples.
- Culture of the organism is difficult and is not routinely attempted. PCR assays for *C. pneumoniae* are currently available only for research purposes.

TREATMENT *C. PNEUMONIAE* INFECTIONS

- Erythromycin or tetracycline (2 g/d for 10–14 days) is recommended.
- Other macrolides (e.g., azithromycin) or quinolones (e.g., levofloxacin) are alternative agents.

For a more detailed discussion, see Yu VL, Pedro-Botet ML, Lin YE: *Legionella* Infections, Chap. 184, p. 1014; Hardy RD: Infections Due to Mycoplasmas, Chap. 212, p. 1163; Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165, in HPIM-19.

98 *Chlamydia trachomatis* and *C. psittaci*

MICROBIOLOGY

- Chlamydiae are obligate intracellular bacteria, possess both DNA and RNA (a characteristic that distinguishes them from viruses), and have a cell wall similar to that of gram-negative bacteria.
- These organisms have a complex reproductive cycle and exist in two forms.
  - The *elementary body* (the infective form) is adapted for extracellular survival, while the *reticulate body* is adapted for intracellular survival and multiplication.
  - Within 18–24 h after infection of the cell, reticulate bodies have replicated and begin to condense into elementary bodies that are released to infect other cells or people.
- Three chlamydial species infect humans: *Chlamydia trachomatis*, *C. psittaci*, and *C. pneumoniae*.
  - CF tests and enzyme immunoassays that detect lipopolysaccharide identify chlamydiae only to the genus level.
  - The microimmunofluorescence (MIF) test can differentiate among the three species.
  - For a discussion of *C. pneumoniae*, see Chap. 97.

C. TRACHOMATIS INFECTIONS

GENITAL INFECTIONS, INCLUDING LYMPHOGRANULOMA VENEREUM

See Chap. 83.

TRACHOMA AND ADULT INCLUSION CONJUNCTIVITIS (AIC)

Etiology

- Trachoma is a chronic conjunctivitis caused by *C. trachomatis* serovars A, B, Ba, and C. Transmission occurs through contact with ocular discharge from infected pts, which is sometimes transferred by flies.
- AIC is an acute eye infection occurring in adults exposed to infected genital secretions and in their newborns. This infection is caused by sexually transmitted *C. trachomatis* strains, usually serovars D–K.

Epidemiology

Trachoma is a leading cause of preventable infectious blindness, with ~6 million pts having been affected. In the hyperendemic regions of northern and sub-Saharan Africa, the Middle East, and parts of Asia, the prevalence of trachoma is ~100% by the third year of life. Reinfection and persistent infection are common.

Clinical Manifestations

Both trachoma and AIC present clinically as conjunctivitis characterized by small lymphoid follicles in the conjunctiva, although trachoma usually starts insidiously before 2 years of age.

- With progression of trachoma, there is inflammatory leukocytic infiltration and superficial vascularization (pannus formation) of the cornea.
  - Scarring eventually distorts the eyelids, turning lashes inward and abrading the eyeball (trichiasis and entropion).
  - The corneal epithelium eventually ulcerates, with subsequent scarring and blindness.
  - Destruction of goblet cells, lacrimal ducts, and glands causes dry-eye syndrome (xerosis), with resultant corneal opacity and secondary bacterial corneal ulcers.
- AIC is an acute unilateral follicular conjunctivitis with preauricular lymphadenopathy and presents similarly to acute conjunctivitis due to adenovirus or HSV.
  - Corneal inflammation is evidenced by discrete opacities, punctate epithelial erosions, and superficial corneal vascularization.
  - Left untreated, the disease may persist for 6 weeks to 2 years.

Diagnosis

Clinical diagnosis of trachoma is based on the presence of two of the following signs: lymphoid follicles on the upper tarsal conjunctiva, typical conjunctival scarring, vascular pannus, or limbal follicles.

- Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears from children with severe inflammation.
- However, chlamydial nucleic acid amplification tests are more sensitive in detecting infection.

TREATMENT **TRACHOMA/AIC**

- AIC responds to azithromycin (a single 1-g oral dose) or doxycycline (100 mg PO bid for 7 days). Treatment of sexual partners is needed to prevent ocular reinfection and chlamydial genital disease.

C. PSITTACI INFECTIONS

Etiology and Epidemiology

Most avian species can harbor *C. psittaci*, but psittacine birds (e.g., parrots, parakeets) are most often infected. Human infections are uncommon and occur only as a zoonosis.

- Exposure is greatest in poultry workers and in owners of pet birds.
- Present in nasal secretions, excreta, tissues, and feathers of infected birds, *C. psittaci* is transmitted to humans by direct contact with infected birds or by inhalation of aerosols. Transmission from person to person has never been documented.

- As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare, with fewer than 50 confirmed cases reported in the United States each year.

Clinical Manifestations

Psittacosis in humans can range in severity from asymptomatic or mild infections to acute primary atypical pneumonia (which can be fatal in 10% of untreated cases) to severe chronic pneumonia.

- After an incubation period of >5–19 days, pts present with fever, chills, muscular aches and pains, severe headaches, hepatomegaly and/or splenomegaly, and GI symptoms.
- Cardiac complications may include endocarditis and myocarditis.

Diagnosis

This diagnosis is confirmed by serologic studies.

- The gold standard is the MIF test.
- Any antibody titer >1:16 or a fourfold rise between paired acute- and convalescent-phase serum samples, in combination with a clinically compatible syndrome, can be used to diagnose psittacosis.

TREATMENT ***C. PSITTACI* INFECTIONS**

- Tetracycline (250 mg PO qid for 3 weeks) is the antibiotic of choice.
- Erythromycin (500 mg PO qid) is an alternative agent.

For a more detailed discussion, see Gaydos CA, Quinn TC: Chlamydial Infections, Chap. 213, p. 1165, in HPIM-19.

99 Herpesvirus Infections

HERPES SIMPLEX VIRUSES

MICROBIOLOGY AND PATHOGENESIS

The herpes simplex viruses HSV-1 and HSV-2 are linear, double-stranded DNA viruses that share ~50% sequence homology. Exposure to HSV at mucosal surfaces or abraded skin sites permits viral entry and replication in cells of the epidermis and dermis prior to infection of neuronal cells and development of a latent infection in ganglia.

- Reactivation occurs when normal viral gene expression resumes, with reappearance of the virus on mucosal surfaces.

- Both antibody-mediated and cell-mediated immunity (including type-specific immunity) are clinically important.

EPIDEMIOLOGY

HSV-1 is acquired more frequently and at an earlier age than HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. Antibodies to HSV-2 usually are not detected until adolescence and correlate with sexual activity. The seroprevalence of HSV-2 is higher in the developing than in the developed world; up to 60% of pregnant women in sub-Saharan Africa are seropositive.

- HSV is transmitted by contact with active lesions or with virus shed from mucocutaneous surfaces by asymptomatic persons.
- HSV reactivation is very common: HSV DNA can be detected on 20–30% of days by PCR, with most genital reactivation episodes lasting <6 h.
- The large reservoir of unidentified carriers and the frequent asymptomatic reactivation of HSV-2 have fostered the continued spread of HSV throughout the world.
- HSV-2 infection is associated with a two- to fourfold increase in HIV-1 acquisition; in fact, 33–50% of HIV-1 infections may be attributable to HSV-2 in men who have sex with men and in populations of sub-Saharan Africa.

CLINICAL MANIFESTATIONS

Both viral subtypes can cause indistinguishable genital and oral–facial infections. Overall, genital HSV-2 is twice as likely to reactivate as genital HSV-1, and HSV-2 infection recurs 8–10 times more often. In contrast, oral–labial HSV-1 infection recurs more frequently than oral–labial HSV-2 infection. The incubation period for primary infection with either virus is 1–26 days (median, 6–8 days).

Oral–Facial Infections

Primary HSV-1 infection results in gingivostomatitis, pharyngitis, and up to 2 weeks of fever, malaise, myalgia, inability to eat, and cervical adenopathy, with lesions on the palate, gingiva, tongue, lip, face, posterior pharynx, and/or tonsillar pillars and occasional exudative pharyngitis.

- Reactivation of HSV from the trigeminal ganglia is associated with asymptomatic viral excretion in the saliva, intraoral mucosal ulcerations, or ulcers on the vermilion border of the lip or external facial skin.
  - Approximately 50–70% of pts undergoing trigeminal nerve-root decompression and 10–15% of pts undergoing dental extraction develop oral–labial herpes a median of 3 days after the procedure.
  - Reactivation of HSV-1 or VZV in the mandibular portion of the facial nerve causes flaccid paralysis (Bell's palsy).
- Immunosuppressed pts can have a severe infection that extends into the mucosa and skin, causing friability, necrosis, bleeding, pain, and inability to eat or drink.
- Pts with atopic dermatitis may also develop severe oral–facial HSV infection (eczema herpeticum), with extensive skin lesions and occasional visceral dissemination.
- HSV infection is the precipitating event in ~75% of cases of erythema multiforme.

Genital Infections (See Chap. 83)

First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms.

- Pts with prior HSV-1 infection have milder cases.
- Reactivation infections are often subclinical or can cause genital lesions or urethritis with dysuria.

- Even without a history of rectal intercourse, perianal lesions can occur as a result of latency established in the sacral dermatome from prior genital tract infection.

Whitlow

In HSV infection of the finger, pts experience an abrupt onset of edema, erythema, pain, and vesicular or pustular lesions of the fingertips that are often confused with the lesions of pyogenic bacterial infection. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common.

Herpes Gladiatorum

HSV infection caused by trauma to the skin during wrestling can occur anywhere on the body but commonly affects the thorax, ears, face, and hands.

Eye Infections

HSV is the most frequent cause of corneal blindness in the United States.

- HSV keratitis presents as acute onset of pain, blurred vision, chemosis, conjunctivitis, and dendritic corneal lesions. Topical glucocorticoids may exacerbate disease. Recurrences are common.
- Other manifestations include chorioretinitis and acute necrotizing retinitis.

Central and Peripheral Nervous System Infections

In the United States, HSV causes 10–20% of all cases of sporadic viral encephalitis, and 95% of these cases are due to HSV-1 (either primary or reactivated infection). The estimated annual incidence is 2.3 cases per 1 million persons.

- Pts present with an acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe. In severe cases, RBCs can be found in the CSF as a result of hemorrhagic necrosis.
- Given the potential severity of infection, antiviral treatment should be started empirically until the diagnosis is confirmed or an alternative diagnosis is made.
- HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days.
  - Of cases of aseptic meningitis, 3–15% are due to HSV.
  - HSV is the most common cause of recurrent lymphocytic meningitis (Mollaret's meningitis).
- Autonomic dysfunction caused by either HSV or VZV most commonly affects the sacral region, resulting in numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, and impotence.
  - Symptoms take days or weeks to resolve.
  - In rare instances, transverse myelitis or Guillain-Barré syndrome follows HSV infection.

Visceral Infections

HSV infection of visceral organs usually results from viremia; multiple-organ involvement is common, but occasionally only the esophagus, lung, or liver is affected.

- In HSV esophagitis, pts present with odynophagia, dysphagia, substernal pain, weight loss, and multiple oval ulcerations on an erythematous base. Detection of HSV is necessary to distinguish this entity from esophagitis of other etiologies (e.g., *Candida* esophagitis).
- HSV pneumonitis is rare except among severely immunocompromised pts and results in focal necrotizing pneumonitis with a mortality rate of >80%.
- Hepatic HSV infection occurs primarily in immunocompromised pts and is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 WBCs/μL).

Neonatal Infections

The frequency of visceral and/or CNS infection is highest among HSV-infected infants <6 weeks of age; the mortality rate without therapy is 65%.

- Infection is usually acquired perinatally from contact with infected genital secretions during delivery.
- Approximately 50–70% of cases are due to HSV-2. The risk is elevated 10-fold for infants born to a mother who has recently acquired HSV.

DIAGNOSIS

Microscopic evaluation, viral culture, serology, and PCR are all clinically useful for diagnosing HSV infection.

- Regardless of the detection method, the sensitivity is greater for vesicular rather than ulcerative mucosal lesions, in primary rather than recurrent disease, and in immunocompromised rather than immunocompetent pts.
- PCR is most sensitive for detection of HSV and should be used whenever possible.
- A Tzanck smear (Giemsa-stained scrapings from the base of lesions) to detect giant cells or intranuclear inclusions characteristic of both HSV and VZV infections has a low level of sensitivity; its use requires clinicians skilled in this technique.
- Serologic tests can be used to demonstrate prior exposure to HSV; no reliable IgM detection method for defining acute HSV infection is available.

TREATMENT INFECTIONS WITH HERPES SIMPLEX VIRUSES

- Table 99-1 details antiviral chemotherapy for HSV infection.
  - All antiviral agents licensed for use against HSV inhibit the viral DNA polymerase.
  - Acyclovir can crystallize in the renal parenchyma, causing transient renal insufficiency; this drug should be given over the course of 1 h to a well-hydrated pt.
  - Acyclovir-resistant strains of HSV are rare but have been identified, primarily in immunocompromised pts. In general, these isolates are also resistant to valacyclovir and famciclovir, which have similar mechanisms of action.

PREVENTION

The use of barrier forms of contraception, especially condoms, decreases the likelihood of HSV transmission, particularly during asymptomatic viral excretion. Chronic daily therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, particularly by susceptible women.

VARICELLA-ZOSTER VIRUS

MICROBIOLOGY AND PATHOGENESIS

VZV—a double-stranded DNA virus in the family Herpesviridae—has a pathogenic cycle similar to that of HSV. Primary infection is transmitted by the respiratory route. The virus replicates and causes viremia, which is reflected by the diffuse and scattered skin lesions in varicella; it then establishes latency in the dorsal root ganglia and can reactivate through unknown mechanisms at a later time.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

VZV causes two distinct entities: primary infection (varicella or chickenpox) and reactivation infection (herpes zoster or shingles). Humans are the only known reservoir for VZV.

TABLE 99-1 ANTIVIRAL CHEMOTHERAPY FOR HERPES SIMPLEX VIRUS (HSV) INFECTION

I. Mucocutaneous HSV infections

A. *Infections in immunosuppressed pts*

1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days.
2. *Suppression of reactivation disease (genital or oral-labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg three to five times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

B. *Infections in immunocompetent pts*

1. *Genital herpes*
   a. *First episodes:* Oral acyclovir (200 mg five times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
   b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-days) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 3 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg five times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
   c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Pts with more than nine episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).

2. *Oral–labial HSV infections*
   a. *First episode:* Oral acyclovir is given (200 mg five times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m^2 qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days.
   b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with six times daily topical penciclovir cream effectively speeds healing of oral–labial HSV. Topical acyclovir cream has also been shown to speed healing.
   c. *Suppression of reactivation of oral–labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 *mg* bid) prevents reactivation of recurrent oral–labial HSV infection associated with severe sun exposure.
3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.
4. *Herpetic whitlow:* Oral acyclovir (200 mg) is given five times daily (alternative: 400 mg tid) for 7–10 days.
5. *HSV proctitis:* Oral acyclovir (400 mg five times per day) is useful in shortening the course of infection. In immunosuppressed pts or in pts with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.
6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

II. Central nervous system HSV infections

A. *HSV encephalitis:* IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid.

B. *HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.

C. *Autonomic radiculopathy:* No studies are available. Most authorities recommend a trial of IV acyclovir.

(*Continued*)

TABLE 99-1 ANTIVIRAL CHEMOTHERAPY FOR HERPES SIMPLEX VIRUS (HSV) INFECTION (*CONTINUED*)

III. Neonatal HSV infections: Oral acyclovir (60 mg/kg per day, divided into three doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months.

IV. Visceral HSV infections

A. *HSV esophagitis:* IV acyclovir (15 mg/kg per day) is given. In some pts with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

B. *HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

VII. Infections due to acyclovir-resistant HSV: IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some pts may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

Chickenpox

Pts present with fever, malaise, and rash characterized by maculopapules, vesicles, and scabs in various stages of evolution. The skin lesions are small, with an erythematous base of 5–10 mm, and appear in successive crops over 2–4 days. Severity varies from person to person, but older pts tend to have more severe disease.

- In immunocompetent hosts, the disease is benign and lasts 3–5 days. In contrast, immunocompromised pts have numerous slower-healing lesions (often with a hemorrhagic base) and are more likely to develop visceral complications that, if not treated, are fatal in 15% of cases.
- The incubation period ranges from 10 to 21 days but is usually 14–17 days. Pts are infectious for 48 h before onset of rash and remain infectious until all vesicles have crusted.
- The virus is highly contagious, with an attack rate of 90% among susceptible persons. Historically, children 5–9 years old accounted for half of all cases; vaccination has dramatically changed the epidemiology of infection and has caused a significant decrease in the annualized incidence of chickenpox.
- Complications of varicella include bacterial superinfection of the skin, CNS involvement, pneumonia, myocarditis, and hepatic involvement.
  - Bacterial superinfection is usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus*.
  - CNS involvement, usually manifesting as acute cerebellar ataxia and meningeal irritation ~21 days after the onset of rash, runs a benign course. Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, or Reye's syndrome (which mandates the avoidance of aspirin administration to children) can occur. There is no specific therapy other than supportive care.
  - VZV pneumonia is the most serious complication and develops more frequently among adults (occurring in up to 20% of cases) than among children. The onset comes 3–5 days into illness, with tachypnea, cough, dyspnea, fever, cyanosis, pleuritic chest pain, and hemoptysis. CXR shows nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash.

Herpes Zoster (Shingles)

Herpes zoster represents a reactivation of VZV from dorsal root ganglia and usually manifests as a unilateral vesicular eruption within a dermatome, often associated with severe pain.

- Dermatomal pain may precede lesions by 48–72 h, and dermatomes T3 to L3 are most frequently involved.
- The usual duration of disease is 7–10 days, but it may take as long as 2–4 weeks for the skin to return to normal.
- With ~1.2 million cases each year in the United States, the incidence is highest among pts ≥50 years of age.
- Pts with herpes zoster can transmit infection to seronegative individuals, with consequent chickenpox.
- Complications include zoster ophthalmicus (which can lead to blindness), Ramsay Hunt syndrome (characterized by pain and vesicles in the external auditory canal, loss of taste in the anterior two-thirds of the tongue, and ipsilateral facial palsy), and postherpetic neuralgia (pain persisting for months after resolution of cutaneous disease).
- Immunocompromised pts—particularly those with Hodgkin's disease and non-Hodgkin's lymphoma—are at greatest risk for severe zoster and progressive disease. Cutaneous dissemination occurs in 40% of these pts and increases the risk for other complications (pneumonitis, meningoencephalitis, hepatitis).

DIAGNOSIS

Definitive diagnosis requires isolation of VZV in culture, detection of VZV by molecular means (PCR, immunofluorescent staining of cells from the lesion base), or serology (seroconversion or a ≥4-fold rise in antibody titer between convalescent- and acute-phase serum specimens).

TREATMENT VARICELLA-ZOSTER VIRUS INFECTIONS

- *Chickenpox:* Antiviral therapy can be helpful if started within 24 h of symptom onset.
  - For children <12 years of age, acyclovir (20 mg/kg PO q6h) is recommended.
  - For adolescents and adults, acyclovir (800 mg PO five times daily), valacyclovir (1 g PO tid), or famciclovir (250 mg PO tid) for 5–7 days is recommended.
  - Good hygiene, meticulous skin care, and antipruritic drugs are important to relieve symptoms and prevent bacterial superinfection of skin lesions.
- *Zoster:* Lesions heal more quickly with antiviral treatment.
  - Famciclovir (500 mg PO tid for 7 days) or valacyclovir (1 g PO tid for 5–7 days) is preferred over acyclovir (800 mg PO five times daily for 7–10 days), given superior pharmacokinetics and pharmacodynamics.
- *VZV infection in severely immunocompromised pts:* Severely immunocompromised pts should receive parenteral acyclovir, at least at the outset (10 mg/kg IV q8h for 7 days), for chickenpox and herpes zoster to reduce the risk of visceral complications, although this regimen does not speed the healing or relieve the pain of skin lesions.
  - Low-risk immunocompromised pts can be treated with oral valacyclovir or famciclovir.
  - If feasible, immunosuppression should be decreased during concomitant acyclovir administration.
- *Zoster ophthalmicus:* Antiviral treatment, analgesics for severe pain, and immediate consultation with an ophthalmologist are required.
- *Postherpetic neuralgia:* Gabapentin, pregabalin, amitriptyline, lidocaine patches, and fluphenazine may relieve pain and can be given along with routine analgesic agents. Prednisone (given along with antiviral therapy at 60 mg/d for the first week of zoster and then at a dose tapered by 50% weekly over the next 2 weeks) can accelerate quality-of-life improvements, including a return to usual activity; prednisone treatment is indicated only for healthy elderly persons with moderate or severe pain at presentation.

PREVENTION

Three methods are used for the prevention of VZV infections.

- *Active immunization:* For all children and seronegative adults, two doses of a live attenuated varicella vaccine are recommended. Irrespective of serologic status, pts >50 years old should receive a vaccine with 18 times the viral content of varicella vaccine; zoster vaccine reduces the incidence of zoster and postherpetic neuralgia.
- *Passive immunization:* Varicella-zoster immune globulin (VZIg) can be given to VZV-susceptible hosts within 10 days (ideally within 96 h) of a significant exposure if the risk of complications from varicella is high (e.g., immunocompromised pts, susceptible pregnant women, premature infants, neonates whose mothers had chickenpox onset within 5 days before or 2 days after delivery).
- *Antiviral treatment:* Seven days after intense exposure, antiviral prophylaxis can be given to high-risk pts who are ineligible for vaccine or for whom the 96-h window after direct contact has passed. This intervention may lessen illness severity.

HUMAN HERPESVIRUS (HHV) TYPES 6, 7, AND 8

- HHV-6 causes exanthem subitum (roseola infantum, a common childhood febrile illness with rash) and 10–20% of febrile seizures without rash in infancy.
  - In older age groups, HHV-6 has been associated with mononucleosis syndromes and (in immunocompromised hosts) encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease.
  - More than 80% of adults are seropositive for HHV-6.
- HHV-7 is frequently acquired during childhood, and infections typically manifest as fever and seizures. The virus is commonly present in saliva.
- HHV-8 infection in healthy children can present as fever and rash; in immunocompromised pts, primary infection may present as fever, splenomegaly, pancytopenia, and rapid-onset Kaposi's sarcoma.
  - HHV-8 is associated with Kaposi's sarcoma, body cavity–based lymphoma in AIDS pts, and multicentric Castleman's disease.
  - Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe).
  - The virus appears to be sexually spread and may also be transmitted in saliva, by organ transplantation, and through IV drug use.



For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Corey L: Herpes Simplex Virus Infections, Chap. 216, p. 1175; Whitley RJ: Varicella-Zoster Virus Infections, Chap. 217, p. 1183; Kotton CN, Hirsch MS: Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8, Chap. 219, p. 1190, in HPIM-19.

100 Cytomegalovirus and Epstein-Barr Virus Infections

CYTOMEGALOVIRUS

MICROBIOLOGY

CMV is a herpesvirus, has double-stranded DNA, and renders infected cells 2–4 times the size of surrounding cells. These cytomegalic cells contain an eccentrically placed intranuclear inclusion surrounded by a clear halo, with an "owl's-eye" appearance.

EPIDEMIOLOGY

CMV disease is found worldwide. In many regions, the vast majority of adults are seropositive, as are ~50% of adults in the United States and Canada. Perinatal and early childhood infections are common; ~1% of U.S. newborns are infected.

- The virus can be spread in breast milk, saliva, feces, and urine.
- Transmission requires repeated or prolonged contact as opposed to casual contact. Sexual transmission is common among adolescents and adults, and CMV has been identified in semen and cervical secretions.
- Latent CMV infection persists throughout life unless reactivation is triggered by depressed cell-mediated immunity (e.g., in transplant recipients or HIV-infected pts).

PATHOGENESIS

Primary CMV infection is associated with a vigorous T lymphocyte response; activated CD8+ T cells predominate among atypical lymphocytes.

- Latent infection occurs in multiple cell types and various organs. Chronic antigen stimulation in the presence of immunosuppression (e.g., in the transplantation setting) and certain immunosuppressive agents (e.g., antithymocyte globulin) promote CMV reactivation.
- CMV disease increases the risk of infection with opportunistic pathogens by depressing T lymphocyte responsiveness.

CLINICAL MANIFESTATIONS

The most common presentation is CMV mononucleosis in immunocompetent pts, but disease can be more severe in immunocompromised pts (including newborns).

Congenital CMV Infection

Cytomegalic inclusion disease occurs in ~5% of infected fetuses in the setting of primary maternal CMV infection in pregnancy.

- Petechiae, hepatosplenomegaly, and jaundice are present in 60–80% of cases; microcephaly with or without cerebral calcifications, intrauterine growth retardation, prematurity, and chorioretinitis are less common.
- Laboratory findings include elevated values in LFTs, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and increased CSF protein levels.
- The mortality rate is 20–30% among infants with severe disease; survivors have intellectual or hearing difficulties.

Perinatal CMV Infection

Perinatal infection with CMV is acquired by breast-feeding or contact with infected maternal secretions (e.g., in the birth canal). Although most pts are asymptomatic, disease similar to—but less severe than—congenital CMV disease can occur.

CMV Mononucleosis

Signs and symptoms last 2–6 weeks and include high fevers, profound fatigue and malaise, myalgias, headache, and splenomegaly. In contrast to EBV infection, exudative pharyngitis and cervical lymphadenopathy are rare in CMV infection.

- Laboratory findings include relative lymphocytosis with >10% atypical lymphocytes, transaminitis, and immunologic abnormalities (e.g., the presence of cryoglobulins, rheumatoid factor, or cold agglutinins).
- The incubation period ranges from 20 to 60 days.
- Recovery is generally complete, but postviral asthenia can persist for months.

CMV Infection in Immunocompromised Pts

CMV is the most common viral pathogen complicating organ transplantation, with the greatest risk of infection 1–4 months after transplantation. HIV-infected pts with CD4+ T cell counts of <50–100/μL also are at risk for severe CMV disease.

- Primary CMV infection (including reinfection with a new, donor-derived strain) is more likely than reactivation to cause severe disease with high viral loads.
  - Reactivation infection is common but less important clinically.
  - The transplanted organ is at particular risk; e.g., CMV pneumonitis tends to follow lung transplantation.
  - The risk of severe disease is reduced by antiviral prophylaxis or preemptive therapy.
- Pts present initially with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias but can ultimately have multiorgan involvement.
  - Respiratory involvement is evidenced by tachypnea, hypoxia, unproductive cough, and chest radiographs demonstrating bilateral interstitial or reticulonodular infiltrates.
  - GI involvement often includes hepatitis and ulcer formation. Colitis is the most common manifestation in organ transplant recipients.
  - CMV encephalitis, particularly in HIV-infected pts, can occur as either progressive dementia or ventriculoencephalitis characterized by cranial nerve deficits, disorientation, and lethargy.
  - CMV retinitis is an important cause of blindness in pts with advanced AIDS.

DIAGNOSIS

Diagnosis requires isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens in conjunction with a compatible clinical syndrome. Immunofluorescence assays for CMV antigens (pp65), PCR, viral culture, and serology are all useful means of detection.

TREATMENT CYTOMEGALOVIRUS INFECTIONS

- When possible, seronegative donors should be used for seronegative transplant recipients.
- Ganciclovir (5 mg/kg IV bid for 14–21 days followed by 5 mg/kg IV qd) or valganciclovir (the oral prodrug of ganciclovir; 900 mg PO bid for 14–21 days followed by 900 mg PO qd) produces response rates of 70–90% among HIV-infected pts with CMV retinitis or colitis.
  - In severe infections, ganciclovir is often combined with CMV immune globulin.
  - Neutropenia is an adverse reaction to ganciclovir treatment that may require administration of colony-stimulating factors.
  - Prophylactic or suppressive treatment can be given to high-risk transplant recipients (those who are seropositive before transplantation or culture positive without symptoms afterward).
  - Resistance to ganciclovir is common among pts treated for >3 months and is usually related to mutations in the CMV *UL97* gene.
  - For CMV retinitis, ganciclovir can be administered via a slow-release pellet sutured into the eye, but this intervention does not provide treatment for the contralateral eye or for systemic disease.
- Foscarnet (180 mg/kg qd divided into 2 or 3 doses for 2 weeks, followed by 90–120 mg/kg IV qd) inhibits CMV DNA polymerase and is active against most ganciclovir-resistant CMV isolates. The primary adverse events include electrolyte disturbances and renal dysfunction.
- Cidofovir (5 mg/kg IV per week for 2 weeks followed by 3–5 mg/kg IV every 2 weeks) is a nucleotide analogue that is also effective against ganciclovir-resistant CMV; however, it can cause severe nephrotoxicity by proximal tubular cell injury. The use of saline hydration and probenecid reduces this adverse effect.
- CMV immune or hyperimmune globulin may reduce the risk of CMV disease in seronegative renal transplant recipients and prevent congenital CMV infection in infants born to women with primary CMV infection during pregnancy.

EPSTEIN-BARR VIRUS

EPIDEMIOLOGY

EBV is a DNA virus in the family Herpesviridae that infects >90% of persons by adulthood.

- Infectious mononucleosis (IM) is a disease of young adults and is more common in areas with higher standards of hygiene; infection occurs at a younger age in areas with deficient standards of hygiene.
- EBV is spread by contact with oral secretions (e.g., by transfer of saliva during kissing) and is shed in oropharyngeal secretions by >90% of asymptomatic seropositive individuals.

PATHOGENESIS

EBV infects the epithelium of the oropharynx and salivary glands as well as B cells in tonsillar crypts prior to a period of viremia.

- B cells undergo polyclonal activation, and memory B cells form the reservoir for EBV. Reactive T cells proliferate, with up to 40% of CD8+ T cells directed against EBV antigens during acute infection.
- Cellular immunity is more important than humoral immunity in controlling infection. If T cell immunity is compromised, EBV-infected B cells may proliferate—a step toward neoplastic transformation.

CLINICAL MANIFESTATIONS

The nature of EBV disease depends on the pt's age and immune status: young children typically develop asymptomatic infections or mild pharyngitis, adolescents and adults develop an IM syndrome, and immunocompromised pts can develop lymphoproliferative disease.

- In IM, a prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, exudative pharyngitis, and lymphadenopathy with tender, symmetric, and movable nodes; splenomegaly is more prominent in the second or third week.
  - The incubation period is ~4–6 weeks.
  - Most pts treated with ampicillin develop a rash that does not represent a true penicillin allergy.
  - Illness lasts for 2–4 weeks, but ~10% of pts have fatigue that persists for ≥6 months. EBV is not, however, a cause of chronic fatigue syndrome.
  - Lymphocytosis occurs in the second or third week, with >10% atypical lymphocytes (enlarged cells with abundant cytoplasm and vacuoles); abnormal liver function is common.
  - Complications include CNS disease (e.g., meningitis, encephalitis), Coombs-positive autoimmune hemolytic anemia, splenic rupture, and upper airway obstruction due to hypertrophy of lymphoid tissue.
- Lymphoproliferative disease—i.e., infiltration of lymph nodes and multiple organs by proliferating EBV-infected B cells—occurs in pts with deficient cellular immunity (e.g., pts with AIDS, those with severe combined immunodeficiency, and those receiving immunosuppressive medications). Pts develop fever and lymphadenopathy or GI symptoms.
- Oral hairy leukoplakia—raised, white, corrugated, EBV DNA–containing lesions on the tongue—is an early manifestation of infection with HIV in adults.
- EBV-associated malignancies include Burkitt's lymphoma (~90% of cases in Africa and ~15% of cases in the United States), anaplastic nasopharyngeal carcinoma in southern China, gastric cancer (with ~9% of these tumors positive for EBV),

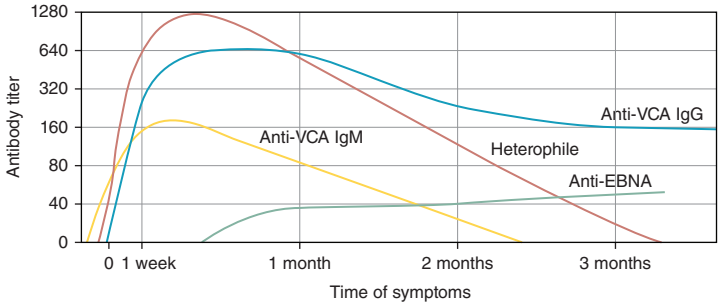


FIGURE 100-1 Pattern of Epstein-Barr virus (EBV) serology during acute infection. EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen. *(From JI Cohen, in NS Young et al [eds]: Clinical Hematology. Philadelphia, Mosby, 2006.)*

Hodgkin's disease (especially the mixed-cellularity type), and CNS lymphoma (especially HIV-related).

DIAGNOSIS

Serologic testing is the mainstay of diagnostic assessment. PCR analysis can be useful in monitoring EBV DNA levels in blood from pts with lymphoproliferative disease.

- Heterophile antibodies (Figure 100-1) form the basis of most rapid testing, which assesses the ability of serum to agglutinate sheep, horse, or cow erythrocytes after adsorption with guinea pig kidney.
  - The antibodies can persist for up to 1 year after infection.
  - The monospot test for heterophile antibodies is ~75% sensitive and ~90% specific in comparison with EBV-specific serologies.
  - Pts <5 years old and elderly pts usually do not develop heterophile antibodies.
- EBV-specific antibody testing can be used in heterophile-negative pts and in pts with atypical disease. Antibodies to viral capsid antigen occur in >90% of cases, with elevated IgM titers present only during the first 2–3 months of disease.
- Antibodies to Epstein-Barr nuclear antigen are not detected until 3–6 weeks after symptom onset and then persist for life.

TREATMENT EPSTEIN-BARR VIRUS INFECTIONS

- IM is treated with supportive measures, including rest and analgesia.
  - Excessive physical activity should be avoided in the first month of illness to reduce the possibility of splenic rupture, which necessitates splenectomy.
  - Administration of glucocorticoids may be indicated for some complications of IM; e.g., these agents may be given to prevent airway obstruction or to treat autoimmune hemolytic anemia, hemophagocytic lymphohistiocytosis, or severe thrombocytopenia.
  - Antiviral therapy (e.g., with acyclovir) is generally not effective for IM but is effective for oral hairy leukoplakia.
- Treatment of posttransplantation EBV lymphoproliferative syndrome is generally directed toward reduction of immunosuppression, although other treatments—e.g., with interferon α, antibody to CD20 (rituximab), and donor lymphocyte infusions—have been used with varying success.

For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Cohen JI: Epstein-Barr Virus Infections, Including Infectious Mononucleosis, Chap. 218, p. 1186; and Kotton CN, Hirsch MS: Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8, Chap. 219, p. 1190, in HPIM-19.

101 Influenza and Other Viral Respiratory Diseases

INFLUENZA

Microbiology and Pathogenesis

Influenza A, B, and C viruses are RNA viruses and members of the family Orthomyxoviridae that have different nucleoprotein (NP) and matrix (M) protein antigens. Influenza A and B viruses are major human pathogens and are morphologically similar; influenza B infection is associated with less severe disease than influenza A infection, and influenza C virus causes subclinical disease.

- Influenza A viruses are subtyped by surface hemagglutinin (H) and neuraminidase (N) antigens.
  - Virus attaches to sialic acid cell receptors via the hemagglutinin. Neuraminidase degrades the receptor and plays a role in the release of virus from infected cells after replication.
  - Antibodies to the H antigen are the major determinants of immunity, while antibodies to the N antigen limit viral spread and contribute to reduction of the infection.
- Influenza is acquired from aerosolized respiratory secretions of acutely ill individuals and possibly by hand-to-hand contact or other personal or fomite contact. Viral shedding usually stops 2–5 days after disease onset.

Epidemiology

Influenza outbreaks occur each year but vary in extent and severity. Influenza A epidemics occur almost exclusively during the winter months in temperate climates but take place year-round in the tropics. These epidemics begin abruptly, peak over 2–3 weeks, last 2–3 months, and then subside rapidly.

- Global pandemics (the most recent of which took place in 2009 and was due to an A/H1N1 virus) occur, by definition, at multiple locations; they carry high attack rates (10–20% of the general population), extend beyond normal seasonality patterns, and are due in part to the propensity of the H and N antigens to undergo periodic antigenic variation.
  - Major changes (which are restricted to influenza A viruses) are called *antigenic shifts* and are associated with pandemics.
  - Minor variations are called *antigenic drifts*.

- Avian influenza viruses (e.g., A/H5N1) cause sporadic human cases, but sustained human-to-human transmission has not been observed; infection is linked to direct contact with infected poultry.
- Swine can sustain simultaneous infection with swine, human, and avian influenza viruses; these multiple-virus infections facilitate reassortment of genetic segments of different viruses. For example, the pandemic A/H1N1 virus of 2009–2010 represented a quadruple reassortment among swine, avian, and human influenza viruses.
- Interpandemic outbreaks of influenza are associated with an average of 226,000 hospitalizations and 23,000 excess deaths per year in the United States. Chronic cardiopulmonary disease and old age are the most prominent risk factors for severe illness.

Clinical Manifestations

Influenza has a wide spectrum of clinical presentations, ranging from a mild illness resembling the common cold to severe prostration with relatively few respiratory symptoms. The classic description involves the abrupt onset of headache, fever, chills, myalgia, and malaise in the setting of respiratory symptoms (e.g., cough, sore throat).

- Pts typically defervesce within 2–3 days, but respiratory symptoms accompanied by substernal pain can persist for ≥1 week. Postinfluenzal asthenia may persist for weeks, particularly in the elderly.
- Complications of influenza (pneumonia and extrapulmonary manifestations) are more common among pts <5 and >65 years old, pregnant women, and pts with chronic disorders (e.g., cardiopulmonary disease, diabetes, renal diseases, hemoglobinopathies, or immunosuppression).
  - *Pneumonia:* Primary influenza pneumonia is the least common but most severe of the pneumonic complications, most often affecting pts with mitral stenosis and pregnant women. Pts have progressive pulmonary disease and high titers of virus in respiratory secretions.
    - *Secondary bacterial pneumonia* is usually due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus influenzae* and presents as the reappearance of fever and respiratory symptoms after 2–3 days of clinical improvement.
    - The most common pneumonic complication involves aspects of viral and bacterial pneumonia.
  - *Extrapulmonary complications:* Reye's syndrome, myositis, rhabdomyolysis, myoglobinuria, and CNS disease (e.g., encephalitis, transverse myelitis, Guillain-Barré syndrome) can occur as complications of influenza infection.
    - Reye's syndrome is a serious complication in children that is associated with influenza B virus (and less commonly with influenza A virus), varicella-zoster virus, and aspirin therapy for the antecedent viral infection.

Laboratory Findings

Reverse-transcription PCR of respiratory samples (e.g., throat swabs, nasopharyngeal washes, sputum) is the most sensitive and specific technique for detecting influenza.

- Rapid tests that detect viral antigens yield results quickly, can sometimes distinguish influenza A and B viruses, and are relatively specific but variably sensitive.
- Serologic testing requires the availability of acute- and convalescent-phase sera and is useful only retrospectively.

TREATMENT INFLUENZA

- See Table 101-1 for specific treatment of influenza.
  - Antiviral agents have been tested in young adults with uncomplicated influenza but not in the treatment or prevention of complications associated with influenza.
  - If started within 2 days of illness due to a susceptible virus (with possible efficacy up to 5 days after onset of symptoms), the neuraminidase inhibitors

TABLE 101-1 ANTIVIRAL MEDICATIONS FOR TREATMENT AND PROPHYLAXIS OF INFLUENZA

	Age Group (Years)		
Antiviral Drug	**Children (≤12)**	**13–64**	**≥65**
Oseltamivir			
Treatment, influenza A and B	Age 1–12, dose varies by weight[a]	75 mg PO bid	75 mg PO bid
Prophylaxis, influenza A and B	Age 1–12, dose varies by weight[b]	75 mg PO qd	75 mg PO qd
Zanamivir			
Treatment, influenza A and B	Age 7–12, 10 mg bid by inhalation	10 mg bid by inhalation	10 mg bid by inhalation
Prophylaxis, influenza A and B	Age 5–12, 10 mg qd by inhalation	10 mg qd by inhalation	10 mg qd by inhalation
Amantadine[c]			
Treatment, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Rimantadine[c]			
Treatment, influenza A	Not approved	100 mg PO bid	100–200 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	100–200 mg/d

[a]<15 kg: 30 mg bid; >15–23 kg: 45 mg bid; >23–40 kg: 60 mg bid; >40 kg: 75 mg bid. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm.*

[b]<15 kg: 30 mg qd; >15–23 kg: 45 mg qd; >23–40 kg: 60 mg qd; >40 kg: 75 mg qd. For children <1 year of age, see *www.cdc.gov/h1n1flu/recommendations.htm.*

[c] Amantadine and rimantadine are not currently recommended (2013–2014) because of widespread resistance in influenza A viruses. Their use may be reconsidered if viral susceptibility is reestablished.

(oseltamivir and zanamivir) and the adamantane agents (amantadine and rimantadine) reduce the duration of signs and symptoms by 1–1.5 days and ~50%, respectively.

  - An IV formulation of peramivir, a neuraminidase inhibitor, has recently been approved by the FDA; an IV formulation of zanamivir is in clinical trials.
  - Zanamivir may exacerbate bronchospasm in asthmatic pts, while oseltamivir has been associated with nausea and vomiting (reactions whose incidence is reduced if the drug is given with food) and with neuropsychiatric side effects in children.
  - Amantadine causes mild CNS side effects (e.g., jitteriness, anxiety, insomnia, difficulty concentrating) in ~5–10% of pts; rimantadine has fewer CNS side effects.
- For uncomplicated influenza in individuals at low risk for complications, symptom-based rather than antiviral therapy may be considered.

Prophylaxis

Annual vaccination with either an inactivated or a live attenuated vaccine is the main public health measure for prevention of influenza.

- Vaccine strains are generated from influenza A and B viruses that have circulated during the previous influenza season and whose circulation during the upcoming season is predicted.
  - For inactivated vaccines, 50–80% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related.
  - Influenza vaccination is currently recommended for all individuals >6 months of age.
- Chemoprophylaxis against influenza (Table 101-1) should be reserved for individuals at high risk of complications who have had close contact with a pt sick with influenza. Chemoprophylaxis can be administered simultaneously with inactivated—but not with live—vaccine.

OTHER COMMON VIRAL RESPIRATORY INFECTIONS

Acute viral respiratory illnesses account for ≥50% of all acute illnesses; adults have 3–4 cases per person per year. The clinical presentations of viral infections generally are not specific enough to allow an etiologic diagnosis, and viral illnesses are typically grouped into clinical syndromes (e.g., the "common cold," pharyngitis, tracheitis, pneumonia). This section will cover the six major groups of respiratory viruses; see Table 101-2 for an overview and Chap. 58 for additional details on viral respiratory infections.

RHINOVIRUSES

Microbiology

Rhinoviruses are nonenveloped, single-stranded RNA viruses in the family Picornaviridae that together are the major cause of the "common cold" (up to 50% of cases).

Epidemiology

Rhinoviruses are spread by direct contact with infected secretions, usually respiratory droplets.

Clinical Manifestations

After an incubation period of 1–2 days, pts develop rhinorrhea, sneezing, nasal congestion, and sore throat that last for 4–9 days. Fever and other systemic signs and symptoms are unusual in adults.

- Severe disease, including fatal pneumonia, is rare but has been described in immunocompromised pts, particularly bone marrow transplant recipients.

Diagnosis

An etiologic diagnosis usually is not attempted, given that the disease is generally mild and self-limited. PCR and tissue culture methods are available.

Treatment

Treatment is limited to symptom relief (e.g., with antihistamines, decongestants).

CORONAVIRUSES

Microbiology

Coronaviruses are pleomorphic, single-stranded RNA viruses.

TABLE 101-2 ILLNESSES ASSOCIATED WITH RESPIRATORY VIRUSES

	Frequency of Respiratory Syndromes		
Virus	**Most Frequent**	**Occasional**	**Infrequent**
Rhinoviruses	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia in children
Coronaviruses[a,b]	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia and bronchiolitis
Human respiratory syncytial virus	Pneumonia and bronchiolitis in young children	Common cold in adults	Pneumonia in elderly and immunosuppressed pts
Parainfluenza viruses	Croup and lower respiratory tract disease in young children	Pharyngitis and common cold	Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed pts
Adenoviruses	Common cold and pharyngitis in children	Outbreaks of acute respiratory disease in military recruits[c]	Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed pts
Influenza A viruses	Influenza[d]	Pneumonia and excess mortality in high-risk pts	Pneumonia in healthy individuals
Influenza B viruses	Influenza[d]	Rhinitis or pharyngitis alone	Pneumonia
Enteroviruses	Acute undifferentiated febrile illnesses[e]	Rhinitis or pharyngitis alone	Pneumonia
Herpes simplex viruses	Gingivostomatitis in children; pharyngotonsillitis in adults	Tracheitis and pneumonia in immunocompromised pts	Disseminated infection in immunocompromised pts
Human metapneumoviruses	Upper and lower respiratory tract disease in children	Upper respiratory tract illness in adults	Pneumonia in elderly and immunosuppressed pts

[a]Severe acute respiratory syndrome–associated coronavirus (SARS-CoV) caused epidemics of pneumonia from November 2002 to July 2003 (see text).
[b]Middle East respiratory syndrome coronavirus (MERS-CoV) has caused severe respiratory illnesses from 2012 to the time of this writing (2015); see text.
[c]Serotypes 4 and 7 most commonly; also serotypes 14 and 21.
[d]Fever, cough, myalgia, malaise.
[e]May or may not have a respiratory component.

Epidemiology and Clinical Manifestations

Coronaviruses often result in the common cold (accounting for 10–35% of cases), with symptoms similar to those caused by rhinoviruses.

- Compared with that for rhinoviruses, the incubation period for coronaviruses is slightly longer (3 days) and the duration of illness is slightly shorter (6–7 days).
- In 2002–2003, a coronavirus-induced severe acute respiratory syndrome (SARS) developed in >8000 pts in 28 countries (with 90% of cases in China and Hong Kong) and was associated with a ~9.5% case–fatality rate; no cases were reported after 2004.
  - SARS has an incubation period of 2–7 days, after which pts develop fever, malaise, headache, myalgias, and then (1–2 days later) a nonproductive cough and dyspnea.
  - Pts can develop ARDS and multiorgan dysfunction in the second week of illness.
- The Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012 and has caused more than 1600 cases, with a 36% case–fatality rate. All cases have been associated with contact or travel to the Arabian Peninsula.
  - After an incubation period of ~5 days, pts develop cough and fever that progress to respiratory failure within a week.

Diagnosis

Laboratory diagnosis of coronavirus-induced colds is rarely required, but ELISA, immunofluorescence, and reverse-transcription PCR (RT-PCR) assays can detect the virus in clinical specimens.

- The coronavirus associated with SARS (SARS-CoV) and MERS-CoV can be detected by RT-PCR or viral culture of respiratory samples.

TREATMENT CORONAVIRUSES

- For the common cold, no treatment beyond symptom relief is generally needed.
- For SARS and MERS, aggressive supportive care is most important. No specific therapy (e.g., with ribavirin, glucocorticoids) has been established as efficacious.

HUMAN RESPIRATORY SYNCYTIAL VIRUS (HRSV)

Microbiology

HRSV is an enveloped, single-stranded RNA virus and a member of the family Paramyxoviridae.

Epidemiology

With an attack rate approaching 100% among susceptible individuals, HRSV is a major respiratory pathogen among young children (particularly those 2–3 months of age) and the foremost cause of lower respiratory disease among infants.

- HRSV accounts for 20–25% of hospital admissions of young children for pneumonia and for up to 75% of cases of bronchiolitis in this age group.
- The virus is transmitted efficiently via contact with contaminated fingers or fomites and by spread of coarse aerosols. The incubation period is ~4–6 days.

Clinical Manifestations

Infants typically develop rhinorrhea, low-grade fever, cough, and wheezing; 25–40% of infections result in lower tract disease, including pneumonia, bronchiolitis, and tracheobronchitis.

- In adults, HRSV typically presents as the common cold, but it can cause lower respiratory tract disease with fever, including severe pneumonia in pts who are elderly or immunosuppressed or who have cardiopulmonary disease. HRSV pneumonia has a case–fatality rate of 20–80% among transplant pts.

Diagnosis

Rapid viral diagnosis is available by immunofluorescence, ELISA, or RT-PCR of nasopharyngeal washes, aspirates, or (less satisfactorily) swabs.

TREATMENT HUMAN RESPIRATORY SYNCYTIAL VIRUS

- Treatment is symptom-based for upper tract disease and mild lower tract disease.
- For severe lower tract disease, intubation and ventilatory assistance should be given as needed.
  - Aerosolized ribavirin has a demonstrated modest beneficial effect for infants with severe HRSV pneumonia, but its efficacy in older children and adults (including immunocompromised pts) has not been established.
  - No benefit has been found in any pt population for IV immunoglobulin (IVIg), immunoglobulin with high titers of antibody to HRSV (RSVIg), or a monoclonal IgG antibody to HRSV (palivizumab).

Prevention

Monthly administration of palivizumab is approved for prophylaxis in children <2 years of age who have bronchopulmonary dysplasia or cyanotic heart disease or who were born prematurely. In settings with high transmission rates (e.g., pediatric wards), contact precautions are useful to limit spread of the virus.

HUMAN METAPNEUMOVIRUS

Microbiology

Human metapneumovirus is a pleomorphic, single-stranded RNA virus of the family Paramyxoviridae.

Epidemiology

Human metapneumovirus accounts for 1–5% of childhood upper respiratory tract infections and for 2–4% of acute respiratory illnesses in ambulatory adults.

Clinical Manifestations

Disease manifestations are similar to those caused by HRSV.

Diagnosis

The diagnosis is made by immunofluorescence, PCR, or tissue culture of nasal aspirates or respiratory secretions.

Treatment

Treatment is primarily supportive and symptom-based.

PARAINFLUENZA VIRUS

Microbiology and Epidemiology

This enveloped, single-stranded RNA virus of the family Paramyxoviridae ranks second only to HRSV as a cause of lower respiratory tract disease among young children and is the most common cause of croup (laryngotracheobronchitis).

Clinical Manifestations

Infections are milder among older children and adults, but severe, prolonged, and fatal infection has been reported among pts with severe immunosuppression, including transplant recipients.

Diagnosis

Tissue culture, rapid testing with immunofluorescence or ELISA (both of which are less sensitive), or PCR of respiratory tract secretions, throat swabs, or nasopharyngeal washings can detect the virus.

TREATMENT **PARAINFLUENZA VIRUS**

Treatment of upper respiratory tract disease is symptom-based. Humidified air may be helpful for mild cases of croup.

- For cases of croup with respiratory distress, intermittent racemic epinephrine and glucocorticoids are beneficial.
- Anecdotal reports describe the use of ribavirin (particularly in immunosuppressed pts), but its clinical utility is still unclear.

ADENOVIRUSES

Microbiology and Epidemiology

Adenoviruses are double-stranded DNA viruses that cause ~10% of acute respiratory infections among children and <2% of respiratory illnesses among civilian adults. Some serotypes are associated with outbreaks among military recruits. Transmission takes place primarily from fall to spring via inhalation of aerosolized virus, through inoculation of the conjunctival sacs, and probably via the fecal–oral route.

Clinical Manifestations

In children, adenovirus causes acute upper and lower respiratory tract infections and outbreaks of pharyngoconjunctival fever (a syndrome of fever, bilateral conjunctivitis, sore throat, and cervical adenopathy typically due to types 3 and 7).

- In adults (particularly military recruits), adenovirus types 4 and 7 cause an acute respiratory disease consisting of a prominent sore throat, fever on the second or third day of illness, cough, coryza, and regional adenopathy. Pharyngeal edema and tonsillar hypertrophy with little or no exudate may be seen.
- In addition to respiratory disease, adenovirus can cause diarrheal illness, hemorrhagic cystitis, and epidemic keratoconjunctivitis. In pts who have received a solid-organ transplant, adenovirus can affect the transplanted organ and disseminate to other organs.

Diagnosis

Definitive diagnosis can be made by isolation of the virus in tissue culture; by rapid testing (immunofluorescence or ELISA) of nasopharyngeal aspirates, conjunctival or respiratory secretions, urine, or stool; or by PCR testing (the diagnostic standard).

Treatment

Treatment is supportive. Ribavirin and cidofovir exhibit in vitro activity against adenovirus and therefore are used occasionally in disseminated adenovirus infections, but definitive efficacy data are not available.



For a more detailed discussion, see Baden LR, Dolin R: Antiviral Chemotherapy, Excluding Antiretroviral Drugs, Chap. 215e; Dolin R: Common Viral Respiratory Infections, Chap. 223, p. 1202; and Cohen YZ, Dolin R: Influenza, Chap. 224, p. 1209, in HPIM-19.

102 Rubeola, Rubella, Mumps, and Parvovirus Infections

MEASLES (RUBEOLA)

Definition and Microbiology

Measles is a highly contagious disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by a generalized maculopapular rash. Measles is caused by a nonsegmented, single-stranded, negative-sense RNA virus of the genus *Morbillivirus* and the family Paramyxoviridae.

Epidemiology

Humans are the only reservoir for measles virus; unvaccinated infants who have lost maternal antibodies account for the bulk of susceptible individuals. However, as measles vaccine coverage increases, the age distribution of the disease shifts upward: in the United States, adolescents and adults are the most likely age groups to acquire measles.

- Routine administration of the measles vaccine has markedly reduced worldwide mortality due to measles; in 2008, there were ~164,000 deaths.
- Pts are contagious for several days before and after the rash appears. The virus is spread primarily via respiratory droplets over short distances. Secondary attack rates among susceptible contacts are >90%.

Clinical Manifestations

Approximately 10 days after infection with measles virus, pts develop fever and malaise, followed by cough, coryza, and conjunctivitis; the characteristic rash occurs 14 days after infection.

- An erythematous, nonpruritic, maculopapular rash begins at the hairline and behind the ears, spreads down the trunk and limbs to include the palms and soles, can become confluent, and begins to fade (in the same order of progression) by day 4.
- Koplik's spots are pathognomonic for measles and consist of bluish-white dots ~1 mm in diameter surrounded by erythema. They appear on the buccal mucosa ~2 days before the rash appears and fade with the onset of rash.
- Pts with impaired cellular immunity may not develop a rash and have a higher case–fatality rate than those with intact immunity.
- Complications include giant-cell pneumonitis, secondary bacterial infection of the respiratory tract (e.g., otitis media, bronchopneumonia), and CNS disorders.
  - Postmeasles encephalitis occurs within 2 weeks of rash onset in ~1 in 1000 cases and is characterized by fever, seizures, and a variety of neurologic abnormalities.
  - Measles inclusion-body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE) occur months to years after acute infection and are caused by persistent measles virus infection.
    - MIBE is a fatal complication that primarily affects pts with defects in cellular immunity.
    - SSPE is a progressive disease characterized by seizures and deterioration of cognitive and motor functions, with death occurring 5–15 years after measles virus infection.

Diagnosis

The characteristic rash and pathognomonic Koplik's spots permit a clinical diagnosis.

- Serologic testing is the most common method of laboratory diagnosis. Measles-specific IgM is usually detectable within 1–3 days of rash onset.
- Viral culture and reverse-transcription PCR analysis of clinical specimens are used occasionally to detect measles.

TREATMENT MEASLES

- Supportive care is the mainstay of treatment, as there is no specific antiviral therapy for measles. Prompt antibiotic therapy for pts with secondary bacterial infections helps reduce morbidity and mortality risks.
- Vitamin A (for children ≥12 months: 200,000 IU/d for 2 days) is recommended by the World Health Organization (WHO) for all children with measles.

Prevention

In the United States, children are routinely immunized with two doses of a live attenuated vaccine containing measles, mumps, and rubella (MMR) antigens.

- Vaccine-induced immunity lasts for at least several decades; rates of secondary vaccine failure 10–15 years after immunization are ~5%. In contrast, natural infection leads to life-long immunity.
- Administration of immunoglobulin within 6 days of exposure, which can prevent or modify the disease in immunocompetent persons, is recommended for children <1 year old, immunocompromised pts, and pregnant women. A dose of 0.25 mL/kg is given to healthy pts and a dose of 0.5 mL/kg to immunocompromised hosts, with a maximal dose of 15 mL.

RUBELLA (GERMAN MEASLES)

Microbiology and Epidemiology

Rubella is a contagious infectious disease caused by a single-stranded, enveloped RNA virus in the family Togaviridae and the genus *Rubivirus*.

- In 2012, there were 94,030 cases of rubella worldwide, although this figure is probably an underestimate because of poor reporting. Since 2004, rubella has not been an endemic disease in the United States.
- Virus is spread via respiratory droplets, and primary implantation and replication occur in the nasopharynx. Placental infection can lead to chronic infection of virtually all fetal organs, which sometimes persists for up to 1 year after birth.

Clinical Manifestations

While acquired rubella infection is generally benign, congenital rubella infection can be more severe.

- *Acquired infection:* With an incubation period of 14 days, acquired rubella is characterized by a generalized maculopapular rash that lasts ≤3 days; ~50% of infections are subclinical or without rash.
  - Occipital and/or postauricular lymphadenopathy may occur during the second week after exposure.
  - In older children and adults, the rash may be preceded by a 1- to 5-day prodrome consisting of low-grade fever, malaise, and upper respiratory symptoms.
  - Arthralgias and arthritis are common among adults, particularly women.
- *Congenital infection:* Congenital rubella infection can lead to a number of physical defects, usually involving the eyes (e.g., cataracts), ears (e.g., deafness), and heart (e.g., pulmonary arterial stenosis).

– Up to 90% of women infected with rubella virus during the first 11 weeks of pregnancy will deliver an infant with congenital rubella.
– The congenital rubella rate is 20% for maternal infections acquired during the first 20 weeks of pregnancy.

Diagnosis

Given the difficulty of diagnosing rubella clinically, serologic testing (for the presence of IgM or a ≥4-fold rise in IgG titer) is generally used for diagnosis.

- If the IgM sample taken within the first 4 days of rash is negative but clinical suspicion remains, testing should be repeated; IgM antibody titers are generally positive for up to 6 weeks.
- Congenital rubella can be diagnosed by detection of IgM antibodies, although titers may be negative during the first month; by isolation of the virus from throat swabs, urine, or CSF; and/or by an IgG titer that does not decline at the expected rate of a twofold dilution per month.
- In the United States, screening of pregnant women for rubella IgG antibodies is part of routine prenatal care; seronegative women should be vaccinated postpartum.

Treatment

Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. No rubella-specific therapies are available.

Prevention

As of 2012, 69% of countries holding membership in the WHO had recommended inclusion of a rubella-containing vaccine in the routine childhood vaccination schedule. One dose induces seroconversion in ≥95% of persons ≥1 year of age and provides long-term (potentially life-long) immunity.

- Pregnant women should not receive the vaccine, and pregnancy should be avoided for at least 28 days after vaccination.
- Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis.

MUMPS

Definition and Microbiology

Mumps is an acute systemic communicable viral infection whose most distinctive feature is swelling of one or both parotid glands. It is caused by mumps virus, a negative-strand nonsegmented RNA paramyxovirus.

Epidemiology

The estimated annual global incidence of mumps is 100–1000 cases per 100,000 population in countries without national mumps vaccination programs. In the United States, there were <300 cases in 2001 because levels of childhood vaccination are high, although occasional outbreaks—particularly among college students—continue to occur because of inadequate coverage in focal areas and waning of vaccine immunity with time.

- The incubation period of mumps is ~19 days, and humans are the only natural hosts.
- Mumps virus is transmitted by respiratory secretions and fomites. Pts are contagious from 1 week before to 1 week after symptom onset and are most contagious 1–2 days before symptom onset.

Clinical Manifestations

Up to half of infections are asymptomatic or lead to nonspecific respiratory symptoms. Unilateral or bilateral parotitis lasting >2 days is present in 70–90% of symptomatic infections.

- A prodrome involving low-grade fever, malaise, myalgia, headache, and anorexia may precede the development of parotitis and last for 1–7 days.
  - Pts with parotitis typically have difficulty eating, swallowing, and/or talking and may have an earache.
  - Glandular swelling disappears within 1 week.
- Epididymo-orchitis is the second most common manifestation of mumps, developing in 15–30% of cases in postpubertal males.
  - Orchitis, characterized by a painful, tender, and enlarged testis, is bilateral in 10–30% of cases and resolves within 1 week.
  - Oophoritis (manifested by lower abdominal pain and vomiting) occurs in ~5% of women with mumps.
  - Sterility after mumps is rare.
- Symptomatic CNS disease (e.g., aseptic meningitis) occurs in <10% of pts and is usually self-limited.
  - In CSF pleocytosis, neutrophils often predominate in the first 24 h before being replaced by lymphocytes on the second day.
  - Cranial nerve palsies occasionally lead to permanent sequelae, particularly deafness.
- Less common manifestations include pancreatitis, myocarditis, thyroiditis, nephritis, and arthritis. Mumps in pregnancy does not appear to lead to premature birth, low birth weight, or fetal malformations.

Diagnosis

Laboratory diagnosis is generally based on detection of viral RNA in clinical samples (e.g., buccal or throat swab, CSF, urine, seminal fluid) via reverse-transcription PCR or serology. Serologic assays are of limited utility since IgM may not be detectable <3 days or >6 weeks after symptom onset and IgG titers often exhibit little fluctuation between acute- and convalescent-phase samples.

Treatment

Mumps is generally a benign, self-resolving illness in which symptom-based and supportive therapies are most helpful.

Prevention

Current United States recommendations are for a two-dose vaccination schedule, with the first dose at ≥1 year old and the second dose at least 28 days after the first. Outbreaks, such as those occurring in 2006 in the United States, the United Kingdom, and Canada, demonstrate that vaccine-induced immunity is not life-long.

PARVOVIRUS INFECTION

Microbiology

Parvovirus B19 (B19V), a nonenveloped single-stranded DNA virus of the family Parvoviridae, is the only member of this family shown definitively to cause significant human disease.

Epidemiology

B19V exclusively infects humans, is endemic worldwide, and is transmitted via the respiratory route. By the age of 15 years, ≥50% of children are seropositive. Of elderly pts, >90% have detectable antibody.

Pathogenesis

B19V replicates in erythroid progenitors, which are among the few cells that express the B19V receptor, blood group P antigen (globoside). Infection leads to high-titer viremia and arrest of erythropoiesis. When an IgM and IgG antibody response is mounted, normal erythropoiesis resumes.

Clinical Manifestations

Most B19V infections are asymptomatic or are associated with only a mild nonspecific illness.

- *Erythema infectiosum (fifth disease):* The main manifestation of symptomatic B19V disease, erythema infectiosum presents as a low-grade fever ~7–10 days after exposure and a facial "slapped-cheek" rash (more common among children) a few days later. Two or three days after the facial rash develops, a lacy, reticular macular rash may spread to the extremities.
- *Polyarthropathy syndrome:* Arthralgias, typically symmetric and affecting the small joints of the hands and occasionally the ankles, knees, and wrists, occur in ~50% of adults (more commonly women). Most cases resolve in a few weeks, but some persist for months.
- *Transient aplastic crisis (TAC):* Pts with chronic hemolytic conditions (e.g., hemoglobinopathies, autoimmune hemolytic anemia) can develop aplastic crisis with B19V infection that can be life-threatening. Pts display symptoms associated with severe anemia.
- *Pure red-cell aplasia/chronic anemia:* Immunosuppressed pts can develop persistent anemia with reticulocytopenia, high levels of B19V DNA in serum, and absent or low levels of B19V IgG. B19V occasionally causes a hemophagocytic syndrome.
- *Hydrops fetalis:* B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss. The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (which occurs predominantly early in the second trimester) is ~9%. The risk of congenital infection is <1%.

Diagnosis

Diagnosis in immunocompetent pts generally relies on detection of B19V-specific IgM antibodies, which can be detected coincident with the rash in erythema infectiosum or by day 3 of TAC.

- B19V-specific IgG is detectable by the seventh day of illness and persists for life.
- Detection of B19V DNA via quantitative PCR should be used to diagnose early TAC or chronic anemia. In acute infection, the viremia load can be $>10^{12}$ B19V DNA IU/mL of serum; pts with TAC or chronic anemia generally have $>10^{5}$ B19V IU/mL.

TREATMENT **PARVOVIRUS INFECTION**

- Treatment of B19V infection is generally supportive as no specific therapy exists. TAC should be treated with transfusions as needed.
- In pts receiving immunosuppressive agents, treatment should be reduced to the extent feasible to allow an immune response. IV immunoglobulin (400 mg/kg daily for 5–10 days) may cure or ameliorate persistent B19V infection in immunosuppressed pts.



For a more detailed discussion, see Brown KE: Parvovirus Infections, Chap. 221, p. 1195; Rainwater-Lovett K, Moss WJ: Measles (Rubeola), Chap. 229, p. 1295; Zimmerman LA, Reef SE: Rubella (German Measles), Chap. 230e; and Rubin SA, Carbone KM: Mumps, Chap. 231e, in HPIM-19.

103 Enteroviral Infections

MICROBIOLOGY

- Enteroviruses are so named because of their ability to multiply in the GI tract, but they do not typically cause gastroenteritis.
- Enteroviruses are members of the family Picornaviridae and encompass >100 human serotypes: 3 serotypes of poliovirus, 21 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, enteroviruses 68–71, and multiple enteroviruses (beginning with enterovirus 73) recently identified by molecular techniques. In the United States, coxsackievirus B1 and echoviruses 18, 9, and 6 account for ~50% of all enteroviral infections.

PATHOGENESIS

- Studies of poliovirus infection form the basis of our understanding of enteroviral pathogenesis.
- After ingestion, poliovirus infects GI tract mucosal epithelial cells, spreads to regional lymph nodes, causes viremia, and replicates in the reticuloendothelial system; in some cases, a second round of viremia occurs.
- Virus gains access to the CNS either via the bloodstream or via direct spread from neural pathways.
- Virus is present in blood for 3–5 days. It is shed from the oropharynx for up to 3 weeks and from the GI tract for up to 12 weeks after infection; hypogammaglobulinemic pts can shed virus for >20 years.
- Infection is controlled by humoral and secretory immunity in the GI tract.

EPIDEMIOLOGY

- Enteroviruses cause disease worldwide, especially in areas with crowded conditions and poor hygiene.
- Infants and young children are most often infected and are the most frequent shedders.
- Transmission takes place mainly by the fecal–oral route, but airborne transmission and placental transmission have been described.
- The incubation period ranges from 2 to 14 days but usually is <1 week in duration. Pts are most infectious shortly before and after the onset of symptoms.

CLINICAL MANIFESTATIONS

Poliovirus

After an incubation period of 3–6 days, ~5% of pts present with a minor illness (abortive poliomyelitis), characterized by fever, malaise, sore throat, myalgias, and headache, that usually resolves within 3 days.

- *Asymptomatic infection*: >90% of all infections
- *Aseptic meningitis (nonparalytic poliomyelitis):* occurs in ~1% of pts. Examination of CSF reveals normal glucose and protein concentrations and lymphocytic pleocytosis (with PMNs sometimes predominating early).
- *Paralytic disease:* the least common form; presents ≥1 day after aseptic meningitis as severe back, neck, and muscle pain as well as gradually developing motor weakness
  - The weakness is usually asymmetric and proximal and is most common in the legs. The arms and the abdominal, thoracic, and bulbar muscles are also frequently involved.

  - Paralysis generally occurs only during the febrile phase.
  - Physical examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas; hyperreflexia may precede the loss of reflexes. Bulbar paralysis is associated with dysphagia, difficulty handling secretions, or dysphonia.
  - Respiratory insufficiency due to aspiration or neurologic involvement may develop. Severe medullary infection may lead to circulatory collapse.
  - Most pts recover some function, but around two-thirds have residual neurologic sequelae.
- *Vaccine-associated poliomyelitis:* The risk of acquiring poliomyelitis after vaccination with the live oral vaccine is estimated to be 1 case per 2.5 million doses and is ~2000 times higher among immunodeficient persons, especially pts with hypo- or agammaglobulinemia.
- *Postpolio syndrome:* new weakness 20–40 years after poliomyelitis. Onset is insidious, progression is slow, and plateau periods can last 1–10 years.

Other Enteroviruses

In the United States, 5–10 million cases of symptomatic enteroviral disease other than poliomyelitis occur each year. More than 50% of nonpoliovirus enteroviral infections are subclinical.

- *Nonspecific febrile illness (summer grippe)*: Pts present with acute-onset fever, malaise, and headache, with occasional upper respiratory symptoms.
  - Disease resolves within a week.
  - Disease frequently occurs during the summer and early fall.
- *Generalized disease of the newborn*: Neonates, typically within the first week of life, present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy.
  - Myocarditis, hypotension, hepatitis, DIC, meningitis, and pneumonia are complications.
  - A history of a recent flu-like illness in the mother should prompt consideration of this disease.
- *Aseptic meningitis and encephalitis*: Enteroviruses cause 90% of cases of aseptic meningitis among children and young adults in which an etiologic agent can be identified; 10–35% of viral encephalitis cases are due to enteroviruses.
  - Pts have an acute onset of fever, chills, headache, photophobia, nausea, and vomiting, with meningismus on examination. Diarrhea, rashes, myalgias, pleurodynia, myocarditis, and herpangina may occur. Encephalitis is much less common and is usually mild, with an excellent prognosis in healthy hosts.
  - CSF examination reveals pleocytosis, with PMNs sometimes predominating early but a shift to lymphocyte predominance within 24 h. Total cell counts usually do not exceed 1000/μL. CSF glucose and protein levels are typically normal.
  - Symptoms resolve within 1 week, but CSF abnormalities persist longer.
- *Pleurodynia (Bornholm disease):* Pts have an acute onset of fever associated with spasms of pleuritic chest pain (more common among adults) or upper abdominal pain (more common among children) that typically last 15–30 min. Fever subsides when pain resolves.
  - Coxsackievirus B is the most common cause.
  - Disease lasts for a few days and can be treated with NSAIDs and heat application to the affected muscles.
- *Myocarditis and pericarditis:* Enteroviruses (e.g., coxsackievirus B) cause up to one-third of cases of acute myocarditis. Pts have upper respiratory symptoms followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure.
  - Disease occurs most often in newborns (who are most severely ill), adolescents, and young adults.

  - A pericardial friction rub, ST-segment and T-wave abnormalities on electrocardiography, and elevated serum levels of myocardial enzymes can be present.
  - Up to 10% of pts develop chronic dilated cardiomyopathy.
- *Exanthems*: Enteroviral infection is the leading cause of exanthems among children in the summer and fall. Echoviruses 9 and 16 are common causes.
- *Hand-foot-and-mouth disease:* generally due to coxsackievirus A16 and enterovirus 71. Pts present with fever, anorexia, and malaise, which are followed by sore throat and vesicles on the buccal mucosa, tongue, and dorsum or palms of the hands and occasionally on the palate, uvula, tonsillar pillars, or feet.
  - The disease is highly infectious, with attack rates of almost 100% among young children. Symptoms resolve within a week.
  - Epidemics of enterovirus 71 infection occurred in Taiwan in 1998 and in China in 2008–2010; the latter resulted in ~500,000 infections and 126 deaths. These epidemics were associated with CNS disease (e.g., brain-stem encephalitis, seizures), myocarditis, and pulmonary hemorrhage. Deaths occurred primarily among children ≤5 years old.
- *Herpangina:* usually caused by coxsackievirus A infection. Pts develop fever, sore throat, odynophagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate and are concentrated in the posterior portion of the mouth.
  - Lesions can persist for weeks.
  - In contrast to herpes simplex stomatitis, enteroviral herpangina is not associated with gingivitis.
- *Acute hemorrhagic conjunctivitis:* associated with enterovirus 70 and coxsackievirus A24. Pts experience an acute onset of severe eye pain, blurred vision, photophobia, and watery eye discharge; edema, chemosis, and subconjunctival hemorrhage are evident. Symptoms resolve within 10 days.

DIAGNOSIS

- Enterovirus can be isolated from throat or rectal swabs, stool, and/or normally sterile body fluids.
  - Positive results for normally sterile body fluids, such as CSF and serum, reflect disease.
  - In contrast, positive stool and throat cultures may simply reflect colonization.
- In general, serotyping is not clinically useful outside of epidemiologic studies.
- PCR detects all serotypes that infect humans, with high sensitivity (70–100%) and specificity (>80%).
  - PCR of CSF is less likely to be positive if pts present ≥3 days after meningitis onset or with enterovirus 71 infection.
  - PCR of serum is also useful in disseminated disease.

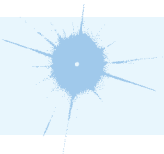
TREATMENT ENTEROVIRAL INFECTIONS

- Most enteroviral illness resolves spontaneously, but immunoglobulin may be helpful in pts with γ globulin defects and chronic infection.
- Glucocorticoids are contraindicated.

PREVENTION AND ERADICATION

- Hand hygiene, use of gowns and gloves, and enteric precautions (for 7 days after disease onset) prevent nosocomial transmission of enteroviruses during epidemics.
- The availability of poliovirus vaccines and the implementation of polio eradication programs have largely eliminated disease due to wild-type poliovirus; of 293 cases in 2012, 85% were from Nigeria, Pakistan, and Afghanistan—the only countries where polio remains endemic. Outbreaks and sporadic disease due to vaccine-derived poliovirus occur.

- Both oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) induce IgG and IgA antibodies that persist for at least 5 years.
- Most developing countries, particularly those with persistent wild-type poliomyelitis, use OPV because of its lower cost and ease of administration. The suboptimal seroconversion rate among children in low-income countries, even after multiple OPV doses, contributes to difficulties in eradication.
- Most industrialized countries have adopted all-IPV childhood vaccination programs.
  - Unvaccinated adults in the United States do not need routine poliovirus vaccination but should receive three doses of IPV (the second dose 1–2 months after the first and the final dose 6–12 months later) if they are traveling to polio-endemic areas or might be exposed to wild-type poliovirus in their communities or workplaces.
  - Adults at increased risk of exposure who have received their primary vaccination series should receive a single dose of IPV.



For a more detailed discussion, see Cohen JI: Enterovirus, Parechovirus, and Reovirus Infections, Chap. 228, p. 1289, in HPIM-19.

104 Insect- and Animal-Borne Viral Infections

RABIES

Microbiology

Rabies is a zoonosis generally transmitted to humans by the bite of a rabid animal and caused by rabies virus—a nonsegmented, negative sense, single-stranded RNA virus in the family Rhabdoviridae. Each animal reservoir harbors distinct rabies virus variants.

Epidemiology

Worldwide, canine rabies causes ~55,000 human deaths each year, most of them affecting rural populations and children in Asia and Africa.

- Endemic canine rabies has been eliminated in the United States and most other resource-rich countries but persists in bats, raccoons, skunks, and foxes. In 2012, there were 6162 confirmed animal cases of rabies in the United States.
- Bats (especially silver-haired and tricolored bats) cause most human cases in North America, although there may be no known history of a bat bite or other bat exposure.

Pathogenesis

The incubation period can range from a few days to >1 year but is usually 20–90 days. During most of this period, rabies virus is present at or close to the site of the bite.

- The virus binds to postsynaptic nicotinic acetylcholine receptors and spreads centripetally along peripheral nerves toward the CNS at a rate of up to ~250 mm/d. Establishment of CNS infection is followed by centrifugal spread along peripheral nerves to other tissues, including salivary glands—hence the excretion of virus in the saliva of rabid animals.
- The most characteristic pathologic CNS finding is the *Negri body*—an eosinophilic cytoplasmic inclusion that is composed of rabies virus proteins and viral RNA and is found primarily within Purkinje cells of the cerebellum and in pyramidal neurons of the hippocampus.

Clinical Manifestations

Rabies usually presents as atypical encephalitis with preservation of consciousness; the disease may be difficult to recognize after the onset of coma. This disease, which usually leads to death despite aggressive therapy, has three phases.

- *Prodrome:* Pts have fever, headache, malaise, nausea, vomiting, and anxiety or agitation lasting 2–10 days. Paresthesias, pain, or pruritus near the site of exposure (which has usually healed at this point) is found in 50–80% of cases and strongly suggests rabies.
- *Acute neurologic phase:* Pts present with the encephalitic (furious) form of rabies in 80% of cases and with the paralytic form in 20%.
  - *Encephalitic form:* Pts develop signs and symptoms common to other viral encephalitides (e.g., fever, confusion, hallucinations, combativeness, and seizures) that last 2–10 days. Autonomic dysfunction is common and includes hypersalivation, gooseflesh, cardiac arrhythmia, and/or priapism.
    - A distinguishing feature of rabies is prominent early brainstem dysfunction resulting in hydrophobia and aerophobia (involuntary, painful contraction of the diaphragm and the accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquid or exposure to a draft of air).
    - Hypersalivation and pharyngeal dysfunction produce characteristic foaming at the mouth.
    - Death usually occurs within days of brainstem involvement. With aggressive supportive care, late complications include cardiopulmonary failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), and GI hemorrhage.
  - *Paralytic form:* For unknown reasons, muscle weakness predominates but cardinal features of rabies encephalitis (hyperexcitability, hydrophobia, aerophobia) are lacking. Muscle weakness usually begins in the bitten extremity and proceeds to quadriparesis.
- *Coma and death:* Even with aggressive supportive measures, recovery is rare. Death usually occurs within 2 weeks.

Diagnosis

In North America, the diagnosis is often considered relatively late in the clinical course. Rabies should be considered for pts with acute atypical encephalitis or acute flaccid paralysis (including those in whom Guillain-Barré syndrome is suspected).

- Most routine laboratory tests in rabies are normal or nonspecific; it is important to test for alternative, potentially treatable diagnoses.
- Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.
  - In a previously unimmunized pt, serum neutralizing antibodies to rabies virus are diagnostic, but these antibodies may not be present until late in the disease course. The presence of rabies virus–specific antibodies in CSF suggests rabies encephalitis, regardless of immunization status.
  - Reverse-transcription PCR (RT-PCR) can detect virus in fresh saliva samples, CSF, and skin and brain tissues.

– Direct fluorescent antibody testing is highly sensitive and specific and can be applied to brain tissue or skin biopsy samples from the nape of the neck (where virus is found in cutaneous nerves at the base of hair follicles).

TREATMENT RABIES

Management is palliative and supportive. There is no established treatment for rabies.

Prevention

Rabies is almost uniformly fatal but is nearly always preventable with appropriate postexposure prophylaxis during the incubation period. Only seven pts have survived infection with rabies virus, and only one of these pts had not received rabies vaccine before disease onset.

- An algorithm for rabies postexposure prophylaxis is depicted in Fig. 104-1.
  - Local wound care (e.g., thorough washing, debridement of devitalized tissue) can greatly reduce the risk of rabies.
  - All previously unvaccinated pts should receive human rabies immune globulin (RIG, 20 IU/kg; 40 IU/kg for equine RIG) no later than 7 days after the first vaccine dose. The entire dose should be infiltrated at the site of the bite; if not anatomically feasible, the residual RIG should be given IM at a distant site.
  - Inactivated rabies vaccine should be given as soon as possible (1 mL IM in the deltoid region), with doses repeated on days 3, 7, and 14 for previously unvaccinated pts; previously vaccinated pts require booster doses only on days 0 and 3.
- Preexposure prophylaxis is occasionally given to persons at high risk (including certain travelers to rabies-endemic areas). A primary vaccine schedule is given on days 0, 7, and 21 or 28.

INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES

Microbiology and Pathogenesis

Most zoonotic viruses only incidentally infect and produce disease in humans; only a few agents are regularly spread among humans by arthropods.

- The major families of arthropod- and rodent-borne viruses include the Arenaviridae, Bunyaviridae, Flaviviridae, Orthomyxoviridae, Reoviridae, Rhabdoviridae, and Togaviridae—all RNA viruses.
- Arthropod-borne viruses infect the vector after a blood meal from a viremic vertebrate (usually nonhuman); after spreading throughout the vector and ultimately reaching the salivary glands, the viruses can be transmitted to another vertebrate during a blood meal.
- Humans become infected with rodent-borne viruses by inhalation of aerosols containing the viruses and through close contact with chronically infected rodents and their excreta.

Clinical Manifestations

Infection is usually subclinical; when disease does occur, it generally does so in one of five occasionally overlapping clinical syndromes: fever and myalgia, encephalitis, arthritis and rash, pulmonary disease, or viral hemorrhagic fever (HF).

Fever and Myalgia This is the most common syndrome associated with zoonotic viruses. Typically, pts have an acute onset of fever, chills, severe myalgia, malaise, and headache; true arthritis is not found. Complete recovery after 2–5 days of illness is usual. Important examples include the following:

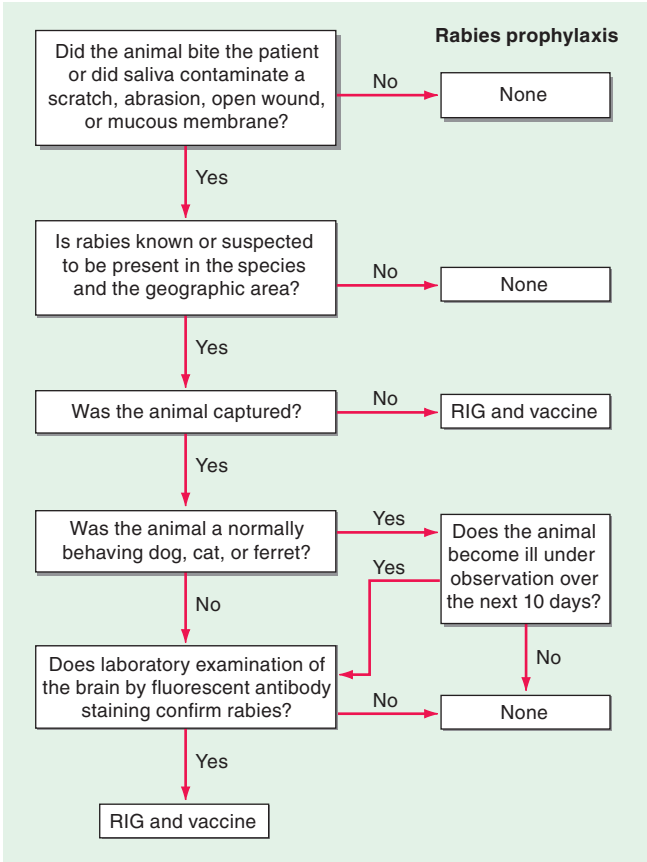


FIGURE 104-1 Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. *(From L Corey, in* Harrison's Principles of Internal Medicine, *15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001, adapted with permission.)*

- *Lymphocytic choriomeningitis (LCM):* This infection is transmitted from chronically infected mice and pet hamsters via aerosols of excreta and secreta. About one-fourth of infected pts have a 3- to 6-day febrile phase, a brief remission, and then recurrent fever, severe headache, nausea, vomiting, and meningeal signs lasting ~1 week.
  - Other manifestations include transient alopecia, arthritis, pharyngitis, cough, maculopapular rash, and orchitis.
  - Pregnant women can have mild infection yet pass on the virus to the fetus, who can develop hydrocephalus and chorioretinitis.
  - The diagnosis should be considered when an adult has aseptic meningitis and any of the following applies: autumn seasonality, a well-marked febrile prodrome, a low CSF glucose level, or CSF mononuclear cell counts >1000/μL.
  - LCM viremia is most likely in the initial febrile phase of illness. LCM can also be diagnosed by IgM-capture ELISA of serum or CSF or by RT-PCR of CSF.

- *Dengue:* With 50–100 million cases annually, dengue is probably the most important arthropod-borne viral disease worldwide. The four serotypes of dengue viruses are all transmitted by the mosquito *Aedes aegypti*, which is also a vector for yellow fever. After an incubation period of 4–7 days, pts experience the sudden onset of fever, frontal headache, retroorbital pain, back pain, severe myalgia (*break-bone fever*), adenopathy, palatal vesicles, and scleral injection.
  - The illness usually lasts 1 week, and a maculopapular rash often appears near the time of defervescence (usually day 3–5).
  - A second infection with a different dengue serotype can lead to severe dengue (previously called *dengue hemorrhagic fever*; see "Hemorrhagic Fever," below).
  - The diagnosis is made by IgM ELISA or paired serologic tests during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is easily isolated from blood during the acute phase by inoculation of mosquitoes or mosquito cell culture. Leukopenia, thrombocytopenia, and increased serum aminotransferase levels may be documented.

Encephalitis Depending on the causative virus, the ratio of clinical to subclinical disease, the mortality rate, and residua vary widely. The pt usually presents with a prodrome of nonspecific signs and symptoms (e.g., fever, abdominal pain, sore throat, respiratory signs) that is followed quickly by headache, meningeal signs, photophobia, and vomiting; involvement of deeper structures leads to lethargy, cognitive deficits, focal neurologic signs, and coma. Acute encephalitis usually lasts from a few days to 2–3 weeks, and recovery may be slow and incomplete. Treatable causes of encephalitis (e.g., HSV) should be ruled out promptly. Some important examples of arboviral encephalitides follow.

- *Japanese encephalitis:* This infection is present throughout Asia and the western Pacific islands. A Parkinsonian presentation and seizures are typical in severe cases. An effective vaccine (ideally given on days 0 and 28, with the second dose administered ≥1 week prior to travel) is available and is indicated for summer travelers to rural Asia, where the risk can be as high as 1 case per 5000 travelers per week.
- *West Nile encephalitis:* Present throughout the Western Hemisphere and now the leading cause of arboviral encephalitis in the United States, West Nile virus is a common cause of febrile disease without CNS infection, but it occasionally causes aseptic meningitis or encephalitis. Encephalitis, serious sequelae, and death are more common among elderly pts, diabetic and hypertensive pts, and pts with previous CNS disease. Unusual clinical features include chorioretinitis, flaccid paralysis, and initial presentation with focal neurologic deficits.
- *Eastern equine encephalitis (EEE):* EEE occurs primarily within endemic swampy foci along the eastern coast of the United States during the summer and early fall. EEE is one of the most severe arboviral diseases and is characterized by rapid onset, rapid progression, high mortality risk (50–75%), and frequent residua. PMN-predominant pleocytosis of the CSF within the first 1–3 days of disease is an indication of severity.

Arthritis and Rash Alphaviruses are common causes of arthritis accompanied by a febrile illness and maculopapular rash, usually during the summer in temperate climates. Examples include the following:

- *Sindbis virus:* Found in northern Europe and southern Africa, this virus, which has an incubation period of <1 week, causes a maculopapular rash that often vesiculates on the trunk and extremities. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days; joint pains may persist for months or years.
- *Chikungunya virus:* Found primarily in Africa, Asia, and the Caribbean, this virus has an incubation period of 2–10 days and results in the abrupt onset of fever, severe arthralgias, migratory polyarthritis mainly affecting small joints, and a rash that begins coincident with defervescence at day 2–3 of illness.

- *Barmah Forest and Ross River viruses:* As causes of epidemic polyarthritis in Australia and the eastern Pacific Islands, these viruses produce a rash and disabling symmetrical joint pain, typically in the absence of other prominent constitutional symptoms, after an incubation period of 7–9 days. Because of joint pain, only ~50% and 90% of pts can resume normal activities at 4 weeks and 3 months, respectively.

Pulmonary Disease After a prodrome (e.g., fever, malaise, myalgias, GI disturbances) of ~3–4 days, pts with hantavirus pulmonary syndrome (HPS) enter a cardiopulmonary phase marked by tachycardia, tachypnea, and mild hypotension. Over the next few hours, the illness may rapidly progress to severe hypoxemia and respiratory failure; the mortality rate is ~30–40% with good management. Pts surviving the first 2 days of hospitalization usually recover with no residua.

- The disease is linked to rodent exposure. Sin Nombre virus infects the deer mouse and is the most important virus causing HPS in the United States.
- Thrombocytopenia (an important early clue), hemoconcentration, proteinuria, and hypoalbuminemia are typical.
- IgM testing of acute-phase serum may give positive results, even during the prodromal stage, and can confirm the diagnosis. RT-PCR of blood clots or tissue usually gives a positive result in the first 7–9 days of illness.
- Treatment is nonspecific and requires intensive respiratory management and other supportive measures.

Viral Hemorrhagic Fever (VHF) The VHF syndrome is a constellation of findings based on vascular instability and decreased vascular integrity. All VHF syndromes begin with the abrupt onset of fever and myalgia and can progress to severe prostration, headache, dizziness, photophobia, abdominal and/or chest pain, anorexia, and GI disturbances. On initial physical examination, there is conjunctival suffusion, muscular or abdominal tenderness to palpation, hypotension, petechiae, and periorbital edema. Laboratory examination usually reveals elevated serum aminotransferase levels, proteinuria, and hemoconcentration. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, convulsions) are poor prognostic signs. Early recognition is important; appropriate supportive measures and, in some cases, virus-specific therapy can be instituted.

- *Lassa fever:* Endemic and epidemic in West Africa, Lassa fever has a more gradual onset than other VHF syndromes. Bleeding is evident in 15–30% of cases. A maculopapular rash is often noted in light-skinned pts with Lassa fever.
  - Pregnant women have higher mortality rates, and the fetal death rate is ~90%.
  - Pts with high-level viremia or a serum aspartate aminotransferase level of >150 IU/mL are at an elevated risk of death, and the administration of ribavirin (32 mg/kg IV × 1 dose, followed by 16 mg/kg q6h for 4 days and then 8 mg/kg q8h for 6 days), which appears to reduce this risk, should be considered.
- *Junin/Argentinian and Machupo/Bolivian HF syndromes:* These syndromes resemble Lassa fever; however, thrombocytopenia, bleeding, and CNS dysfunction (e.g., confusion, cerebellar signs) are common.
  - Passive antibody treatment for Junin/Argentinian HF is effective, and an effective vaccine exists.
  - Ribavirin at the doses recommended for Lassa fever is likely to be effective in all South American VHF syndromes.
- *Rift Valley fever:* Although Rift Valley fever virus typically causes fever and myalgia, VHF can occur with prominent liver involvement, renal failure, and probably DIC.
  - Retinal vasculitis can occur in ~10% of otherwise mild infections, and pts' vision can be permanently impaired.
  - There is no proven therapy for Rift Valley fever. A live attenuated vaccine is in trials.

- *HF with renal syndrome (HFRS):* This entity is most often caused in Europe by Puumala virus, in the Balkans by Dobrava-Belgrade virus, and in eastern Asia by Hantaan virus.
  - Severe cases of HFRS evolve in identifiable stages: the *febrile* stage with myalgia, lasting 3 or 4 days; the *hypotensive* stage, often associated with shock and lasting from a few hours to 48 h; the *oliguric* stage with renal failure, lasting 3–10 days; and the *polyuric* stage with diuresis and hyposthenuria.
  - Infections with Puumala virus result in a much-attenuated picture but the same general presentation.
  - IgM-capture ELISA is positive within 2 days of admission and confirms the diagnosis.
  - The mainstay of therapy is expectant management of shock and renal failure. Ribavirin may reduce rates of mortality and morbidity in severe cases if treatment is begun within the first 4 days of illness.
- *Yellow fever:* A former cause of major epidemics, yellow fever causes a typical VHF syndrome with prominent hepatic necrosis, most commonly in urban South America and Africa. Pts are viremic for 3–4 days and can have jaundice, hemorrhage, black vomit, anuria, and terminal delirium. Vaccination of visitors to endemic areas and control of the mosquito vector *A. aegypti* prevent disease.
- *Severe dengue:* Previous infection with a heterologous dengue virus serotype may elicit nonprotective antibodies and exacerbate disease if pts are reinfected. In mild cases, lethargy, thrombocytopenia, and hemoconcentration occur 2–5 days after typical dengue fever, usually at the time of defervescence. In severe cases, frank shock occurs, with cyanosis, hepatomegaly, ascites and pleural effusions, and GI bleeding. The period of shock lasts 1–2 days.
  - The risk decreases considerably after age 12. Severe dengue is more common among females than among males, among whites than among blacks, and among well-nourished than among malnourished persons; it is also more common if dengue virus 1—as opposed to dengue virus 4—precedes infection with dengue virus 2.
  - With good care, the overall mortality rate is as low as 1%. Control of *A. aegypti*, the mosquito vector, is the key to control of the disease.

EBOLA AND MARBURG VIRUS INFECTIONS

Microbiology

The family Filoviridae contains two genera, *Marburgvirus* and *Ebolavirus*, that consist of negative-sense, single-stranded RNA viruses capable of infecting humans. *Ebolavirus* has five species named for their original site of recognition, and *Marburgvirus* has two species.

- Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of high mortality rates (except for Reston virus, an Ebola virus, which is nonpathogenic for humans) and aerosol infectivity.

Epidemiology

- Filoviruses pathogenic for humans are exclusively endemic to Equatorial Africa.
- As of February 2016, there had been ~31,000 human filovirus infections and ~13,000 deaths (mortality rate, ~40%), the overwhelming majority of which occurred during an outbreak in 2014–2015.
- Since the discovery of filoviruses in 1967, there have been ~50 natural host-to-human spillover events. Bats are thought to be the reservoir for Marburg and Ebola viruses.
- Human-to-human transmission occurs through direct contact or exposure to infected bodily fluids and tissues; there is no evidence of such transmission by aerosol or respiratory droplets.

Pathogenesis

The pathogenic hallmarks of filovirus infection include pronounced suppression of the immune system, severe disturbance of the clotting system, and impairment of vascular integrity. Although petechiae, ecchymoses, and other hemorrhagic signs are detected in internal organs, mucous membranes, and skin, actual severe blood loss is a rare event.

Clinical Manifestations

After a 3- to 25-day incubation period, pts develop a biphasic syndrome with a 1- to 2-day relative remission separating the two phases.

- The first phase lasts 5–7 days and is characterized by an abrupt onset of fever, chills, severe headache, cough, myalgia, pharyngitis, and arthralgia and the development of a maculopapular rash.
- The second phase involves the GI tract (e.g., abdominal pain, vomiting, diarrhea), respiratory tract (e.g., chest pain, cough), vascular system (e.g., postural hypotension, edema), CNS (e.g., confusion, headache, coma), and hemorrhagic manifestations.
- Early leukopenia followed by leukocytosis with a left shift, thrombocytopenia, elevated levels of liver enzymes, and prolonged coagulation is common.
- Pts typically die 4–14 days after infection. Survivors may have prolonged and incapacitating sequelae (e.g., arthralgia, asthenia, iridocyclitis, hearing loss, psychosis, transverse myelitis).
- Filoviruses can persist in the liver, eyes, or testicles of survivors for months after convalescence and can be reactivated (causing recurrent disease) or transmitted sexually.

Diagnosis

High concentrations of virus in blood can be documented by antigen-capture ELISA, virus isolation, or RT-PCR. Other diagnoses that must be excluded (as they closely mimic infection with Ebola or Marburg virus) include other VHF (particularly yellow fever), falciparum malaria, typhoid fever, and gram-negative septicemia.

TREATMENT EBOLA AND MARBURG VIRUS INFECTIONS

- Any treatment must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment (e.g., gowns, gloves, shoe covers, face shields) to prevent further transmission.
- Treatment of filovirus infections is entirely supportive as no efficacious virus-specific therapy is available.
- Several experimental therapies, including vaccines, are currently being evaluated and have demonstrated some promise in small-scale studies.



For a more detailed discussion, see Jackson AC: Rabies and Other Rhabdovirus Infections, Chap. 232, p. 1299; Kuhn JH, Peters CJ: Arthropod-Borne and Rodent-Borne Virus Infections, Chap. 233, p. 1304; and Kuhn JH: Ebolavirus and Marburgvirus Infections, Chap. 234, p. 1323, in HPIM-19.

105 HIV Infection and AIDS

DEFINITION

AIDS was originally defined empirically by the Centers for Disease Control and Prevention (CDC) as "the presence of a reliably diagnosed disease that is at least moderately indicative of an underlying defect in cell-mediated immunity in the absence of any known cause for such a defect." Following the recognition of the causative virus, HIV, and the development of sensitive and specific tests for HIV infection, the definition of AIDS has undergone substantial revision. The current surveillance definition categorizes HIV-infected persons on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte counts (**Tables 226-1**, and **226-2**, pp. 1215 and 1216, in HPIM-19). From a practical standpoint, the clinician should view HIV disease as a spectrum of disorders ranging from primary infection, with or without the acute HIV syndrome, to the asymptomatic infected state, to advanced disease characterized by opportunisitic infections and neoplasms.

ETIOLOGY AND TRANSMISSION

AIDS is caused by infection with the human retroviruses HIV-1 or 2. HIV-1 is the most common cause worldwide. These viruses are passed through sexual contact; through transfusion of contaminated blood or blood products; through sharing of contaminated needles and syringes among injection drug users; intrapartum or perinatally from mother to infant; or via breast milk. There is no evidence that the virus can be passed through casual or family contact or by insects such as mosquitoes. There is a definite, though small, occupational risk of infection for health care workers and laboratory personnel who work with HIV-infected specimens. The risk of transmission of HIV from an infected health care worker to his or her pts through invasive procedures is extremely low.

EPIDEMIOLOGY

As of January 1, 2014, an estimated 1,194,039 cumulative cases of AIDS had been diagnosed in the United States; approximately 660,000 people with an AIDS diagnosis have died. However, the death rate from AIDS has decreased substantially over the past two decades, primarily due to the increased use of effective antiretroviral drugs. Currently, an estimated 1.2 million people are living with HIV infection in the United States; approximately 13% of these individuals are unaware that they are infected. An estimated 50,000 individuals are newly infected each year in the United States; this figure has remained stable for at least 15 years. Among adults and adolescents newly diagnosed with HIV infection in 2013, ~80% were men and ~20% were women. Of new HIV/AIDS diagnoses among men, ~81% were due to male-to-male sexual contact, ~10% to heterosexual contact, and ~5% to injection drug use. Among women, ~87% were due to heterosexual contact and ~12% to injection drug use. HIV infection/AIDS is a global pandemic, especially in developing countries. At the end of 2014, the estimated number of cases of HIV infection worldwide was ~36.9 million, more than two-thirds of which were in sub-Saharan Africa; ~47% of cases were in women and 2.6 million were in children. In 2014, there were 2 million new HIV infections worldwide and 1.2 million deaths.

PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* that are defined phenotypically by the expression on the

cell surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. A co-receptor must be present with CD4 for efficient entry of HIV-1 into target cells. The two major co-receptors for HIV-1 are the chemokine receptors CCR5 and CXCR4. The CD4+ T lymphocyte and cells of monocyte lineage are the principal cellular targets of HIV.

Primary Infection

Following initial transmission, the virus infects CD4+ cells, probably T lymphocytes, monocytes, or bone marrow–derived dendritic cells. Both during this initial stage and later in infection, the lymphoid system is a major site for the establishment and propagation of HIV infection. The gut-associated lymphoid tissue (GALT) plays a role in the establishment of infection and in the early depletion of memory CD4+ T cells.

Essentially all pts undergo a viremic stage during primary infection; in some pts this is associated with the "acute retroviral syndrome," a mononucleosis-like illness (see below). This phase is important in disseminating virus to lymphoid and other organs throughout the body, and it is ultimately contained only partially by the development of an HIV-specific immune response.

Establishment of Chronic and Persistent Infection

Despite the robust immune response that is mounted following primary infection, the virus is not cleared from the body. Instead, a chronic infection develops that persists for a median time of 10 years before the untreated pt becomes clinically ill. During this period of clinical latency, the number of CD4+ T cells gradually declines, but few, if any, clinical signs and symptoms may be evident. However, active viral replication can almost always be detected by as plasma viremia and the demonstration of virus replication in lymphoid tissue. The level of steady-state viremia (referred to as the *viral set point*) at ~6 months to 1 year postinfection has important prognostic implications for the progression of HIV disease; individuals with a low viral set point at 6 months to 1 year after infection progress to AIDS more slowly than do those whose set point is very high at this time (Fig. 226-22, p. 1231, in HPIM-19).

Advanced HIV Disease

In untreated pts or in pts in whom therapy has not controlled viral replication (see below), after some period of time (often years), CD4+ T cell counts will fall below a critical level (~200/μL) and pts become highly susceptible to opportunistic diseases. The presence of a CD4+ T cell count of <200/μL or an AIDS-defining opportunistic disease establishes a diagnosis of AIDS. Control of plasma viremia by effective antiretroviral therapy, particularly maintaining the plasma viral load consistently at <50 copies of RNA per mL, even in individuals with low CD4+ T cell counts, has dramatically increased survival in these pts, including those whose CD4+ T cell counts may not increase significantly as a result of therapy.

IMMUNE ABNORMALITIES IN HIV DISEASE

A broad range of immune abnormalities has been documented in HIV-infected pts, resulting in varying degrees of immunodeficiency. These include both quantitative and qualitative defects in lymphocytes, and qualitative defects in monocyte/macrophage and natural killer (NK) cell function. Autoimmune phenomena also have been observed in HIV-infected individuals.

IMMUNE RESPONSE TO HIV INFECTION

Both humoral and cellular immune responses to HIV develop soon after primary infection (see summary in Table 226-7 and Fig. 226-26, p. 1243, in HPIM-19). Humoral responses include antibodies with HIV binding and neutralizing activity, as well as antibodies participating in antibody-dependent cellular cytotoxicity

(ADCC). Cellular immune responses include the generation of HIV-specific CD4+ and CD8+ T lymphocytes, as well as NK cells and mononuclear cells mediating ADCC. CD8+ T lymphocytes may also suppress HIV replication in a noncytolytic, non-MHC-restricted manner. This effect is mediated by soluble factors such as the CC-chemokines RANTES, MIP-1α, and MIP-1β. For the most part, the natural immune response to HIV is not adequate. Broadly reacting neutralizing antibodies against HIV are not easily generated in infected individuals, and eradication of the virus from infected individuals by naturally occurring immune responses has not been reported.

DIAGNOSIS OF HIV INFECTION

Laboratory diagnosis of HIV infection depends on the demonstration of anti-HIV antibodies and/or the detection of HIV or one of its components.

The standard screening test for HIV infection is the detection of anti-HIV antibodies using an enzyme immunoassay (EIA). This test is highly sensitive (>99.5%) and is quite specific. Most commercial EIA kits are able to detect antibodies to both HIV-1 and 2 and many also detect the HIV core antigen p24. The Western blot detects antibodies to HIV antigens of specific molecular weights. Antibodies to HIV begin to appear within 2 weeks of infection, and the period of time between initial infection and the development of detectable antibodies is rarely >3 months. Plasma p24 antigen levels rise during the first few weeks following infection, prior to the appearance of anti-HIV antibodies. A guideline for the use of these serologic tests in the diagnosis of HIV infection is depicted in Fig. 105-1.

HIV can be cultured directly from tissue, peripheral blood cells, or plasma, but this is most commonly done in a research setting. HIV genetic material can be detected using reverse transcriptase PCR (RT-PCR), branched DNA (bDNA), or nucleic acid sequence–based assay (NASBA). These tests are useful in pts with a

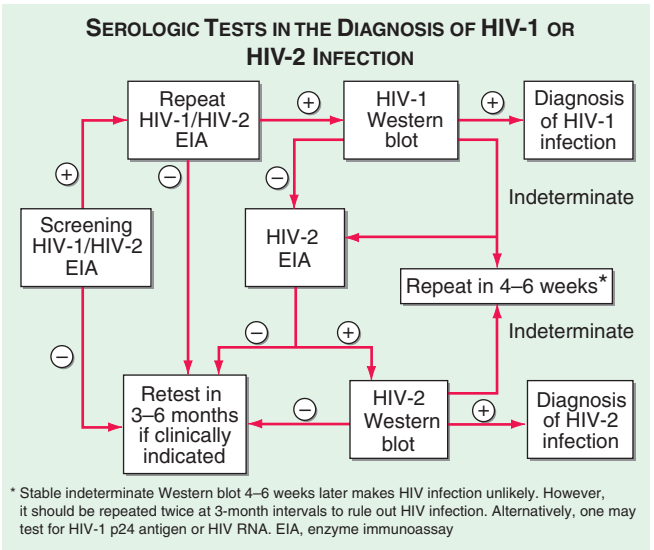


FIGURE 105-1 Algorithm for the use of serologic tests in the diagnosis of HIV-1 or HIV-2 infection.

positive or indeterminate EIA and an indeterminate Western blot. They turn positive early in infection and will usually be positive in pts in whom serologic testing may be unreliable (such as those with hypogammaglobulinemia).

LABORATORY MONITORING OF PTS WITH HIV INFECTION

Measurement of the CD4+ T cell count and level of plasma HIV RNA are important parts of the routine evaluation and monitoring of HIV-infected individuals. The CD4+ T cell count is a generally accepted indicator of the immunologic competence of the pt with HIV infection, and there is a close relationship between the CD4+ T cell count and the clinical manifestations of AIDS (Fig. 226-31, p. 1248, in HPIM-19). Pts with CD4+ T cell counts <200/μL are at higher risk of infection with *Pneumocystis jiroveci*. Once the count declines to <50/μL, pts are also at higher risk for developing CMV disease and infection with *Mycobacterium avium intracellulare*. Pts should have their CD4+ T cell count measured at the time of diagnosis and every 3–6 months thereafter. (Measurements may be done more frequently in pts with declining counts.) While the CD4+ T cell count provides information on the current immunologic status of the pt, the HIV RNA level predicts what will happen to the CD4+ T cell count in the near future. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–4 months thereafter in the untreated pt. Measurement of plasma HIV RNA is also useful in making therapeutic decisions about antiretroviral therapy (see below). Following the initiation of therapy or any change in therapy, HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. During therapy, levels of HIV RNA should be monitored every 3–6 months to evaluate the continuing effectiveness of therapy.

The sensitivity of an individual's HIV virus(es) to different antiretroviral agents can be tested by either genotypic or phenotypic assays. In the hands of experts, the use of resistance testing to select a new antiretroviral regimen in pts failing their current regimen leads to a ~0.5-log greater decline in viral load compared with the efficacy of regimens selected solely on the basis of drug history. HIV resistance testing may also be of value in selecting an initial treatment regimen in geographic areas with a high prevalence of baseline resistance.

CLINICAL MANIFESTATIONS OF HIV INFECTION

A complete discussion is beyond the scope of this chapter. The major clinical features of the various stages of HIV infection are summarized below (see also Chap. 226, HPIM-19).

Acute HIV (Retroviral) Syndrome

Approximately 50–70% of infected individuals experience an acute syndrome following primary infection. The acute syndrome follows infection by 3–6 weeks. It can have multiple clinical features (Table 105-1), lasts 1–2 weeks, and resolves spontaneously as an immune response to HIV develops and the viral load diminishes from its peak levels. Most pts will then enter a phase of clinical latency, although an occasional pt will experience rapidly progressive immunologic and clinical deterioration.

Asymptomatic Infection

The length of time between HIV infection and development of disease in untreated individuals varies greatly, but the median is estimated to be 10 years. HIV disease with active viral replication usually progresses during this asymptomatic period, and, in the absence of combination antiretroviral therapy (cART) CD4+ T cell counts fall. The rate of disease progression is directly correlated with plasma HIV RNA levels. Pts with high levels of HIV RNA progress to symptomatic disease faster than to those with low levels of HIV RNA.

TABLE 105-1 CLINICAL FINDINGS IN THE ACUTE HIV SYNDROME

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	Dermatologic
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

Source: From B Tindall, DA Cooper: *AIDS* 5:1, 1991.

Symptomatic Disease

Symptoms of HIV disease can develop at any time during the course of HIV infection. In general, the spectrum of illness changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in pts with CD4+ T cell counts <200/μL. Overall, the clinical spectrum of HIV disease is constantly changing as pts live longer and new and better approaches to treatment and prophylaxis of opportunistic infections are developed. In addition, a variety of neurologic, cardiovascular, renal, metabolic, and hepatic problems are increasingly seen in pts with HIV infection and may be a direct consequence of HIV infection. The key element to treating symptomatic complications of HIV disease, whether primary or secondary, is achieving good control of HIV replication through the use of cARTand instituting primary and secondary prophylaxis as indicated. Major clinical syndromes seen in the symptomatic stage of HIV infection are summarized below.

- *Persistent generalized lymphadenopathy:* Palpable adenopathy at two or more extrainguinal sites that persists for >3 months without explanation other than HIV infection. Many pts will go on to disease progression.
- *Constitutional symptoms:* Fever persisting for >1 month, involuntary weight loss of >10% of baseline, diarrhea for >1 month in absence of explainable cause.
- *Neurologic disease:* Most common is HIV-associated neurocognitive disease (HAND); other neurologic complications include opportunistic infections such as toxoplasmosis and cryptococcal menigitis, primary CNS lymphoma, CNS Kaposi's sarcoma, aseptic meningitis, myelopathy, peripheral neuropathy, and myopathy.
- *Secondary infectious diseases:* Common secondary infectious agents include *P. jiroveci* (pneumonia), CMV (chorioretinitis, colitis, pneumonitis, adrenalitis), *Candida albicans* (oral thrush, esophagitis), *M. avium intracellulare* (localized or disseminated infection), *M. tuberculosis* (pulmonary or disseminated), *Cryptococcus neoformans* (meningitis, disseminated disease), *Toxoplasma gondii* (encephalitis, intracerebral mass lesion), herpes simplex virus (severe mucocutaneous lesions, esophagitis), *Cryptosporidium* spp. or *Isospora belli* (diarrhea), JC virus (progressive multifocal leukoencephalopathy), bacterial pathogens (pneumonia, sinusitis, skin).
- *Secondary neoplasms:* Kaposi's sarcoma (cutaneous and visceral, more fulminant course than in non-HIV-infected pts), lymphoma (primarily B cell, may be CNS or systemic). Kaposi's sarcoma, body cavity lymphomas and multicentric Castleman's disease are associated witih HHV-8 infection while the B cell lymphomas are often associated with EBV.
- *Other diseases:* A variety of organ-specific syndromes can be seen in HIV-infected pts, either as primary manifestations of the HIV infection or as complications of treatment. Diseases commonly associated with aging are also seen with an increased frequency in pts with HIV infection.

TREATMENT HIV INFECTION (SEE ALSO CHAP. 226, HPIM-19)

General principles of pt management include counseling, psychosocial support, and screening for infections and other conditions and require comprehensive knowledge of the disease processes associated with HIV infection.

ANTIRETROVIRAL THERAPY (SEE TABLE 105-2) The cornerstone of medical management of HIV infection is combination antiretroviral therapy, or cART. Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life of pts with HIV infection. Data from observational studies and randomized controlled trials have demonstrated that cART is of benefit to the pt at any stage of HIV infection and is also associated with a decreased risk of transmitting infection to an uninfected partner. However, several important questions related to the treatment of HIV disease lack definitive answers. Among them are what is the best initial cART regimen, when should a given regimen be changed, and which drugs in a regimen should be changed when a change is made. The drugs that are currently licensed for the treatment of HIV infection are listed in Table 105-2. These drugs fall into four main categories: those that inhibit the viral reverse transcriptase enzyme, those that inhibit the viral protease enzyme, those that inhibit viral entry, and those that inhibit the viral integrase. In addition, more than a dozen combination drugs that combine 2 or more agents have been licensed (Table 105-2A). There are numerous drug–drug interactions that must be taken into consideration when using antiretroviral medications.

Nucleoside/Nucleotide Analogues These agents act by causing premature DNA-chain termination during the reverse transcription of viral RNA to proviral DNA and should be used in combination with other antiretroviral agents. The most common usage is together with another nucleoside/nucleotide analogue and a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor (see below).

Nonnucleoside Reverse Transcriptase Inhibitors These agents interfere with the function of HIV-1 reverse transcriptase by binding to regions outside the active site and causing conformational changes in the enzyme that render it inactive. These agents are very potent; however, when they are used as monotherapy, they result in the rapid emergence of drug-resistant mutants. Five members of this class, *nevirapine*, *delavirdine*, *efavirenz*, *etravirine*, *and rilpivirine* are currently available for clinical use. These drugs are licensed for use in combination with other antiretrovirals.

Protease Inhibitors These drugs are potent and selective inhibitors of the HIV-1 protease enzyme and are active in the nanomolar range. Unfortunately, as in the case of the nonnucleoside reverse transcriptase inhibitors, this potency is accompanied by the rapid emergence of resistant isolates when these drugs are used as monotherapy. Thus, the protease inhibitors should be used only in combination with other antiretroviral drugs.

HIV Entry Inhibitors These agents act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion. A variety of small molecules that bind to HIV-1 co-receptors are currently in clinical trials. The first drugs in this class to be licensed are the fusion inhibitor *enfuvirtide* and the entry inhibitor *maraviroc*.

HIV Integrase Inhibitors These drugs interfere with the integration of proviral DNA into the host cell genome. The first agent in this class, *raltegravir*, was approved in 2007 for use in treatment-experienced pts. Two other integrase inhibitors, dolutegravir and elvitegravir, are also licensed.

Choice of Antiretroviral Treatment Strategy The large number of available antiretroviral agents makes the subject of antiretroviral therapy one of the more complicated in the management of HIV-infected pts.

TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION

Drug	Status	Indication	Dose in Combination	Supporting Data	Toxicity
Nucleoside or Nucleotide Reverse Transcriptase Inhibitors					
Zidovudine (AZT, azidothymidine, Retrovir, 3′azido-3′-deoxythymidine)	Licensed	Treatment of HIV infection in combination with other antiretroviral agents	200 mg q8h or 300 mg bid	19 vs 1 death in original placebo-controlled trial in 281 patients with AIDS or ARC	Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea, nail pigmentation, lipid abnormalities, lipoatrophy, hyperglycemia
		Prevention of maternal-fetal HIV transmission		In pregnant women with CD4+ T cell count ≥200/μL, AZT PO beginning at weeks 14–34 of gestation plus IV drug during labor and delivery plus PO AZT to infant for 6 weeks decreased transmission of HIV by 67.5% (from 25.5% to 8.3%), *n* = 363	
Lamivudine (Epivir, 2′3′-dideoxy-3′-thiacytidine, 3TC)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	150 mg bid 300 mg qd	In combination with AZT superior to AZT alone with respect to changes in CD4+ T cell counts in 495 patients who were zidovudine-naïve and 477 patients who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine, they were 10–50 cells/μL above baseline; 54% decrease in progression to AIDS/death compared with AZT alone	Flare of hepatitis in HBV-co-infected patients who discontinue drug

Emtricitabine (FTC, Emtriva)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	200 mg qd	Comparable to stavudine in combination with didanosine and efavirenz in 571 treatment-naïve patients; similar to 3TC in combination with AZT or stavudine + NNRTI or PI in 440 patients doing well for ≥12 weeks on a 3TC regimen	Hepatotoxicity in HBV-co-infected patients who discontinue drug, skin discoloration
Abacavir (Ziagen)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	300 mg bid	Abacavir + AZT + 3TC equivalent to indinavir + AZT + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/μL in each group) at 24 weeks	Hypersensitivity reaction In HLA-B5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite
Tenofovir (Viread)	Licensed	For use in combination with other antiretroviral agents when treatment is indicated	300 mg qd	Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatment-experienced patients	Renal, osteomalacia, flare of hepatitis in HBV-co-infected patients who discontinue drug
Non-Nucleoside Reverse Transcriptase Inhibitors					
Nevirapine (Viramune)	Licensed	In combination with other antiretroviral agents for treatment of progressive HIV infection	200 mg/d × 14 days then 200 mg bid *or* 400 mg extended release qd	Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides	Skin rash, hepatotoxicity

(*Continued*)

TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

Drug	Status	Indication	Dose in Combination	Supporting Data	Toxicity
Efavirenz (Sustiva)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	600 mg qhs	Efavirenz + AZT + 3TC comparable to indinavir + AZT + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group achieved viral load <50 copies/mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment "failures"); CD4 cell increase (~140/μL in each group) at 24 weeks	Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic
Etravirine (Intelence)	Licensed	In combination with other antiretroviral agents in treatment-experienced patients whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications	200 mg bid	Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen	Rash, nausea, hypersensitivity reactions

Rilpivirine (Edurant)	Licensed	In combination with other drugs in previously untreated patients when treatment is indicated.	25 mg qd	Noninferior to efavirenz with respect to suppression at week 48 in 1368 treatment-naive individuals except in patients with pretherapy HIV RNA levels >100,000 where it was inferior	Nausea, dizziness, somnolence, vertigo, less CNS toxicity and rash than Efavirenz
Protease Inhibitors					
Ritonavir (Norvir)	Licensed	In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted	600 mg bid (also used in lower doses as pharmacokinetic booster)	Reduction in the cumulative incidence of clinical progression or death from 34% to 17% in patients with CD4+ T cell count <100/μL treated for a median of 6 months	Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities, may alter levels of many other drugs, paresthesias, hepatitis
Atazanavir (Reyataz)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	400 mg qd or300 mg qd + ritonavir100 mg qd when given with efavirenz	Comparable to efavirenz when given in combination with AZT + 3TC in a study of 810 treatment-naïve patients; comparable to nelfinavir when given in combination with stavudine + 3TC in a study of 467 treatment-naïve patients	Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash transaminase elevations, renal stones
Darunavir (Prezista)	Licensed	In combination with 100 mg ritonavir for combination therapy in treatment-experienced adults	600 mg + 100 mg ritonavir twice daily with food	At 24 weeks, patients with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a –1.89-log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with –0.48 log and 17 cells in the control arm	Diarrhea, nausea, headache, skin rash, hepatotoxicity, hyperlipidemia, hyperglycemia

(*Continued*)

TABLE 105-2 ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION (*CONTINUED*)

Drug	Status	Indication	Dose in Combination	Supporting Data	Toxicity
Entry Inhibitors					
Enfuvirtide (Fuzeon)	Licensed	In combination with other agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy	90 mg SC bid	In treatment of experienced patients, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks)	Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia
Maraviroc (Selzentry)	Licensed	In combination with other antiretroviral agents in adults infected with only CCR5-tropic HIV-1	150–600 mg bid depending on concomitant medications (see text)	At 24 weeks, among 635 patients with CCR5-tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo	Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms
Integrase Inhibitor					
Raltegravir (Isentress)	Licensed	In combination with other antiretroviral agents	400 mg bid	At 24 weeks, among 436 patients with 3-class drug resistance, 76% of patients randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to receive placebo	Nausea, headache, diarrhea, CPK elevation, muscle weakness, rhabdomyolysis

Elvitegravir	Licensed	In combination with other antiretroviral agents	1 tablet daily	Noninferior to raltegravir or atazanavir/ritonavir in treatment-experienced patients.	Diarrhea, nausea, upper respiratory infections, headache
Dolutegravir (Tivicay)	Licensed	In combination with other antiretroviral agents	50 mg daily for treatment-naïve patients; 50 mg twice daily for treatment-experienced patients or those also receiving efavirenz or rifampin	Noninferior to raltegravir, superior to efavirenz or darunavir/ritonavir	Insomnia, headache, hypersensitivity reactions, hepatotoxicity

Abbreviations: ARC, AIDS-related complex; NRTIs, nonnucleoside reverse transcriptase inhibitors.

TABLE 105-2A COMBINATION ANTIRETROVIRAL DRUGS USED IN THE TREATMENT OF HIV INFECTION

Drug Name	Components	Drug Name	Components
Atripla	Efavireniz, tenofovir DF (TDF), emtricitabine	Odefsey	Rilpivirine, TAF, emtricitabine
Combivir	Zidovudine, lamivudine	Prezcobix	Darunavir–cobicistat
Complera	Rilpivirine, TDF, emtricitabine	Stribild	Elvitegravir-cobicistat, TDF, emtricitabine
Epzicom	Abacavir, lamivudine	Triumeq	Dolutegravir, abacavir, lamivudine
Evotaz	Atazanavir–cobicistat	Trizivir	Abacavir, zidovudine, lamivudine
Genvoya	Elvitegravir-cobicistat, tenofovir alafenamide (TAF), emtricitabine	Truvada	TDF, emtricitabine
Kaletra	Lopinavir–ritonavir		

Source: AIDSinfo Drug Database, https://aidsinfo.nih.gov/drugs.

TABLE 105-3 PRINCIPLES OF THERAPY OF HIV INFECTION

1. Ongoing HIV replication leads to immune system damage and progression to AIDS.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Rates of disease progression differ among individuals, and treatment decisions should be individualized based on plasma HIV RNA levels and CD4+ T cell counts.
4. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.
5. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the pt has not been previously treated and that are not cross-resistant with antiretroviral agents that the pt has already received.
6. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
7. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the pt.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
10. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the pt to be compliant.

Source: Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services (**Table 105-3**). Treatment decisions must take into account the fact that one is dealing with a chronic infection and that complete eradication of HIV infection has not been achieved with currently available cART regimens. Thus, therapeutic decisions must take into account the balance between risks and benefits. At present most guidelines recommend cART for anyone with a diagnosis of HIV infection. In addition, one may wish to administer a 4-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV (see below).

When the decision to initiate therapy is made, the physician must decide which drugs to use in the initial regimen. The options for initial therapy most commonly in use today are (1) two nucleoside/nucleotide analogues (one of which is usually tenofovir or abacavir, and the other of which is usually lamivudine or emtricitabine) combined with an integrase inhibitor; (2) two nucleoside/nucleotide analogues and a protease inhibitor; or (3) two nucleoside/nucleotide analogues and a nonnucleoside reverse transcriptase inhibitor. There are no clear data at present on which to base a distinction between these approaches.

Following the initiation of therapy, one should expect a 1-log (tenfold) reduction in plasma HIV RNA within 1–2 months; eventually a decline in plasma HIV RNA to <50 copies/mL; and a rise in CD4+ T cell count of 100–150/μL during the first year. Failure to achieve and maintain an HIV RNA level <50 copies/mL is an

TABLE 105-4 INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY IN PTS WITH HIV INFECTION[a]

Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy
A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
Persistently declining CD4+ T cell numbers
Clinical deterioration
Side effects

[a]Generally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given pt. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.
Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents,* USPHS.

indication to consider a change in therapy. Other reasons for changing therapy are listed in Table 105-4. When changing therapy because of treatment failure, it is important to attempt to provide a regimen with at least two new drugs. In the pt in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable.

Treatment of Secondary Infections and Neoplasms Specific for each infection and neoplasm (see Chap. 226, in HPIM-19).

Prophylaxis against Secondary Infections

(See also Table 226-11, pp. 1251–1253, in HPIM-19)

Primary prophylaxis is clearly indicated for *P. jiroveci* pneumonia (especially when CD4+ T cell counts fall to <200 cells/μL), for *M. avium* complex infections in pts with CD4+ T cell counts <50 cells/μL, and for *M. tuberculosis* infections in pts with a positive PPD or anergy if at high risk of TB. Vaccination with the influenza and pneumococcal polysaccharide vaccines is generally recommended for all pts and may need to be repeated in pts with CD4+ T cell counts <200/μL when their counts increase to >200/μL. Secondary prophylaxis, when available, is indicated for virtually every infection experienced by HIV-infected pts until they have significant immunologic recovery.

HIV AND THE HEALTH CARE WORKER

There is a small but definite risk to health care workers of acquiring HIV infection via needle stick exposures, large mucosal surface exposures, or exposure of open wounds to HIV-infected secretions or blood products. The risk of HIV transmission after a skin puncture by an object contaminated with blood from a person with documented HIV infection is ~0.3%, compared with a 20–30% risk for hepatitis B infection from a similar incident. Postexposure prophylaxis may be effective in decreasing the likelihood of acquisition of infection through accidental exposure in the health care setting. In this regard, a U.S. Public Health Service working group has recommended that chemoprophylaxis be given as soon as possible after occupational exposure. While the precise regimen remains a subject of debate, the U.S. Public Health Service guidelines recommend a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for high-risk or otherwise complicated exposures. Regardless of which regimen is used, treatment should be initiated as soon as possible after exposure and take into count any available resistance data on the infecting virus.

Prevention of exposure is the best strategy and includes following universal precautions and proper handling of needles and other potentially contaminated objects.

Transmission of TB is another potential risk for all health care workers, including those dealing with HIV-infected pts. All workers should know their PPD status, which should be checked yearly.

VACCINES

A clinical trial conducted in Thailand demonstrated moderate (31% effective) protection against acquisition of HIV infection. However, this modest degree of efficacy does not justify deployment of the vaccine; active investigation continues in the pursuit of a safe and effective vaccine against HIV, including focusing on the induction of broadly neutralizing antibodies to HIV.

PREVENTION

Education, counseling, and behavior modification along with the consistent and correct use of condoms in risk situations remain the cornerstones of HIV prevention efforts. Avoidance of shared needle use by injection drug users (IDUs) is critical. If possible, breast-feeding should be avoided by HIV-positive women, as the virus can be transmitted to infants via this route. In societies where withholding of breast-feeding is not feasible, treatment of the mother, if possible, greatly decreases the chances of transmission. Recent studies have demonstrated the important role of medically supervised adult male circumcision in the prevention of acquisition of heterosexually transmitted HIV infection in men. In addition, pre-exposure prophylaxis with cART in men who have sex with men and in heterosexual men and women engaging in risk behaviors, has proven to be an effective means of prevention. Finally, treatment of the HIV-infected partner in heterosexual discordant couples has proved highly effective in preventing transmission of HIV to the uninfected partner.

For a more detailed discussion, see Fauci AS, Lane HC: Human Immunodeficiency Virus Disease: AIDS and Related Disorders, Chap. 226, p. 1215, in HPIM-19.

106 Fungal Infections

GENERAL CONSIDERATIONS

- *Yeasts* (e.g., *Candida*, *Cryptococcus*) appear microscopically as round, budding forms; *molds* (e.g., *Aspergillus*, *Rhizopus*) appear as filamentous forms called *hyphae*; and *dimorphic fungi* (e.g., *Histoplasma*) are spherical in tissue but appear as molds in the environment.
  - *Endemic* fungi (e.g., *Coccidioides*) are not part of the normal human microbiota and infect hosts preferentially by inhalation.
  - *Opportunistic* fungi (e.g., *Candida* and *Aspergillus*) invade the host from normal sites of colonization (e.g., mucous membranes or the GI tract).

- Definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response.

ANTIFUNGAL AGENTS

Amphotericin B (AmB)

AmB is the broadest-spectrum antifungal agent but has significant toxicities, including nephrotoxicity, fever, chills, and nausea.

- AmB has fungicidal activity and is available only for parenteral administration.
- Lipid formulations lack nephrotoxicity and infusion reactions; whether there is a clinically significant difference in efficacy between the deoxycholate and lipid formulations remains controversial.

Azoles

The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall, resulting in fungistatic activity. Azoles cause little or no nephrotoxicity and are available in oral preparations.

- *Fluconazole:* Fluconazole is available in both oral and IV formulations, has a long half-life, and penetrates into most body fluids, including ocular fluids and CSF.
  - Toxicity is minimal but includes (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, dry mouth, and metallic taste.
  - Fluconazole is useful for coccidioidal and cryptococcal meningitis and for candidemia, but it is notably ineffective against aspergillosis or mucormycosis.
  - It is effective as fungal prophylaxis in bone-marrow and high-risk liver transplant recipients.
- *Voriconazole:* Available in oral and IV formulations, voriconazole is considered the first-line agent against *Aspergillus* and has a broader spectrum than fluconazole against *Candida* species (including *C. glabrata* and *C. krusei*). It is also active against *Scedosporium* and *Fusarium*.
  - Disadvantages of voriconazole (compared to fluconazole) include multiple drug interactions, hepatotoxicity, skin rashes (including photosensitivity), visual disturbances, and the need to monitor drug levels.
  - As it is metabolized completely by the liver, dose adjustments are required in pts with liver failure. Dose adjustments for renal insufficiency are not required, but the parenteral formulation should be avoided in pts with severe renal insufficiency given the presence of cyclodextrin.
- *Itraconazole:* Available in oral and IV formulations, itraconazole is the drug of choice for mild to moderate blastomycosis and histoplasmosis. It is approved by the FDA for use in febrile neutropenic pts. Disadvantages of itraconazole include its poor penetration into CSF, the use of cyclodextrin in both the oral suspension and the IV preparation, the variable absorption of the drug in capsule form, and the need for monitoring of blood levels in pts taking capsules for disseminated mycoses.
- *Posaconazole:* Approved for prophylaxis of aspergillosis and candidiasis in high-risk immunocompromised pts, posaconazole is also effective against fluconazole-resistant *Candida* isolates and may be useful as salvage therapy for some other fungal infections.

Echinocandins

The echinocandins, including caspofungin, anidulafungin, and micafungin, act by inhibiting the β-1,3-glucan synthase that is necessary for fungal cell wall synthesis. These agents are considered fungicidal for *Candida* and fungistatic for *Aspergillus*.

- Among the safest antifungal agents, echinocandins offer broad-spectrum fungicidal activity against all *Candida* species, and caspofungin has been efficacious as salvage therapy for aspergillosis.

- If anidulafungin or micafungin is used in combination with cyclosporine, no dose adjustment is needed for either drug.

Flucytosine

Flucytosine has excellent CSF penetration, but development of resistance has led to its almost always being used in combination with AmB (e.g., for cryptococcal meningitis). Adverse effects include bone marrow suppression.

Griseofulvin and Terbinafine

Griseofulvin is used primarily for ringworm infection. Terbinafine is used for onychomycosis and ringworm and is as effective as itraconazole.

Topical Agents

Many drug classes are used for topical treatment of common fungal skin infections: azoles (e.g., clotrimazole, miconazole), polyene agents (e.g., nystatin), and other classes (e.g., ciclopirox olamine, terbinafine).

CANDIDIASIS

Microbiology and Epidemiology

Candida is a small, thin-walled, ovoid yeast that reproduces by budding and occurs in three forms in tissue: blastospores, pseudohyphae, and hyphae.

- *Candida* is ubiquitous in nature and inhabits the GI tract, the female genital tract, and the skin. Dissemination probably results from fungal entry into the bloodstream from mucosal surfaces after the organisms have multiplied to large numbers as a result of bacterial suppression by antibacterial drugs.
- *C. albicans* is common, but non-*albicans* species (e.g., *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*) now cause ~50% of all cases of candidemia and disseminated candidiasis.
  - *Candida* spp. represent the fourth most common blood-culture isolate from hospitalized pts in the United States.
  - Pts with a compromised immune system, pts with indwelling catheters, pts with severe burns, and neonates of low birth weight are at risk for hematogenous dissemination.

Clinical Manifestations

The severity of candidal infections ranges from mild to life threatening, with deep organ infections being at the more severe end of the spectrum.

- *Mucocutaneous candidiasis: Thrush* is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus.
  - *Vulvovaginal candidiasis* presents as pruritus, pain, and a vaginal discharge that may contain whitish "curds."
  - Other cutaneous infections include paronychia, balanitis, and intertrigo (erythematous irritation with pustules in skin folds).
  - *Chronic mucocutaneous candidiasis* is a heterogeneous infection of hair, nails, skin, and mucous membranes that persists despite therapy and is associated with a dysfunctional immune system.
- *Deeply invasive candidiasis:* These infections are most commonly due to hematogenous seeding of organs during candidemia, but they can also be due to contiguous spread of organisms after disruption of normal anatomic barriers (e.g., kidney infection associated with an indwelling urinary catheter).
  - Nearly any organ can be infected, but the brain, chorioretina, heart, and kidneys are most commonly involved. Except in neutropenic pts, the liver and spleen are less often infected.
  - Skin involvement manifests as macronodular lesions.

– Chorioretinal or skin involvement predicts a high probability of abscess formation in deep organs from generalized hematogenous seeding.

Diagnosis

The most challenging aspect of diagnosis is determining which pts have hematogenously disseminated disease; recovery of *Candida* from sputum, urine, or peritoneal catheters may reflect colonization rather than deep infection.

- The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae in the presence of inflammation in appropriate clinical samples.
- The β-glucan test has a negative predictive value of ~90% and can help exclude disseminated disease.

TREATMENT CANDIDIASIS

- *Mucocutaneous candidiasis:* Azoles are preferred; nystatin is an alternative.
  - Topical applications are appropriate when possible.
  - Oral therapy can be used for vulvovaginal infections (fluconazole, 150 mg PO as a single dose) and esophageal infections (fluconazole, 100–200 mg/d; or itraconazole, 200 mg/d).
- *Candidemia and suspected disseminated candidiasis:* All pts with candidemia should be treated with a systemic antifungal agent for at least 2 weeks after the last positive blood culture.
  - Lipid formulations of AmB, echinocandins, and fluconazole or voriconazole are all effective; no agent within a given class is clearly superior to the others.
  - The choice of antifungal drug depends on local epidemiology and susceptibility profiles.
  - Neutropenic or hemodynamically unstable pts should be treated with broader-spectrum agents (e.g., AmB, echinocandins) until the pathogen is specifically identified and a clinical response assessed.
  - Fluconazole is preferred for nonneutropenic, hemodynamically stable pts when azole resistance is not considered likely.
  - When possible, foreign materials (e.g., catheters) should be removed or replaced.
  - All pts with candidemia should undergo an ophthalmologic examination because of high rates of *Candida* endophthalmitis, which may require partial vitrectomy.
  - *Candida* endocarditis should be treated with valve removal and long-term antifungal administration (see Chap. 80).
  - *Candida* meningitis is often treated with a polyene plus flucytosine (25 mg/kg qid).
  - Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term antifungal therapy.

Prevention

Allogeneic stem cell and high-risk liver transplant recipients typically receive prophylaxis with fluconazole (400 mg/d). Some centers also use antifungal prophylaxis for neutropenic pts.

ASPERGILLOSIS

Microbiology and Epidemiology

Aspergillus, a mold with septate hyphae branching at 45° angles, has vast numbers of conidia (spores). It has a worldwide distribution and typically grows in decomposing

plant materials and in bedding. *A. fumigatus* is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes.

- Inhalation is common; only intense exposures cause disease in healthy, immunocompetent individuals.
- The primary risk factors for invasive aspergillosis are profound neutropenia, glucocorticoid use, therapy with immune modulators (e.g., TNF-α inhibitors, daclizumab, rituximab), and severe liver disease.
- Pts with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary diseases (e.g., tuberculosis, sarcoidosis).

Clinical Manifestations

More than 80% of invasive disease cases involve the lungs; in pts who are significantly immunocompromised, virtually any organ can be affected.

- *Invasive pulmonary aspergillosis:* Pts can be asymptomatic or can present with fever, cough, chest discomfort, hemoptysis, and shortness of breath.
  - Acute and subacute forms have courses of ≤1 month and 1–3 months, respectively.
  - Early diagnosis requires a high index of suspicion, screening for circulating antigen (in leukemia), and urgent CT of the chest.
- *Invasive sinusitis:* Pts have fever, nasal or facial discomfort, and nasal discharge. The sinuses are involved in 5–10% of cases of invasive aspergillosis; sinus involvement is especially likely in leukemic pts and hematopoietic stem cell transplant recipients.
- *Disseminated aspergillosis: Aspergillus* disseminates from lung to brain, skin, thyroid, bone, and other organs, after which pts develop skin lesions and deteriorate clinically over 1–3 days, with fever and signs of mild sepsis. Blood cultures are usually negative.
  - *Cerebral aspergillosis:* Single or multiple lesions, hemorrhagic infarction, and cerebral abscess are common. The presentation can be acute or subacute, with mood changes, focal signs, seizures, and a decline in mental status. MRI is the most useful investigation.
  - *Cutaneous aspergillosis:* Dissemination of *Aspergillus* occasionally results in cutaneous features, usually an erythematous or purplish nontender area that develops into a necrotic eschar.
- *Chronic pulmonary aspergillosis:* Pts develop one or more cavities that expand over months or years, with pulmonary symptoms, fatigue, and weight loss. Pericavitary infiltrates and multiple cavities are typical. Without treatment, pulmonary fibrosis can develop.
- *Aspergilloma:* A fungal ball occurs in up to 20% of residual chest cavities ≥2.5 cm in diameter. Life-threatening hemoptysis may occur.
- *Chronic sinusitis:* Pts develop one of three presentations: a fungal ball in the maxillary sinus; chronic invasive sinusitis that is slowly destructive; or chronic granulomatous sinusitis, which is most common in the Middle East and India and is often caused by *A. flavus*.
- *Allergic bronchopulmonary aspergillosis (ABPA):* A hypersensitivity reaction leads to bronchial plugging, coughing fits, and dyspnea, primarily affecting asthmatics and pts with cystic fibrosis. Total IgE levels are usually >1000 IU/mL.

Diagnosis

Culture, molecular testing, antigen detection, and histopathology usually confirm the diagnosis; ~40% of cases of invasive aspergillosis are diagnosed only at autopsy.

- Culture may be falsely positive (e.g., in pts with airway colonization) or falsely negative; only 10–30% of pts with invasive *Aspergillus* have a positive culture at any time.

- Galactomannan antigen testing of serum from high-risk pts is best done prospectively, as positive results precede clinical disease; false-positive results can occur (in association, for example, with certain β-lactam/β-lactamase inhibitor antibiotic combinations).
- A *halo sign* on high-resolution thoracic CT scan (a localized ground-glass appearance representing hemorrhagic infarction surrounding a nodule) suggests the diagnosis.

TREATMENT ASPERGILLOSIS

- See Table 106-1 for recommended treatments and doses.
  - The duration of treatment for pts with invasive aspergillosis varies from ~3 months to years, depending on the host and the response.
  - Chronic cavitary pulmonary aspergillosis probably requires treatment for life.
- Surgical treatment is important for some forms of aspergillosis (e.g., maxillary sinus fungal ball; single aspergilloma; invasive disease of bone, heart valve, brain, or sinuses).

Outcome

Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The overall mortality rate is ~50% with treatment, but the disease is uniformly fatal without therapy.

CRYPTOCOCCOSIS

Microbiology and Epidemiology

Cryptococcus is a yeast-like fungus. *C. neoformans* and *C. gattii* are pathogenic for humans and can cause cryptococcosis; most clinical laboratories do not routinely distinguish between these species.

- Worldwide, there are ~1 million cases of cryptococcosis, with >600,000 deaths annually. Most cases are in pts with AIDS.
- Cryptococcosis due to *C. neoformans* is rare in the absence of impaired immunity; in contrast, *C. gattii*–related disease often occurs in immunocompetent pts.
- *C. neoformans* is found in soil contaminated with pigeon droppings, whereas *C. gattii* is associated with eucalyptus trees. Most cases are acquired via inhalation, which results in pulmonary infection.

Clinical Manifestations

The clinical manifestations of cryptococcosis reflect the site of fungal infection, usually involving the CNS and/or the lungs.

- CNS involvement most commonly presents as chronic meningoencephalitis, with headache, fever, lethargy, sensory and memory deficits, cranial nerve paresis, visual deficits, and meningismus (absent in some cases) lasting for weeks.
- Pulmonary cryptococcosis is generally asymptomatic but can present as cough, increased sputum production, and chest pain. *Cryptococcomas* are granulomatous pulmonary masses associated with *C. gattii* infections.
- Skin lesions are common in pts with disseminated cryptococcosis and can be highly variable, including papules, plaques, purpura, vesicles, tumor-like lesions, and rashes.

Diagnosis

Diagnosis requires the demonstration of *C. neoformans* in normally sterile tissue (e.g., positive cultures of CSF or blood).

TABLE 106-1 TREATMENT OF ASPERGILLOSIS[a]

Indication	Primary Treatment	Evidence Level[b]	Precautions	Secondary Treatment	Comments
Invasive[c]	Voriconazole	AI	Drug interactions (especially with rifampin), renal failure (IV only)	AmB, caspofungin, posaconazole, micafungin	As primary therapy, voriconazole carries 20% more responses than AmB. Consider initial combination therapy with an echinocandin in non-neutropenic pts.
Prophylaxis	Posaconazole, itraconazole solution	AI	Diarrhea and vomiting with itraconazole, vincristine interaction	Micafungin, aerosolized AmB	Some centers monitor plasma levels of itraconazole and posaconazole.
Single aspergilloma	Surgery	BII	Multicavity disease: poor outcome of surgery, medical therapy preferable	Itraconazole, voriconazole, intracavity AmB	Single large cavities with an aspergilloma are best resected.
Chronic pulmonary[c]	Itraconazole, voriconazole	BII	Poor absorption of itraconazole capsules with proton pump inhibitors or H_2 blockers	Posaconazole, IV AmB, IV micafungin	Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic.
ABPA/SAFS	Itraconazole	AI	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole, posaconazole	Long-term therapy is helpful in most cases. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis.

[a]For information on duration of therapy, see text.
[b]Evidence levels are those used in treatment guidelines (TJ Walsh et al: Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America [IDSA]. Clin Infect Dis 46:327, 2008).
[c]An infectious disease consultation is appropriate for these pts.
Note: The oral dose is usually 200 mg bid for voriconazole and itraconazole and 400 mg bid for posaconazole suspension. The IV dose of voriconazole for adults is 6 mg/kg twice at 12-h intervals (loading doses) followed by 4 mg/kg q12h; a larger dose is required for children and teenagers. Plasma monitoring is helpful in optimizing the dosage. Caspofungin is given as a single loading dose of 70 mg and then at 50 mg/d; some authorities use 70 mg/d for pts weighing >80 kg, and lower doses are required with hepatic dysfunction. Micafungin is given as 50 mg/d for prophylaxis and as at least 150 mg/d for treatment; this drug has not yet been approved by the FDA for this indication. AmB deoxycholate is given at a daily dose of 1 mg/kg if tolerated. Several strategies are available for minimizing renal dysfunction. Lipid-associated AmB is given at 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet). Different regimens are available for aerosolized AmB, but none is FDA approved. Other considerations that may alter dose selection or route include age; concomitant medications; renal, hepatic, or intestinal dysfunction; and drug tolerability.
Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AmB, amphotericin B; SAFS, severe asthma with fungal sensitization.

- India ink smear of CSF is a useful rapid diagnostic technique but may yield negative results in pts with a low fungal burden.
- Cryptococcal antigen testing of CSF and/or serum provides strong presumptive evidence for cryptococcosis; such testing often yields negative results in pulmonary cryptococcosis and is of limited utility in monitoring response to therapy.

TREATMENT CRYPTOCOCCOSIS

- Immunocompetent pts
  - Pulmonary cryptococcosis is treated with fluconazole (200–400 mg/d) for 3–6 months.
  - Severe extrapulmonary cryptococcosis may initially require AmB (0.5–1.0 mg/kg daily for 4–6 weeks).
  - CNS disease is treated with an induction phase of AmB (0.5–1.0 mg/kg qd) followed by prolonged consolidation therapy with fluconazole (400 mg/d).
  - Meningoencephalitis is treated with AmB (0.5–1.0 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks or with the same drugs at the same dosages for 2 weeks followed by fluconazole (400 mg/d) for ≥10 weeks.
- Immunosuppressed pts are treated with the same initial regimens except that maintenance therapy with fluconazole is given for a prolonged period (sometimes throughout life) to prevent relapse.
  - HIV-infected pts with CNS involvement are typically treated with AmB (0.7–1.0 mg/kg daily) plus flucytosine (100 mg/kg qd) for at least 2 weeks followed by fluconazole (400 mg/d) for 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d).
  - An alternative regimen involves fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg qd) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy.
- Newer triazoles (e.g., voriconazole, posaconazole) appear effective, but clinical experience is still limited.

MUCORMYCOSIS

Microbiology and Epidemiology

Mucormycosis is caused by fungi of the order Mucorales, most commonly *Rhizopus oryzae*; despite the name of the disease, *Mucor* species are only rarely the cause.

- Mucorales have characteristic wide (≥6- to 30-μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles.
- These ubiquitous environmental fungi primarily affect pts with diabetes, solid organ or hematopoietic stem cell transplants, prolonged neutropenia, malignancy, and deferoxamine treatment for iron overload syndromes.

Clinical Manifestations

Mucormycosis is highly invasive and relentlessly progressive, with a mortality rate of >40%. The disease is usually categorized by the anatomic site involved.

- *Rhinocerebral mucormycosis:* In this, the most common form of the disease, pts initially have nonspecific symptoms that include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling.
  - If untreated, the infection can spread from the ethmoid sinus to the orbit, affecting extraocular muscle function and being associated with proptosis and chemosis.
  - The visual appearance of infected tissue may progress from normal to erythematous to violaceous to a black necrotic eschar.

- *Pulmonary mucormycosis:* In this second most common manifestation, pts typically present with fever, dyspnea, cough, and chest pain. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Differentiation from aspergillosis is critical as treatment regimens differ; the presence of ≥10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely.
- *Cutaneous mucormycosis:* Caused by external implantation or hematogenous dissemination, necrotizing fasciitis due to mucormycosis has a mortality rate of ~80%.
- *Hematogenously disseminated mucormycosis:* Infection can disseminate from any primary site of infection to any organ but most commonly metastasizes to the brain (with a mortality rate of ~100%).

Diagnosis

Although definitive diagnosis requires a positive culture from a sterile site, a positive culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage [BAL] fluid) in a pt with a consistent clinical history should prompt treatment pending confirmation of the diagnosis.

- The fact that only ~50% of pts have positive cultures is due, in part, to the organisms' being killed by the tissue homogenization required for preparation of culture.
- The laboratory should be notified that mucormycosis is being considered so that tissue sections instead of tissue homogenates can be cultured.

TREATMENT MUCORMYCOSIS

- The successful treatment of mucormycosis requires four steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement; and (4) prompt antifungal therapy.
- AmB (AmB deoxycholate, 1–1.5 mg/kg qd; or liposomal AmB, 5–10 mg/kg qd) is preferred.
  - Limited retrospective data suggest that combinations of echinocandins and liposomal AmB may be more effective.
  - Although posaconazole has in vitro activity against Mucorales, few clinical data support its use.
  - Initial clinical trials suggest that liposomal AmB combined with deferasirox (an iron chelator that is fungicidal for clinical isolates of Mucorales; 20 mg/kg PO qd for 2–4 weeks) results in improved survival rates.
  - Treatment should be continued until (1) resolution of clinical signs and symptoms of infection, (2) resolution or stabilization of residual radiographic signs of disease on serial imaging, and (3) resolution of underlying immunosuppression.

HISTOPLASMOSIS

Microbiology and Epidemiology

Histoplasma capsulatum, a dimorphic fungus, causes histoplasmosis.

- Mycelia are infectious and have microconidial and macroconidial forms. Microconidia are inhaled, reach the alveoli, and are transformed into yeasts with occasional narrow budding. A granulomatous reaction results; in pts with impaired cellular immunity, infection may disseminate.
- Histoplasmosis is the most prevalent endemic mycosis in North America and is also found in Central and South America, Africa, and Asia. In the United States, histoplasmosis is endemic in the Ohio and Mississippi river valleys.
- The fungus is found in soil, particularly that enriched by droppings of birds and bats.

Clinical Manifestations

Depending on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host, disease can range from asymptomatic to life-threatening.

- Immunocompetent pts usually have asymptomatic or mild and self-limited disease.
  - Approximately 1–4 weeks after exposure, some pts develop a flu-like illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain. 5–10% of pts with acute histoplasmosis develop arthralgia or arthritis, often associated with erythema nodosum.
  - Hilar or mediastinal lymphadenopathy may occur and can cause vascular or tracheoesophageal compression.
- Immunocompromised pts, who are more likely to develop progressive disseminated histoplasmosis (PDH), account for ~70% of cases.
  - The clinical spectrum ranges from a rapidly fatal course with diffuse interstitial or reticulonodular lung infiltrates, shock, and multiorgan failure to a subacute course with focal organ involvement, hepatosplenomegaly, fever, and weight loss.
  - Meningitis, oral mucosal ulcerations, GI ulcerations, and adrenal insufficiency can occur.
- Chronic cavitary histoplasmosis most often affects smokers with structural lung disease (e.g., emphysema) and presents as productive cough, dyspnea, low-grade fever, night sweats, and weight loss.

Diagnosis

Fungal culture remains the gold standard, but cultures are often negative in less severe cases and may take up to 1 month to become positive.

- In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood; cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis.
- Fungal stains of cytopathology or biopsy materials may be helpful in diagnosing PDH.
- *Histoplasma* antigen assay of body fluids (e.g., blood, urine, CSF, BAL fluid) is useful in diagnosing PDH or acute disease and in monitoring the response to treatment.
- Serology can be helpful in diagnosis but requires ≥1 month for antibody production.

TREATMENT HISTOPLASMOSIS

- See Table 106-2 for treatment recommendations.
- Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy.

COCCIDIOIDOMYCOSIS

Microbiology and Epidemiology

Coccidioidomycosis is caused by the two species of the dimorphic soil-dwelling fungus *Coccidioides*: *C. immitis* and *C. posadasii*. These organisms exist as branching, filamentous molds.

- Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. The disease is highly endemic in California, Arizona, and other areas of the southwestern United States, with ~43 cases per 100,000 residents in 2011; northern Mexico and localized regions in Central and South America also account for cases of infection.

TABLE 106-2 RECOMMENDATIONS FOR THE TREATMENT OF HISTOPLASMOSIS

Type of Histoplasmosis	Treatment Recommendations	Comments
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Pts with mild cases usually recover without therapy, but itraconazole should be considered if the pt's condition has not improved after 1 month.
Chronic/cavitary pulmonary	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until cerebrospinal fluid or CT abnormalities clear.

Abbreviation: AmB, amphotericin B.

- Direct exposure to soil harboring *Coccidioides* increases risk, but infection, which results from inhalation of airborne arthroconidia, can occur without overt soil exposure and may be related to other climatic factors (e.g., periods of dryness after rainy seasons).

Clinical Manifestations

Approximately 60% of infected pts are asymptomatic; the remaining 40% have primarily pulmonary disease characterized by fever, cough, and pleuritic chest pain.

- Primary pulmonary infection is sometimes associated with erythema nodosum, erythema multiforme, arthralgias, and arthritis.
  - A history of night sweats, profound fatigue, eosinophilia, and hilar or mediastinal lymphadenopathy suggests the disease.
  - Pneumonic complications include pulmonary nodules (resembling pulmonary malignancies) and pulmonary cavities (a thin-walled lesion in a bronchus that is associated with cough, hemoptysis, and pleuritic chest pain).
- Disseminated infection affects <1% of infected pts, most commonly pts with depressed cellular immunity and pregnant women.
  - Common sites for dissemination include bone, skin, joint, soft tissue, and meninges.
  - Pts with meningitis present with persistent headache, lethargy, confusion, mild to moderate nuchal rigidity, and CSF with lymphocytic pleocytosis and profound hypoglycorrhachia. The mortality rate is ~100% without treatment.

Diagnosis

Clinical findings that suggest coccidioidomycosis include eosinophilia, hilar or mediastinal adenopathy on radiographic imaging, marked fatigue, and failure to improve with antibiotic therapy. Serology and culture are the primary means of diagnosis. Alert the laboratory of the possible diagnosis to avoid exposure.

- Tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion, and an enzyme immunoassay (EIA) are available to detect IgM and IgG antibodies.
  - TP antibody does not gauge disease progression and is not found in CSF.
  - Rising CF titers in serum are associated with clinical progression, and CF antibody in CSF indicates meningitis.
  - EIA frequently yields false-positive results.
- Examination of sputum or other respiratory fluids after Papanicolaou or Gomori methenamine silver staining reveals spherules in many pts with pulmonary disease.

TREATMENT COCCIDIOIDOMYCOSIS

- The vast majority of pts with coccidioidomycosis do not require treatment. Exceptions include the following:
  - Pts with focal primary pneumonia *and* underlying cellular immunodeficiency or prolonged symptoms (i.e., symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of >10%, a serum CF antibody titer of >1:16, and extensive pulmonary involvement apparent on CXR) should be treated with fluconazole (≥400 mg/d) or itraconazole (400–600 mg/d).
  - Pts with diffuse pulmonary disease are often treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 5 mg/kg IV qd), with a switch to prolonged therapy with an oral triazole once clinical improvement occurs.
  - Pts with chronic pulmonary disease or disseminated infection are treated with a triazole for ≥1 year. Relapse occurs in 15–30% of individuals once therapy is discontinued.
  - Pts with meningitis require lifelong triazole therapy; fluconazole is the drug of choice. If triazole therapy fails, intrathecal or intraventricular AmB may be used. Relapse occurs in 80% of pts when therapy is stopped.

BLASTOMYCOSIS

Microbiology and Epidemiology

Blastomyces dermatitidis is a dimorphic fungus that is found in the southeastern and south-central states bordering the Mississippi and Ohio river basins, in areas of the United States and Canada bordering the Great Lakes and the St. Lawrence River, and sporadically in Africa, the Middle East, and India. Infection is caused by inhalation of *Blastomyces* from moist soil rich in organic debris.

Clinical Manifestations

Acute pulmonary infection can present as abrupt-onset fever, chills, pleuritic chest pain, myalgias, and arthralgias. However, most pts with pulmonary blastomycosis have chronic indolent pneumonia with fever, weight loss, productive cough, and hemoptysis. Skin disease is common and can present as verrucous (more common) or ulcerative lesions. Blastomycosis can include osteomyelitis in one-fourth of infections and CNS disease in ~40% of pts with AIDS.

Diagnosis

Smears of clinical samples or cultures of sputum, bronchial washings, pus, or tissue are required for diagnosis. Antigen detection in urine and serum may help diagnose infection and monitor pts during therapy.

TREATMENT BLASTOMYCOSIS

- Every pt should be treated because of the high risk of dissemination.
  - For immunocompetent pts with nonsevere disease that does not involve the CNS, itraconazole (200–400 mg/d for 6–12 months) is recommended.
  - Immunocompetent pts with severe disease or CNS manifestations should be treated initially with AmB (deoxycholate, 0.7–1 mg/kg IV qd; liposomal, 3–5 mg/kg IV qd); once their clinical condition improves, therapy can be switched to itraconazole (or, for those with CNS disease, fluconazole, 800 mg/d).
  - Immunocompromised pts with any form of infection should be treated initially with AmB, with a switch to a triazole, as above, once clinical improvement has occurred.

MALASSEZIA INFECTION

Malassezia species are components of the normal skin flora and can cause tinea (pityriasis) versicolor, round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. *M. furfur* causes catheter-related fungemia in premature neonates receiving IV lipids by central venous catheter. Topical creams and lotions for 2 weeks are effective in treating superficial *Malassezia* infections; fungemia caused by *Malassezia* species is treated with AmB or fluconazole, prompt removal of the catheter, and discontinuation of the lipid infusion.

SPOROTRICHOSIS

Microbiology and Epidemiology

Sporothrix schenckii is a dimorphic fungus found worldwide in soil, on plants, and on animals. Infection, which results from inoculation of the organism into the skin, is most common among people who participate in landscaping, gardening, or tree farming.

Clinical Manifestations

Lymphocutaneous sporotrichosis involves secondary lesions (papules that are not very painful and often ulcerate) developing along lymphatic channels proximally from the initial site of inoculation. Other presentations include a fixed lesion (verrucous or ulcerative) at the initial site of inoculation without lymphatic spread, osteoarticular disease (chronic synovitis or septic arthritis in alcoholics), pulmonary disease (most common among pts with chronic obstructive pulmonary disease), and disseminated disease (numerous skin lesions with occasional spread to visceral organs in immunocompromised pts).

Diagnosis

Culture of material from a skin lesion or histopathologic examination of a skin biopsy sample can confirm the diagnosis.

TREATMENT SPOROTRICHOSIS

- Cutaneous and lymphocutaneous sporotrichosis is treated with itraconazole (200 mg/d) until 2–4 weeks *after* lesions resolve, usually for a total of 3–6 months.
- For extracutaneous disease, itraconazole (200 mg bid for ≥12 months) can be given, but initial therapy with liposomal AmB (3–5 mg/kg qd) is more effective for life-threatening pulmonary disease or disseminated infection.

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis (South American blastomycosis) is caused by *Paracoccidioides brasiliensis*, a dimorphic fungus acquired by inhalation from environmental

sources. Acute infection occurs in young or immunocompromised pts and manifests as disseminated infection of the reticuloendothelial system. Chronic infection accounts for 90% of cases and presents primarily as progressive pulmonary disease with occasional ulcerative and nodular mucocutaneous lesions in the nose and mouth. Diagnosis relies on culture of the organism. Itraconazole (100–200 mg/d for 6–12 months) is effective, but AmB may be required for seriously ill pts.

PENICILLIOSIS

Penicillium marneffei is a leading cause of opportunistic infection in pts with immunocompromise (e.g., due to AIDS) in Southeast Asia and is acquired by spore inhalation. Clinical manifestations are similar to those of disseminated histoplasmosis, with fever, fatigue, weight loss, lymphadenopathy, hepatomegaly, and skin lesions resembling molluscum contagiosum. The organism grows readily in culture and produces a distinctive red pigment. AmB is the initial treatment of choice for severely ill pts; less severe disease may be treated with itraconazole (200 mg bid for 12 weeks). Suppressive therapy with itraconazole (200 mg/d) may be indicated for pts with HIV infection or AIDS.

FUSARIOSIS

Fusarium species are found worldwide in soil and on plants; inhalation, ingestion, and direct inoculation of spores can cause disease, particularly disseminated disease in immunocompromised pts. Fusariosis is angioinvasive and has clinical manifestations similar to those of aspergillosis. One difference is that painful nodular or necrotic skin lesions are extremely common with disseminated fusariosis. Blood cultures are positive in 50% of cases; the organism is difficult to differentiate from *Aspergillus* in tissue. *Fusarium* species are often resistant to antifungal agents; liposomal AmB (≥5 mg/kg qd), voriconazole (200–400 mg bid), or posaconazole (300 mg/d) is recommended. Even with treatment, mortality rates are ~50%.

SCEDOSPORIOSIS

Pseudallescheria boydii, *Scedosporium apiospermum*, and *S. prolificans* are molds that are angioinvasive, causing pneumonia and widespread dissemination with abscesses (including brain abscess) in immunocompromised hosts. Most disseminated infections are fatal. These organisms are resistant to AmB, echinocandins, and some azoles, but some infections have been cured with voriconazole.

DERMATOPHYTOSIS

See Chap. 60.



For a more detailed discussion, see Edwards JE Jr: Diagnosis and Treatment of Fungal Infections, Chap. 235, p. 1329; Hage CA, Wheat LJ: Histoplasmosis, Chap. 236, p. 1332; Ampel NM: Coccidioidomycosis, Chap. 237, p. 1334; Sullivan DC, Nolan RL III: Blastomycosis, Chap. 238, p. 1337; Casadevall A: Cryptococcosis, Chap. 239, p. 1339; Edwards JE Jr: Candidiasis, Chap. 240, p. 1342; Denning DW: Aspergillosis, Chap. 241, p. 1345; Spellberg B, Ibrahim AS: Mucormycosis, Chap. 242, p. 1350; Kauffman CA: Superficial Mycoses and Less Common Systemic Mycoses, Chap. 243, p. 1353, in HPIM-19.

107 *Pneumocystis* Infections

Pneumocystis, an opportunistic fungal pulmonary pathogen, is an important cause of pneumonia in immunocompromised hosts.

MICROBIOLOGY

- *P. jirovecii* infects humans, whereas *P. carinii*—the original species described—infects rodents.
- Developmental stages include the small trophic form, the cyst, and the intermediate precyst stage.

EPIDEMIOLOGY

- *Pneumocystis* is found worldwide, and most people are exposed to the organism early in life.
- Infections resulting from environmental sources and person-to-person transmission have been demonstrated; the role of airborne transmission is unclear.
- Defects in cellular and humoral immunity (e.g., due to HIV infection, malignancy, transplantation, immunosuppressive medications) predispose to *Pneumocystis* pneumonia (PCP). The incidence among HIV-infected pts is inversely related to the CD4+ T-cell count: ≥80% of cases occur at counts <200 cells/μL, and most cases develop at counts <100/μL.

PATHOGENESIS

- The organisms are inhaled into the alveolar space, where they proliferate, provoking a mononuclear cell response. Alveoli become filled with and are damaged by proteinaceous material, with consequently increased alveolar–capillary injury and surfactant abnormalities.
- On histology, alveoli are seen to be filled with foamy, vacuolated exudates.

CLINICAL MANIFESTATIONS

- Pts develop dyspnea, fever, and nonproductive cough.
  - HIV-infected pts often have an indolent course that presents as mild exercise intolerance or chest tightness without fever or cough. Over days to months, these pts develop the more typical symptoms of PCP.
  - Some pts with HIV infection and most pts with other types of immunosuppression have more acute disease that progresses over a few days to respiratory failure.
- Physical examination findings are nonspecific and invariably include hypoxemia. Pts may initially have a normal chest examination but later, without treatment, develop diffuse rales and signs of consolidation.
- Serum levels of LDH may be elevated because of pulmonary damage, but this finding is neither sensitive nor specific.
- CXR classically reveals bilateral diffuse interstitial infiltrates that are perihilar and symmetrical, although this finding is not specific for PCP. Cysts and pneumothoraces are common CXR findings. Chest CT shows diffuse ground-glass opacities in virtually all pts with PCP, and a normal chest CT essentially rules out the diagnosis.
- Rare cases of disseminated infection have been described, generally involving lymph nodes, spleen, and liver.

DIAGNOSIS

- Histopathologic staining makes the definitive diagnosis.
  - Cell-wall stains (e.g., methenamine silver) are used for *Pneumocystis* cysts and Wright-Giemsa stains for the nuclei of all developmental stages.
  - Immunofluorescence with monoclonal antibodies increases diagnostic sensitivity.
- The demonstration of organisms in bronchoalveolar lavage fluid is almost 100% sensitive and specific for PCP in immunocompromised pts.
- While detection of organisms in expectorated sputum or throat swabs has very low sensitivity, detection in an induced sputum sample can be—depending on the experience of the center conducting the test—highly sensitive (up to 90%) and specific.
- DNA amplification by PCR is most sensitive but may not distinguish colonization from infection.

TREATMENT *PNEUMOCYSTIS* INFECTIONS

- Trimethoprim-sulfamethoxazole (TMP-SMX) for 14–21 days is the regimen of choice for all pts. For doses and adverse effects of TMP-SMX and alternative regimens, see **Table 107-1**.
- For HIV-infected (and likely all) pts with moderate to severe cases (a room air Pao_2 ≤70 mmHg or a $PAo_2 - Pao_2$ gradient ≥35 mmHg), adjunctive glucocorticoids improve the survival rate.

TABLE 107-1 TREATMENT OF PNEUMOCYSTOSIS (14–21 DAYS)

Drug(s)	Dose, Route	Adverse Effects
First-Choice Agent		
TMP-SMX	TMP (5 mg/kg) plus SMX (25 mg/kg) q6–8h PO or IV (two double-strength tablets tid or qid)	Fever, rash, cytopenias, hepatitis, hyperkalemia
Alternative Agents		
TMP	5 mg/kg q6–8h PO	Hemolysis (G6PD deficiency), methemoglobinemia, rash, fever, gastrointestinal disturbances
plus		
Dapsone	100 mg qd PO	
Atovaquone	750 mg bid PO	Rash, fever, hepatitis
Clindamycin	300–450 mg q6h PO or 600 mg q6–8h IV	Hemolysis (G6PD deficiency), methemoglobinemia, neutropenia, rash
plus		
Primaquine	15–30 mg qd PO	
Pentamidine	3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias (torsades des pointes), pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Adjunctive Agent		
Prednisone or methylprednisolone	40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV	Peptic ulcer disease, hyperglycemia, mood alteration, hypertension

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole.

- For pts with HIV infection who present with PCP before the initiation of antiretroviral therapy (ART), ART should usually be started within the first 2 weeks of therapy for PCP.
- Pts typically do not respond to therapy for 4–8 days. Pts whose condition continues to deteriorate after 3–4 days or has not improved after 7–10 days should be reevaluated for other infectious processes and for noninfectious processes (e.g., CHF, pulmonary emboli) that may be causing pulmonary dysfunction.

PROGNOSIS

- Factors that influence mortality risk include advanced age, high degree of immunosuppression, preexisting lung disease, low serum albumin level, need for mechanical ventilation, and development of a pneumothorax.

PREVENTION

- The most effective method for preventing PCP is to eliminate the cause of immunosuppression (e.g., withdraw immunosuppressive therapy, treat HIV infection).
- Prophylaxis is indicated for HIV-infected pts with CD4+ T-cell counts <200/μL or a history of oropharyngeal candidiasis and for any pt with a history of PCP. Guidelines for other compromised hosts are less clear, but prophylaxis should be considered for pts receiving >20 mg of prednisone daily (or its equivalent) for ≥30 days.
- For prophylactic regimens, see Table 107-2. TMP-SMX is the drug of choice.

TABLE 107-2 PROPHYLAXIS OF PNEUMOCYSTOSIS

Drug(s)	Dose, Route	Comments
First-Choice Agent		
TMP-SMX	One tablet (double- or single-strength) qd PO	Incidence of hypersensitivity is high. Rechallenge for non-life-threatening hypersensitivity; consider dose-escalation protocol.
Alternative Agents		
Dapsone	50 mg bid or 100 mg qd PO	Hemolysis is associated with G6PD deficiency.
Dapsone ***plus*** Pyrimethamine ***plus*** Leucovorin	50 mg qd PO 50 mg weekly PO 25 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Dapsone ***plus*** Pyrimethamine ***plus*** Leucovorin	200 mg weekly PO 75 mg weekly PO 25 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Pentamidine	300 mg monthly via Respirgard II nebulizer	Aerosol may cause bronchospasm. Pentamidine is probably less effective than TMP-SMX or dapsone regimens.
Atovaquone	1500 mg qd PO	Requires fatty meal for optimal absorption.

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole.

For a more detailed discussion, see Masur H, Morris A: *Pneumocystis* Infections, Chap. 244, p. 1358, in HPIM-19.

108 Protozoal Infections

MALARIA

Microbiology and Epidemiology

Six major species of *Plasmodium* cause nearly all cases of human disease: *P. falciparum*, *P. vivax*, two morphologically identical sympatric species of *P. ovale*, *P. malariae*, and *P. knowlesi*.

- *P. falciparum*, the cause of most cases of severe disease and most deaths, predominates in Africa, New Guinea, and Hispaniola.
- *P. vivax* is more common in Central America.
- *P. falciparum* and *P. vivax* are equally prevalent in South America, the Indian subcontinent, eastern Asia, and Oceania.
- *P. ovale* makes up <1% of isolates outside Africa.
- *P. malariae* is found in most areas (especially throughout sub-Saharan Africa) but is less common.
- *P. knowlesi* (the monkey malaria parasite) can reliably be identified only by molecular techniques and is present in Borneo and Southeast Asia.
- Malaria is the most important parasitic disease in humans, causing ~2000 deaths each day.

Pathogenesis

After introduction of *sporozoites* into the bloodstream by female anopheline mosquitoes, the parasite travels to the liver and reproduces asexually to form *merozoites* that infect RBCs. The merozoites transform into *trophozoites*, feed on intracellular proteins (principally hemoglobin), multiply 6- to 20-fold every 48 h (*P. knowlesi*, 24 h; *P. malariae*, 72 h), and cause the RBCs to rupture, releasing daughter merozoites. The process then repeats.

- Some parasites develop into long-lived sexual forms called *gametocytes*, whose uptake by another female anopheline mosquito allows transmission.
- In *P. vivax* or *P. ovale* infection, dormant forms called *hypnozoites* remain in liver cells and may cause disease 3 weeks to >1 year later.
- RBCs infected with *P. falciparum* may exhibit *cytoadherence* (attachment to venular and capillary endothelium), *rosetting* (adherence to uninfected RBCs), and *agglutination* (adherence to other infected RBCs). The result is sequestration of *P. falciparum* in vital organs, with consequent underestimation (through parasitemia determinations) of parasite numbers in the body. Sequestration is central to the pathogenesis of falciparum malaria but is not evident in the other human malarias.
- In nonimmune individuals, infection triggers nonspecific host defense mechanisms such as increased splenic filtration.

  - With repeated exposure to malaria, pts develop resistance to high-level parasitemia and disease but not to infection.
  - Hemoglobinopathies (e.g., sickle cell disease, ovalocytosis, thalassemia) and G6PD deficiency are more common in endemic areas and protect against death from malaria.

Clinical Manifestations

Pts initially develop nonspecific symptoms (e.g., headache, fatigue, myalgias) that are followed by fever.

- Febrile paroxysms at regular intervals are unusual and suggest infection with *P. vivax* or *P. ovale*.
- Splenomegaly, hepatomegaly, mild anemia, and jaundice may develop.
- The diagnosis of severe falciparum malaria requires one or more of the following: impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, ARDS, circulatory shock, DIC, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and a parasitemia level of >5%.
  - Cerebral malaria manifests as diffuse symmetric encephalopathy, typically without focal neurologic signs.
  - Coma is an ominous sign associated with mortality rates of ~20%.
- Pregnant women have unusually severe illness. Premature labor, fetal distress, stillbirth, and delivery of low-birth-weight infants are common.
- Tropical splenomegaly (hyperreactive malarial splenomegaly) may result as a chronic complication of malaria and is characterized by massive splenomegaly, hepatomegaly, and an abnormal immunologic response to infection.

Diagnosis

Although antibody-based diagnostic tests are being used with increasing frequency, demonstration of asexual forms of the parasite on peripheral-blood smears is required for diagnosis.

- Thick and thin smears should be examined; thick smears and the less sensitive thin smears detect parasitemia levels as low as 0.001% and <0.05%, respectively.
- If the level of clinical suspicion is high and smears are initially negative, they should be repeated q12–24h for 2 days.
- Other laboratory findings generally include normochromic, normocytic anemia; elevated inflammatory markers; and thrombocytopenia (~10^5/μL).

TREATMENT MALARIA

- See **Table 108-1** for treatment regimens. IV artesunate is approved by the US Food and Drug Administration for emergency use against severe malaria through the Centers for Disease Control and Prevention (CDC) (Malaria Hotline: 855-856-4713; Emergency Operations Center [after hours]: 770-488-7100).
- Pts receiving quinidine should undergo cardiac monitoring; a total plasma level of >8 μg/mL, increased QT intervals (>0.6 s), or QRS widening by >25% is an indication for slowing the infusion rate.
- Exchange transfusions can be considered for severely ill pts, although indications for their use are not yet agreed upon.
- All pts with severe malaria should receive a continuous infusion of dextrose. Unconscious pts should have blood glucose levels measured q4–6h.
- Parasite counts and hematocrits for pts with severe malaria and pts with uncomplicated disease should be measured q6–12h and q24h, respectively.
- Primaquine (0.5 mg of base/kg for 14 days) eradicates persistent liver stages and prevents relapse in *P. vivax* or *P. ovale* infection. G6PD deficiency must be ruled out before treatment.

TABLE 108-1 REGIMENS FOR THE TREATMENT OF MALARIA[a]

Type of Disease or Treatment	Regimen(s)
Uncomplicated Malaria	
Known chloroquine-sensitive strains of *Plasmodium vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*, *P. falciparum*[b]	Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) ***or*** Amodiaquine (10–12 mg of base/kg qd for 3 days)
Radical treatment for *P. vivax or P. ovale* infection	In addition to chloroquine or amodiaquine as detailed above, primaquine (0.5 mg of base/kg qd in tropical regions and 0.25 mg/kg for temperate-origin *P. vivax*) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks. Primaquine should not be given in severe G6PD deficiency.
Sensitive *P. falciparum* malaria[c]	Artesunate[d] (4 mg/kg qd for 3 days) *plus* sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* amodiaquine (10 mg of base/kg qd for 3 days)[e]
Multidrug-resistant *P. falciparum* malaria	Either artemether-lumefantrine[d] (1.5/9 mg/kg bid for 3 days with food) ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* mefloquine (24–25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)[e] ***or*** Dihydroartemisinin-piperaquine[d] (2.5/20 mg/kg qd for 3 days)
Second-line treatment/ treatment of imported malaria	Either artesunate[d] (2 mg/kg qd for 7 days) or quinine (10 mg of salt/kg tid for 7 days) *plus 1 of the following 3:* 1. Tetracycline[f] (4 mg/kg qid for 7 days) 2. Doxycycline[f] (3 mg/kg qd for 7 days) 3. Clindamycin (10 mg/kg bid for 7 days) ***or*** Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food)
Severe Falciparum Malaria[g]	
	Artesunate[d] (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary)[h] ***or, if unavailable,*** Artemether[d] (3.2 mg/kg stat IM followed by 1.6 mg/kg qd) ***or, if unavailable,***

(*Continued*)

TABLE 108-1 REGIMENS FOR THE TREATMENT OF MALARIA[a] (*CONTINUED*)

Type of Disease or Treatment	Regimen(s)
	Quinine dihydrochloride (20 mg of salt/kg[i] infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h[j]) ***or, if unavailable,*** Quinidine (10 mg of base/kg[i] infused over 1–2 h, followed by 1.2 mg of base/kg per hour[j] with electrocardiographic monitoring)

[a]In endemic areas, except in pregnant women and infants, a single dose of primaquine (0.25 mg of base/kg) should be added as a gametocytocide to all falciparum malaria treatments to prevent transmission. This addition is considered safe even in G6PD deficiency.
[b]Very few areas now have chloroquine-sensitive *P. falciparum* malaria (Fig. 248-2 in HPIM-19).
[c]In areas where the partner drug to artesunate is known to be effective.
[d]Artemisinin derivatives are not readily available in some temperate countries.
[e]Fixed-dose coformulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations.
[f]Tetracycline and doxycycline should not be given to pregnant women or to children <8 years of age.
[g]Oral treatment should be substituted as soon as the pt recovers sufficiently to take fluids by mouth.
[h]Artesunate is the drug of choice when available. The doses in children weighing <20 kg should be 3 mg/kg. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine.
[i]A loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine.
[j]Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

Personal Protection Measures

Measures that can protect persons against infection include avoidance of mosquito exposure, with particular caution at peak feeding times (dusk to dawn); use of insect repellents containing DEET (10–35%) or (if DEET is unacceptable) picaridin (7%); suitable clothing; and insecticide-impregnated bed nets.

Chemoprophylaxis

See Table 108-2 for prophylaxis options.

- Mefloquine is the only drug advised for pregnant women traveling to areas with drug-resistant malaria and is generally considered safe in the second and third trimesters; data regarding use in the first trimester, although limited, are reassuring.

TABLE 108-2 DRUGS USED IN THE PROPHYLAXIS OF MALARIA

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone-proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum*	One adult tablet PO[a]	5–8 kg: ½ pediatric tablet[b] daily ≥8–10 kg: ¾ pediatric tablet daily ≥10–20 kg: One pediatric tablet daily ≥20–30 kg: Two pediatric tablets daily ≥30–40 kg: Three pediatric tablets daily ≥40 kg: One adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone-proguanil should be taken with food or a milky drink.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	300 mg of base (500 mg of salt) PO once weekly	5 mg/kg of base (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c]	100 mg PO qd (except in pregnant women; see Comments)	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children <8 years of age and in pregnant women.
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.

Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant *P. falciparum*[c]	228 mg of base (250 mg of salt) PO once weekly	≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly 10–19 kg: ¼ tablet once weekly 20–30 kg: ½ tablet once weekly 31–45 kg: ¾ tablet once weekly ≥46 kg: 1 tablet once weekly	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.
Primaquine	For prevention of malaria in areas with mainly *P. vivax*	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level.
	Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax* and *P. ovale*	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD deficiency as well as during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level.

[a]An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

[b]A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.

[c]Very few areas now have chloroquine-sensitive malaria (Fig. 248-2 in HPIM-19).

Source: CDC: *www.cdc.gov/malaria/travelers/drugs.html.*

BABESIOSIS

Microbiology

Babesiosis is caused by intraerythrocytic protozoa of the genus *Babesia*. *B. microti*, the cause of most cases, is the etiologic agent in the northeastern and upper midwestern United States, and *B. duncani* is responsible for disease on the West Coast. *B. divergens* causes disease in Europe. The deer tick (*Ixodes scapularis*) transmits *B. microti*.

Epidemiology

In the United States, infections occur most frequently in the Northeast and upper Midwest. In 2011, >1100 cases were reported in the United States, with ~75% of cases presenting in July and August; this number is probably an underestimate, given that most pts experience a mild and self-limiting disease and may not seek medical attention.

Clinical Manifestations

Most pts develop a mild illness, but immunosuppressed pts may have more severe disease.

- After an incubation period of 1–4 weeks, pts gradually develop fevers, fatigue, and weakness. Other symptoms may include chills, sweats, myalgias, arthralgias, headache, and—less often—photophobia, shortness of breath, and abdominal pain.
- Severe babesiosis is associated with parasitemia levels of >4%.
  - Risk factors include an age of >50 years, male gender, asplenia, HIV infection/AIDS, malignancy, hemoglobinopathy, and immunosuppression.
  - Complications include ARDS, DIC, CHF, renal failure, and splenic infarcts and rupture.
  - The fatality rate is 5–9% among all hospitalized pts and 20% among immunocompromised pts.

Diagnosis

Giemsa-stained thin smears identify intraerythrocytic *Babesia* parasites, which appear round, pear-shaped, or ameboid.

- Ring forms resembling *P. falciparum* but without pigment are most common.
- Tetrads ("Maltese crosses")—formed by four budding merozoites—are pathognomonic for *B. microti* and other small *Babesia* species.
- PCR and serology can also be used for diagnostic purposes.

TREATMENT BABESIOSIS

- Mild to moderate illness should be treated with atovaquone (750 mg PO q12h) plus azithromycin (500 mg PO on day 1 followed by 250 mg/d PO) for 7–10 days.
  - Clindamycin plus quinine is equally effective but not as well tolerated.
- Severe disease should be treated with clindamycin (300–600 mg q6h IV or 600 mg q8h PO) plus quinine (650 mg q6–8h PO) for 7–10 days.
  - High-dose azithromycin (600–1000 mg/d) plus atovaquone is an alternative.
  - Consider exchange transfusion in pts with high-level parasitemia (>10%); hemoglobin levels of ≤10 g/dL; or pulmonary, hepatic, or renal compromise.
  - Immunocompromised pts generally need longer courses of treatment (e.g., 6 weeks), with at least 2 weeks of therapy after parasites are no longer detected on blood smear.
- *B. duncani* and *B. divergens* infections can be treated with IV clindamycin and quinine for 7–10 days.

LEISHMANIASIS

Microbiology

Leishmania species are extracellular, flagellated promastigotes while dwelling in their sandfly vector, but are obligate intracellular, nonflagellated amastigotes while living in vertebrate hosts, including humans.

- Organisms of the *L. donovani* complex usually cause visceral leishmaniasis and are present in Asia, the Middle East, the horn of Africa, the Mediterranean, and Central and South America.
- *L. tropica*, *L. major*, and *L. aethiopica* cause Old World cutaneous leishmaniasis and are present in Asia and in northern and sub-Saharan Africa.
- The *L. mexicana* complex causes New World cutaneous leishmaniasis and is present in Central America and northern South America.

Epidemiology

More than 1.5 million cases of leishmaniasis occur annually worldwide, of which 0.7–1.2 million are cutaneous and 200,000–400,000 are visceral.

Clinical Manifestations

Visceral leishmaniasis (kala-azar): Pts most commonly present with an abrupt onset of moderate- to high-grade fever associated with rigor and chills.

- Splenomegaly, hepatomegaly, and (except in the Indian subcontinent) lymphadenopathy are common.
- Leukopenia, anemia, thrombocytopenia, a polyclonal increase in serum immunoglobulins, and hepatic transaminitis are common.
- Up to 50% of pts in India, East Africa, and the Sudan may develop hypopigmented skin lesions (post–kala-azar dermal leishmaniasis) concurrent with or after cure of visceral leishmaniasis. In some cases, these pts may require unusually long treatment courses.

Cutaneous leishmaniasis: After an incubation period of days or weeks, papular lesions progress to nodules that ulcerate over weeks or months. Lesions usually heal spontaneously after 2–15 months.

- The margins of the ulcer are raised and indurated, and the base of the ulcer is usually painless.
- Disease due to *L. tropica* may involve *leishmaniasis recidivans*: development of new scaly, erythematous papules in the area of a healed sore.

Mucosal leishmaniasis: This disfiguring sequela of New World cutaneous leishmaniasis results from dissemination of parasites from the skin to the naso-oropharyngeal mucosa.

- Disease may occur 1–5 years after the initial cutaneous episode.
- Persistent nasal congestion and bleeding are followed by progressive ulcerative destruction.
- These lesions do not resolve spontaneously.

Diagnosis

- *Visceral leishmaniasis:* Identification of amastigotes in smears of tissue aspirates is the gold standard for diagnosis.
  - The sensitivity of splenic smears is >95%, but splenic aspiration may be very dangerous; smears of bone marrow and lymph node aspirates have sensitivities of 60–85% and 50%, respectively.

- Several serologic techniques, including a rapid test, are available and offer good sensitivity and specificity.

- *Cutaneous and mucosal leishmaniasis:* Diagnosis is made by microscopy, culture, or PCR examination of aspirates and biopsy specimens from skin lesions and lymph nodes.

TREATMENT LEISHMANIASIS

- *Visceral leishmaniasis:* The pentavalent antimonial (Sb^V) compounds sodium stibogluconate and meglumine antimoniate (20 mg/kg per day IV or IM for 28–30 days) are the first-line therapeutic agents and provide cure rates >90%.
  - Amphotericin B (AmB; either deoxycholate or a lipid formulation) is recommended in areas with Sb^V resistance (e.g., northeastern India) or if initial Sb^V therapy fails.
  - Paromomycin and the oral agent miltefosine have been approved for the treatment of visceral leishmaniasis in India.
  - Liposomal AmB is the drug of choice for HIV-infected pts.
- *Cutaneous leishmaniasis:* Although lesions generally resolve spontaneously, treatment may be needed if lesions spread or persist.
  - Topical agents can be effective for a few small lesions. Systemic treatment is needed for multiple lesions; lesions on the face, hands, or joints; and lesions of New World cutaneous leishmaniasis.
  - Administration of Sb^V (20 mg/kg daily for 20 days) constitutes the most effective treatment. Exceptions include disease due to *L. guyanensis* (pentamidine isethionate preferred) or *L. aethiopica* (paromomycin preferred).
- *Mucosal leishmaniasis:* Sb^V (20 mg/kg for 30 days) is recommended.
  - Pts require long-term follow-up, and neither relapse nor failure of therapy is uncommon.
  - AmB and potentially miltefosine can be used in cases of relapse or therapy failure.

TRYPANOSOMIASIS

CHAGAS DISEASE

Microbiology and Pathology

Trypanosoma cruzi causes Chagas disease (American trypanosomiasis) and is transmitted among mammalian hosts by hematophagous reduviid bugs. Organisms disseminate through the lymphatics and the bloodstream, often parasitizing muscles particularly heavily.

Epidemiology

T. cruzi is found exclusively in the Americas and causes disease mostly among the poor in rural areas of Mexico and Central and South America. An estimated 8 million people are chronically infected, with 14,000 deaths annually.

Clinical Manifestations

An indurated area of erythema and swelling (the *chagoma*) with local lymphadenopathy develops ≥1 week after parasite invasion and generally precedes malaise, fever, anorexia, and edema of the face and lower extremities.

- *Romaña's sign*—unilateral painless edema of the palpebrae and periocular tissues—occurs when the conjunctiva is the portal of entry.
- Acute disease resolves spontaneously within 4–8 weeks, and pts enter an asymptomatic phase of chronic infection.

- Symptomatic chronic disease becomes apparent years or even decades after initial infection.
  - Cardiac symptoms are common and include rhythm disturbances, segmental or dilated cardiomyopathy, and thromboembolism.
  - Pts can develop megaesophagus and suffer from dysphagia, odynophagia, chest pain, and regurgitation.
  - Megacolon may develop, leading to abdominal pain, chronic constipation, fecaloma formation, obstruction, and volvulus.

Diagnosis

Microscopic examination of fresh anticoagulated blood, the buffy coat, or blood smears may reveal organisms in cases of acute Chagas disease. Serology has no major diagnostic role in acute disease, but PCR assays can be helpful. Chronic Chagas disease is diagnosed by detection of specific IgG antibodies. Given the frequency of false-positive results, a positive result should be confirmed by at least two additional assays.

TREATMENT CHAGAS DISEASE

- Only two drugs—nifurtimox and benznidazole—are available to treat Chagas disease; neither is entirely effective.
  - Nifurtimox (8–10 mg/kg qd in four divided oral doses for 90–120 days) reduces symptom duration, parasitemia level, and mortality rate but offers a parasitologic cure in only ~70% of cases.
  - Benznidazole (5 mg/kg qd in two or three divided doses for 60 days) is the drug of choice in Latin America and may provide parasitologic cure rates >90%.
  - Both drugs have a number of side effects.
- Treatment of chronic Chagas disease is controversial; no adequate studies demonstrate efficacy. However, a panel of experts convened by the CDC recommends that pts <50 years old with presumably long-standing *T. cruzi* infection be offered treatment.

SLEEPING SICKNESS

Microbiology and Epidemiology

Sleeping sickness (human African trypanosomiasis, HAT) is caused by parasites of the *T. brucei* complex and is transmitted via tsetse flies.

- *T. b. rhodesiense* causes the East African form and *T. b. gambiense* the West African form; these two forms are epidemiologically and clinically distinct illnesses.
- Humans are the only reservoir for *T. b. gambiense*; infection occurs primarily in rural populations and rarely develops in tourists. *T. b. rhodesiense* has reservoirs in antelope and cattle; tourists can be infected when visiting areas where infected game and vectors are present.
- HAT was nearly eradicated in the mid-1960s, resurged in the 1990s, and is now decreasing in incidence because of renewed control activities. Fewer than 10,000 cases were reported to the World Health Organization in 2009.

Clinical Manifestations

A trypanosomal chancre develops ~1 week after the bite of an infected tsetse fly. A systemic febrile illness without involvement of the CNS (stage 1 disease) then evolves as the parasites disseminate through the bloodstream and lymphatics.

- Bouts of high-grade fever lasting several days are separated by afebrile periods. Malaise, headache, arthralgias, hepatosplenomegaly, and other nonspecific manifestations can develop.

- Lymphadenopathy with discrete, rubbery, nontender nodes is prominent in *T. b. gambiense* disease. Enlargement of nodes of the posterior cervical triangle (*Winterbottom's sign*) is a classic manifestation.
- With CNS invasion (stage 2 disease), pts develop progressive indifference and daytime somnolence, a state that sometimes alternates with restlessness and insomnia. Extrapyramidal signs may include choreiform movements, tremors, and fasciculations; ataxia is common.
- Disease due to *T. b. rhodesiense* is more acute and, if untreated, can lead to death in weeks to months; in contrast, disease due to *T. b. gambiense* can smolder for months or years.

Diagnosis

Examination of fluid from the chancre, thin or thick blood smears, buffy coats, lymph node aspirates, bone marrow biopsy specimens, or CSF can reveal the parasite.

- Parasitemia is more likely in stage 1 than in stage 2 disease and in pts infected with *T. b. rhodesiense* rather than *T. b. gambiense.*
- CSF should be examined whenever the diagnosis is being considered. Increased opening pressure, increased protein level, and increased mononuclear cell counts are common.

TREATMENT **SLEEPING SICKNESS**

Stage 1 disease

- *T. b. rhodesiense:* suramin (a test dose of 100–200 mg followed by 20 mg/kg IV on days 1, 5, 12, 18, and 26)
  - Hypersensitivity reactions and renal damage are the most important adverse effects.
  - A urinalysis should be done before each dose. Treatment should be discontinued if hematuria or increasing proteinuria is found or if casts are present in the sediment.
- *T. b. gambiense:* pentamidine (4 mg/kg daily IM or IV for 10 days)
  - Serious adverse reactions include nephrotoxicity, abnormal liver function, neutropenia, hypoglycemia, and sterile abscesses.
  - Suramin is an alternative agent.

Stage 2 disease

- *T. b. rhodesiense:* melarsoprol (2.2 mg/kg IV daily for 10 days). To reduce reactive encephalopathy, administer prednisolone (1 mg/kg) with each dose of melarsoprol.
- *T. b. gambiense:* Eflornithine (100 mg/kg IV qid for 2 weeks) is the first-line agent. Either melarsoprol (2.2 mg/kg qd IV for 10 days) or nifurtimox (5 mg/kg PO tid for 7 days) plus eflornithine (100 mg/kg IV bid for 7 days) is an alternative.

TOXOPLASMOSIS

Microbiology and Epidemiology

Toxoplasmosis is caused by the intracellular parasite *Toxoplasma gondii*; cats and their prey are the definitive hosts. The primary route of transmission to humans is ingestion of tissue cysts from soil, food (e.g., undercooked meat), or water contaminated by cat feces.

- Roughly one-third of women who contract *T. gondii* during pregnancy transmit the parasite to the fetus, with a 65% risk of transmission if maternal infection is acquired in the third trimester.

- In the United States and most European countries, seroconversion rates increase with age and exposure; 10–67% of persons >50 years old are seropositive.

Pathogenesis

Both humoral and cellular immunity are important, but subclinical infection commonly persists for the pt's lifetime. Immunocompromised hosts lack factors required to control infection; the consequences are progressive focal destruction and organ failure.

Clinical Manifestations

Disease in immunocompetent hosts is usually asymptomatic (80–90% of cases) and self-limited and does not require therapy. In contrast, immunocompromised pts, including newborns, can develop severe infections typically involving the CNS.

- In the minority of immunocompetent pts who develop symptoms of acute infection, cervical lymphadenopathy is the most common finding; nodes are nontender and discrete. Generalized lymphadenopathy, fever <40°C (104°F), headache, malaise, and fatigue occur in 20–40% of pts. Clinical disease usually resolves within several weeks, although lymphadenopathy may persist for several months.
- Immunocompromised pts develop acute toxoplasmosis through reactivation of latent infection in 95% of cases; the remainder of cases are due to new acquisition of parasites.
  - CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Pts may develop changes in mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%). The brainstem, basal ganglia, pituitary gland, and corticomedullary junction are most often involved.
- Multiple organs (e.g., lungs, GI tract, skin, eyes, heart, liver) can be affected.
  - *Toxoplasma* pneumonia is often confused with *Pneumocystis* pneumonia because of an overlapping pt population and similar clinical presentations (i.e., fever, dyspnea, and nonproductive cough rapidly progressing to respiratory failure).
- Congenital infection, which affects 400–4000 infants each year in the United States, may initially be asymptomatic but can result in reactivation and clinical disease (e.g., chorioretinitis) decades later.
- *Toxoplasma* causes ~35% of all cases of chorioretinitis in the United States and Europe. Blurred vision, macular involvement with loss of central vision, scotoma, photophobia, and eye pain are manifestations of infection. On examination, yellow-white cotton-like patches with indistinct margins of hyperemia are seen. Older lesions appear as white plaques with distinct borders and black spots.

Diagnosis

Culture of the parasite is difficult and can be done only at specialized laboratories. Serology is the primary method of diagnosis.

- Results of IgM, IgG, and antibody avidity levels can be combined to help determine when infection may have occurred. (Of note, IgM can persist for >1 year.) These tests, along with a more extensive panel of serologic tests, can be performed at the *Toxoplasma* Serology Laboratory at the Palo Alto Medical Foundation (www.pamf.org/serology/clinicianguide.html).
- In immunocompromised pts, a presumptive clinical diagnosis can be based on clinical presentation, history of exposure (e.g., a positive IgG result), and radiologic evaluation. Radiologic studies demonstrate bilateral contrast-enhancing lesions, typically in the basal ganglia and corticomedullary junction. These lesions can be difficult to distinguish from CNS lymphoma, although the latter more frequently consists of only a single lesion. A brain biopsy may be required for definitive diagnosis.

- Congenital toxoplasmosis is diagnosed by PCR of amniotic fluid (to detect the B1 gene of the parasite) and by the persistence of IgG antibody or a positive IgM titer after the first week of life; IgG antibody determinations should be repeated every 2 months.
- Ocular toxoplasmosis is diagnosed by the detection of typical lesions on ophthalmologic examination and the demonstration of a positive IgG titer in serum.

TREATMENT TOXOPLASMOSIS

- Immunocompetent pts with only lymphadenopathy do not require treatment unless they have persistent, severe symptoms.
- Immunocompromised pts should receive pyrimethamine plus sulfadiazine.
  - In resource-poor settings, trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily) is an effective alternative.
  - Either dapsone plus pyrimethamine or atovaquone with or without pyrimethamine is an alternative for pts who cannot take TMP-SMX.
- Congenital infection is treated daily for 1 year with oral pyrimethamine (1 mg/kg), sulfadiazine (100 mg/kg), and folinic acid.
- Ocular toxoplasmosis is treated with pyrimethamine and either sulfadiazine or clindamycin (and sometimes with prednisone) for 1 month.

Chemoprophylaxis

The risk of disease is very high among AIDS pts who are seropositive for *T. gondii* and have a CD4+ T lymphocyte count of <100/μL. TMP-SMX (one double-strength tablet daily) should be given to these pts as prophylaxis against both *Pneumocystis* pneumonia and toxoplasmosis. Primary or secondary prophylaxis can be stopped if, after institution of antiretroviral treatment, the CD4+ T lymphocyte count remains >200/μL for 3 months.

Personal Protection Measures

Toxoplasma infection can be prevented by the avoidance of undercooked meats and oocyst-contaminated materials (e.g., a cat's litter box).



For a more detailed discussion, see Reed SL, Davis CE: Laboratory Diagnosis of Parasitic Infections, Chap. 245e; Moore TA: Agents Used to Treat Parasitic Infections, Chap. 246e; White NJ, Breman JG: Malaria, Chap. 248, p. 1368; Vannier EG, Krause PJ: Babesiosis, Chap. 249, p. 1384; White NJ, Breman JG: Atlas of Blood Smears of Malaria and Babesiosis, Chap. 250e; Sundar S: Leishmaniasis, Chap. 251, p. 1387; Kirchhoff LV, Rassi A Jr: Chagas Disease and Trypanosomiasis, Chap. 252, p. 1394; Kim K, Kasper LH: *Toxoplasma* Infections, Chap. 253, p. 1398, in HPIM-19.

109 Helminthic Infections and Ectoparasite Infestations

HELMINTHS

NEMATODES

The nematodes, or roundworms, that are of medical significance can be broadly classified as either tissue or intestinal parasites.

Tissue Nematode Infections

With the exception of trichinellosis, these infections are due to invasive larval stages that do not reach maturity in humans.

Trichinellosis

Microbiology and Epidemiology Eight species of *Trichinella* cause human infection; two—*T. spiralis* and *T. pseudospiralis*—are found worldwide.

- Infection results when humans ingest meat (usually pork) that contains encysted *Trichinella* larvae.
  - The larvae invade the small-bowel mucosa.
  - After 1 week, female worms release new larvae that migrate to striated muscle via the circulation and encyst.
- The host immune response has few deleterious effects on muscle-dwelling larvae.
- About 12 cases of trichinellosis are reported annually in the United States.

Clinical Manifestations Most light infections (<10 larvae per gram of muscle) are asymptomatic. A burden of >50 larvae per gram can cause fatal disease.

- In the first week of infection, large numbers of parasites invading the gut usually cause diarrhea, abdominal pain, constipation, nausea, and/or vomiting.
- In the second week of infection, pts develop symptoms related to larval migration and muscle invasion: hypersensitivity reactions with fever and hypereosinophilia; periorbital and facial edema; and hemorrhages in conjunctivae, retina, and nail beds. Deaths are usually due to myocarditis with arrhythmias or heart failure.
- Approximately 2–3 weeks after infection, larval encystment in muscle causes myositis, myalgias, muscle edema, and weakness (especially in extraocular muscles; the biceps; and muscles of the jaw, neck, lower back, and diaphragm).
- Symptoms peak at 3 weeks; convalescence is prolonged.

Diagnosis Eosinophilia develops in >90% of pts, peaking at a level of >50% at 2–4 weeks after infection.

- An increase in parasite-specific antibody titers after the third week of infection confirms the diagnosis.
- Detection of larvae by microscopic examination of ≥1 g of fresh muscle tissue (i.e., not routine histopathologic sections) also confirms the diagnosis. Yields are highest near tendon insertions.

TREATMENT TRICHINELLOSIS

- Mebendazole (200–400 mg tid for 3 days; then 400 mg tid for 8–14 days) or albendazole (400 mg bid for 8–14 days) is active against enteric-stage parasites; the efficacy of these drugs against encysted larvae is inconclusive.

- Glucocorticoids (e.g., prednisone at 1 mg/kg daily for 5 days) may reduce severe myositis and myocarditis.

Prevention

Cooking pork until it is no longer pink or freezing it at –15°C (5°F) for 3 weeks kills larvae and prevents infection by most *Trichinella* spp.

Visceral and Ocular Larva Migrans

Microbiology and Epidemiology Humans are incidental hosts for nematodes that cause visceral larva migrans. Most cases are caused by the canine ascarid *Toxocara canis*. Infection results when humans—most often preschool children—ingest soil contaminated by puppy feces that contain infective *T. canis* eggs. Larvae penetrate the intestinal mucosa and disseminate hematogenously to a wide variety of organs (e.g., liver, lungs, CNS), provoking intense eosinophilic granulomatous responses.

Clinical Manifestations Symptomatic infections result in fever, malaise, anorexia, weight loss, cough, wheezing, rashes, hepatosplenomegaly, and occasional profound eosinophilia (up to 90%). Ocular disease usually develops in older children or young adults and includes an eosinophilic mass that mimics retinoblastoma, endophthalmitis, uveitis, and/or chorioretinitis.

Diagnosis The clinical diagnosis can be confirmed by an ELISA for toxocaral antibodies. Stool examination for eggs is ineffective because larvae do not develop into adult worms in humans.

TREATMENT VISCERAL AND OCULAR LARVA MIGRANS

- The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy.
- For pts with severe disease, glucocorticoids can reduce inflammatory complications.
- Anthelmintic drugs, including mebendazole and albendazole, have not been shown to alter the course of larva migrans.
- Ocular disease can be treated with albendazole (800 mg bid) and glucocorticoids for 5–20 days.

Cutaneous Larva Migrans This disease is caused by larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. Larvae in contaminated soil penetrate human skin; intensely pruritic, erythematous lesions form along the tracks of larval migration and advance several centimeters each day. Ivermectin (a single dose of 200 μg/kg) or albendazole (200 mg bid for 3 days) can relieve the symptoms of this self-limited infestation.

Intestinal Nematode Infections

Intestinal nematodes infect >1 billion persons worldwide, most commonly in regions with poor sanitation and particularly in developing countries in the tropics or subtropics. Because most helminthic parasites do not self-replicate, clinical disease (as opposed to asymptomatic infection) generally develops only with prolonged residence in an endemic area and is typically related to infection intensity.

Ascariasis

Microbiology Ascariasis is caused by *Ascaris lumbricoides*, the largest intestinal nematode, which reaches lengths up to 40 cm.

- Humans—primarily younger children—are infected by ingestion of fecally contaminated soil that contains ascarid eggs.

- Larvae hatch in the intestine, invade the mucosa, migrate to the lungs, break into the alveoli, ascend the bronchial tree, are swallowed, mature in the small intestine, and produce up to 240,000 eggs per day that pass in the feces.

Clinical Manifestations Most infections have a low worm burden and are asymptomatic. During lung migration of the parasite (~9–12 days after egg ingestion), pts may develop a cough and substernal discomfort, occasionally with dyspnea or blood-tinged sputum, fever, and eosinophilia.

- Eosinophilic pneumonitis (Löffler's syndrome) may be evident.
- Heavy infections with numerous entangled worms can occasionally cause pain, small-bowel obstruction, perforation, volvulus, biliary obstruction and colic, or pancreatitis.

Laboratory Findings Ascaris eggs (65 by 45 μm) can be found in fecal samples. Adult worms can pass in the stool or, much less commonly, through the mouth or nose.

TREATMENT ASCARIASIS

A single dose of albendazole (400 mg), mebendazole (500 mg), or ivermectin (150–200 μg/kg) is effective; these medications are contraindicated in pregnancy.

Hookworm

Microbiology Two hookworm species, *Ancylostoma duodenale* and *Necator americanus*, cause human infections. Infectious larvae present in soil penetrate the skin, reach the lungs via the bloodstream, invade the alveoli, ascend the airways, are swallowed, reach the small intestine, mature into adult worms, attach to the mucosa, and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid.

Clinical Manifestations Most infections are asymptomatic. Chronic infection causes iron deficiency and—in marginally nourished persons—progressive anemia and hypoproteinemia, weakness, and shortness of breath. Larvae may cause pruritic rash ("ground itch") at the site of skin penetration as well as serpiginous tracks of SC migration (similar to those of cutaneous larva migrans).

Laboratory Findings Hookworm eggs (40 by 60 μm) can be found in the feces. Stool concentration may be needed for the diagnosis of light infections.

TREATMENT HOOKWORM

- Albendazole (400 mg once) or mebendazole (500 mg once) is effective, although there is some concern that these agents are becoming less effective. Nutritional support, iron replacement, and deworming are undertaken as needed.

Strongyloidiasis

Microbiology and Epidemiology Unlike other helminths, *Strongyloides stercoralis* can replicate in the human host, permitting ongoing cycles of autoinfection from endogenously produced larvae.

- Infection results when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes.
  - Larvae travel through the bloodstream to the lungs, break through into alveolar spaces, ascend the bronchial tree, are swallowed, reach the small intestine, mature

into adult worms, and penetrate the mucosa of the proximal small bowel; eggs hatch in the intestinal mucosa.
  - Rhabditiform larvae can pass with the feces into the soil or can develop into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to establish ongoing autoinfection.
- Autoinfection is constrained by unknown factors of the host immune system, disruption of which (e.g., by glucocorticoid therapy) can lead to hyperinfection.

Clinical Features Uncomplicated disease is associated with mild cutaneous and/or abdominal manifestations such as recurrent urticaria, larva currens (a pathognomonic serpiginous, pruritic, erythematous eruption along the course of larval migration that may advance up to 10 cm/h), abdominal pain, nausea, diarrhea, bleeding, and weight loss.

- Disseminated disease involves tissues outside the GI tract and lungs, including the CNS, peritoneum, liver, and kidney.
  - Gram-negative sepsis, pneumonia, or meningitis can complicate or dominate the clinical course.
  - Disease can be fatal in pts given glucocorticoids; disseminated infection is uncommon among pts with HIV-1 infection.
- Fluctuating eosinophilia is common in uncomplicated disease but is uncommon in disseminated disease.

Diagnosis A single stool examination detects rhabditiform larvae (~250 μm long) in about one-third of uncomplicated infections. Duodenojejunal contents can be sampled if stool examinations are repeatedly negative.

- Antibodies can be detected by ELISA.
- In disseminated infection, filariform larvae can be found in stool or at sites of larval migration (e.g., sputum, bronchoalveolar lavage fluid, surgical drainage fluid).

TREATMENT STRONGYLOIDIASIS

- Ivermectin (200 μg/kg daily for 2 days) is more effective than albendazole (400 mg daily for 3 days). Asymptomatic pts should be treated, given the potential for later fatal hyperinfection.
- Disseminated disease should be treated with ivermectin for at least 5–7 days (or until the parasites are eradicated).
- In immunocompromised hosts, the course of ivermectin should be repeated 2 weeks after initial treatment.

Enterobiasis

Microbiology and Epidemiology Enterobiasis (pinworm) is caused by *Enterobius vermicularis* and affects ~40 million people in the United States (primarily children).

- Gravid female worms migrate nocturnally from the cecum to the perianal region, each releasing up to 2000 immature eggs that become infective within hours.
- Autoinfection and person-to-person transmission result from perianal scratching and transport of infective eggs to the mouth.

Clinical Manifestations Perianal pruritus is the cardinal symptom and is often worst at night. Eosinophilia is uncommon.

Diagnosis Eggs (55 by 25 μm and flattened on one side) are detected by microscopic examination of cellulose acetate tape applied to the perianal region in the morning.

TREATMENT ENTEROBIASIS

- One dose of mebendazole (100 mg) or albendazole (400 mg) is given, with the same treatment repeated after 2 weeks. Household members should also be treated to avoid reservoirs of potential reinfection.

Filarial and Related Infections

Filarial worms, which infect >170 million people worldwide, are nematodes that dwell in the SC tissue and lymphatics. Usually, infection is established only with repeated and prolonged exposures to infective larvae; however, filarial disease is characteristically more intense and acute in newly exposed individuals than in natives of endemic areas.

- Filarial parasites have a complex life cycle, including infective larval stages carried by insects and adult worms that reside in humans.
  - The offspring of adults are microfilariae (200–250 μm long, 5–7 μm wide) that either circulate in the blood or migrate through the skin.
  - Microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae.
- A bacterial endosymbiont, *Wolbachia*, is found in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* spp. and has become a target for antifilarial chemotherapy.

Lymphatic Filariasis

Microbiology Lymphatic filariasis is caused by *Wuchereria bancrofti* (most commonly), *Brugia malayi*, or *B. timori*, which can reside in and cause inflammatory damage to lymphatic channels or lymph nodes.

Clinical Manifestations Subclinical microfilaremia, hydrocele, acute adenolymphangitis (ADL), and chronic lymphatic disease are the main clinical presentations.

- ADL is associated with high fever, lymphatic inflammation, and transient local edema. Both the upper and lower extremities can be involved in both bancroftian and brugian filariasis, but *W. bancrofti* almost exclusively affects genital lymphatics.
- ADL may progress to more chronic lymphatic obstruction and elephantiasis with brawny edema, thickening of the SC tissues, and hyperkeratosis. Superinfection is a problem.

Diagnosis Detection of the parasite is difficult, but microfilariae can be found in peripheral blood, hydrocele fluid, and occasionally other body fluids.

- Timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved (primarily nocturnal in many regions).
- Two assays are available to detect *W. bancrofti* circulating antigens, and a PCR has been developed to detect DNA of both *W. bancrofti* and *B. malayi* in the blood.
- High-frequency ultrasound (with Doppler techniques) of the scrotum or the female breast can identify motile adult worms.
- The presence of antifilarial antibody supports the diagnosis, but cross-reactivity with other helminthic infections makes interpretation of this finding difficult.

TREATMENT LYMPHATIC FILARIASIS

- Pts with active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound) should be treated with diethylcarbamazine (DEC, 6 mg/kg daily for 12 days), which has macro- and microfilaricidal properties.

Albendazole (400 mg bid for 21 days), albendazole and DEC both given daily for 7 days, doxycycline (100 mg bid for 4–6 weeks), and the addition of DEC to a 3-week course of doxycycline are alternative regimens with macrofilaricidal efficacy.

- A single dose of albendazole (400 mg) combined with DEC (6 mg/kg) or ivermectin (200 µg/kg) has sustained microfilaricidal activity and is used in lymphatic filariasis eradication campaigns.
- For pts with chronic lymphatic filariasis, treatment regimens should focus on hygiene, prevention of secondary bacterial infections, and physiotherapy. Drug treatment should be reserved for individuals with evidence of active infection, although a 6-week course of doxycycline improves filarial lymphedema irrespective of disease activity.

Onchocerciasis

Microbiology and Epidemiology Onchocerciasis ("river blindness") is caused by *Onchocerca volvulus*, which infects 37 million people worldwide and is transmitted by the bite of an infected blackfly near free-flowing rivers and streams.

- Larvae deposited by the blackfly develop into adult worms (females and males are ~40–60 cm and ~3–6 cm in length, respectively) that are found in SC nodules (*onchocercomata*). About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodules and concentrate in the dermis.
- In contrast to lymphatic filariasis, onchocerciasis is characterized by microfilarial induction of inflammation.

Clinical Manifestations Onchocerciasis most commonly presents as dermatologic manifestations (an intensely pruritic papular rash or firm nontender onchocercomata), but visual impairment is the most serious complication in pts with moderate or heavy infections.

- Conjunctivitis with photophobia is an early ocular finding.
- Sclerosing keratitis (the leading cause of onchocercal blindness in Africa, affecting 1–5% of pts), anterior uveitis, iridocyclitis, and secondary glaucoma due to pupillary deformities are more serious ocular complications.

Diagnosis A definitive diagnosis is based on the finding of an adult worm in an excised nodule or of microfilariae in a skin snip.

- Specific antibody assays and PCR to detect onchocercal DNA are available in reference laboratories.
- Eosinophilia and elevated serum IgE levels are common but nonspecific.

TREATMENT ONCHOCERCIASIS

- Ivermectin (a single dose of 150 µg/kg), given yearly or semiannually, is microfilaricidal and is the mainstay of treatment.
  - In African regions where *O. volvulus* is coendemic with *Loa loa*, ivermectin is contraindicated because of the risk of severe posttreatment encephalopathy.
  - Doxycycline therapy for 6 weeks is macrofilaristatic, rendering adult female worms sterile for long periods, and also targets the *Wolbachia* endosymbiont.
- Nodules on the head should be excised to avoid ocular infection.

TREMATODES

- The trematodes, or flatworms, may be classified according to the tissues invaded by the adult stage of the fluke: blood, biliary tree, intestines, or lungs.

- The life cycle involves a definitive mammalian host (e.g., humans), in whom adult worms produce eggs through sexual reproduction, and an intermediate host (e.g., snails), in which miracidial forms undergo asexual reproduction to form cercariae. Worms do not multiply within the definitive host.
- Human infection results from either direct penetration of intact skin or ingestion.
- Infections with trematodes that migrate through or reside in host tissues are associated with a moderate to high degree of peripheral-blood eosinophilia.

Schistosomiasis

Microbiology and Epidemiology Five species cause human schistosomiasis: *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* cause intestinal and hepatic schistosomiasis, and *S. haematobium* causes urogenital schistosomiasis.

- After infective cercariae penetrate intact skin, they mature into schistosomula and migrate through venous or lymphatic vessels to the lungs and ultimately the liver parenchyma. Sexually mature worms migrate to the veins of the bladder and pelvis (*S. haematobium*) or the mesentery (*S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*) and deposit eggs.
  - Some mature ova are extruded into the intestinal or urinary lumina, from which they may be voided and ultimately may reach water and perpetuate the life cycle.
  - The persistence of ova in tissues leads to a granulomatous host response and fibrosis.
- These blood flukes infect 200–300 million persons (mostly children and young adults) in South America, the Caribbean, Africa, the Middle East, and Southeast Asia.

Clinical Manifestations

Schistosomiasis occurs in three stages that vary by species, intensity of infection, and host factors (e.g., age, genetics).

- *Cercarial invasion*, most often with *S. mansoni* and *S. japonicum* infections, causes a pruritic maculopapular rash ("swimmers' itch") 2–3 days later.
- *Acute schistosomiasis* (Katayama fever) presents 4–8 weeks after skin invasion as a serum sickness–like illness characterized by fever, generalized lymphadenopathy, hepatosplenomegaly, and significant eosinophilia.
- *Chronic schistosomiasis* causes manifestations that depend primarily on the schistosome species.
  - Intestinal species cause colicky abdominal pain, bloody diarrhea, anemia, hepatosplenomegaly, portal hypertension, and esophageal varices with bleeding.
  - Urinary species cause dysuria, frequency, hematuria (sometimes only at the end of voiding), obstruction with hydroureter and hydronephrosis, fibrosis of bladder granulomas, and late development of squamous cell carcinoma of the bladder.
  - Pulmonary disease (e.g., endarteritis obliterans, pulmonary hypertension, cor pulmonale) and CNS disease (e.g., Jacksonian epilepsy, transverse myelitis) can occur and are due to granulomas and fibrosis.

Diagnosis Diagnosis is based on geographic history, clinical presentation, and presence of schistosome ova in excreta.

- Serologic assays for schistosomal antibodies (available through the CDC in the United States) may yield positive results before eggs are seen in excreta.
- Infection may also be diagnosed by examination of tissue samples, typically from rectal biopsies.

TREATMENT SCHISTOSOMIASIS

- Because antischistosomal therapy has no significant impact on maturing worms, supportive measures and the consideration of glucocorticoid treatment constitute initial management for acute schistosomiasis.

- After the acute critical phase has resolved, a single day of treatment with praziquantel (20 mg/kg bid for *S. mansoni*, *S. intercalatum*, and *S. haematobium* infections; 20 mg/kg tid for *S. japonicum* and *S. mekongi* infections) results in parasitologic cure in ~85% of cases and reduces egg counts by >90%.
- Late established manifestations, such as fibrosis, do not improve with treatment.

Prevention Travelers to endemic regions should avoid contact with all freshwater bodies.

Liver (Biliary) Flukes

- Clonorchiasis (due to *Clonorchis sinensis*) and opisthorchiasis (due to *Opisthorchis viverrini* and *O. felineus*) occur in Southeast Asia and Eastern Europe.
  - Infection is acquired by ingestion of contaminated raw freshwater fish; larvae travel through the ampulla of Vater and mature in biliary canaliculi.
  - Most infected individuals are minimally symptomatic; chronic or repeated infection causes cholangitis, cholangiohepatitis, and biliary obstruction and is associated with cholangiocarcinoma.
  - Therapy for acute infection consists of praziquantel administration (25 mg/kg tid for 2 or 3 days).
- Fascioliasis (due to *Fasciola hepatica* and *F. gigantica*) is endemic in sheep-raising countries and has a worldwide prevalence of 17 million cases.
  - Infection is acquired by ingestion of contaminated aquatic plants (e.g., watercress, water caltrop, water chestnuts).
  - Acute disease develops 1–2 weeks after infection and causes fever, RUQ pain, hepatomegaly, and eosinophilia. Chronic infection is infrequently associated with bile duct obstruction and biliary cirrhosis.
  - For treatment, triclabendazole is given as a single dose of 10 mg/kg.
- Stool ova and parasite (O & P) examination diagnoses infection with liver flukes. Serologic testing is helpful, particularly in lightly infected pts.

Lung Flukes

- Infection with *Paragonimus* spp. is acquired by ingestion of contaminated crayfish and freshwater crabs.
- Acute infection causes lung hemorrhage, necrosis with cyst formation, and parenchymal eosinophilic infiltrates. A productive cough with brownish or bloody sputum, in association with peripheral-blood eosinophilia, is the usual presentation in pts with heavy infection.
  - In chronic cases, bronchitis or bronchiectasis may predominate.
  - CNS disease can also occur and can result in seizures.
- The diagnosis is made by O & P examination of sputum or stool; serology can be helpful.
- Praziquantel (25 mg/kg tid for 2 days) is the recommended therapy.

CESTODES

The cestodes, or tapeworms, are segmented worms that can be classified into two groups according to whether humans are the definitive or the intermediate host. The tapeworm attaches to intestinal mucosa via sucking cups or hooks located on the scolex. Proglottids (segments) form behind the scolex and constitute the bulk of the tapeworm.

Taeniasis Saginata and Taeniasis Asiatica

Microbiology Humans are the definitive host for *Taenia saginata*, the beef tapeworm, and *T. asiatica*, the swine tapeworm, which inhabit the upper jejunum. Eggs are excreted in feces and ingested by cattle or other herbivores (*T. saginata*) or pigs

(*T. asiatica*); larvae encyst (cysticerci) in the striated muscles of these animals. When humans ingest raw or undercooked meat, the cysticerci mature into adult worms in ~2 months.

Clinical Manifestations Pts become aware of the infection by noting passage of motile proglottids in their feces. They may experience perianal discomfort, mild abdominal pain, nausea, change in appetite, weakness, and weight loss.

Diagnosis The diagnosis is made by detection of eggs or proglottids in the stool; eggs may be detected in the perianal area by the cellophane-tape test (as in pinworm infection). Eosinophilia and elevated IgE levels may occur.

TREATMENT TAENIASIS SAGINATA AND TAENIASIS ASIATICA

Praziquantel is given in a single dose of 10 mg/kg.

Taeniasis Solium and Cysticercosis

Microbiology and Pathogenesis Humans are the definitive host and pigs the usual intermediate host for *T. solium*, the pork tapeworm.

- The disease has two forms, which depend on the form of parasite ingested.
  - By ingesting undercooked pork containing cysticerci, humans develop intestinal tapeworms and a disease similar to taeniasis saginata.
  - If humans ingest *T. solium* eggs (e.g., as a result of close contact with a tapeworm carrier or via autoinfection), they develop cysticercosis due to larvae penetrating the intestinal wall and migrating to many tissues.

Clinical Manifestations Intestinal infections are generally asymptomatic except for fecal passage of proglottids. The presentation of cysticercosis depends on the number and location of cysticerci as well as the extent of associated inflammatory responses or scarring.

- Cysticerci can be found anywhere in the body but most often are detected in the brain, skeletal muscle, SC tissue, or eye.
- Neurologic manifestations are most common and include seizures (due to inflammation surrounding cysticerci in the brain), hydrocephalus (from obstruction of CSF flow by cysticerci and accompanying inflammation or by arachnoiditis), and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, changes in vision).

Diagnosis Intestinal infection is diagnosed by detection of eggs or proglottids in stool. A consensus conference has delineated criteria for the diagnosis of cysticercosis (Table 109-1). Findings on neuroimaging include cystic lesions with or without enhancement, one or more nodular calcifications, or focal enhancing lesions.

TREATMENT TAENIASIS SOLIUM AND CYSTICERCOSIS

- Intestinal infections respond to a single dose of praziquantel (10 mg/kg), but this treatment may evoke an inflammatory response in the CNS if there is cryptic cysticercosis.
- Neurocysticercosis can be treated with albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). A combination of albendazole and praziquantel (50 mg/kg in three divided doses per day) may be more effective in pts with multiple lesions.
  - Given the potential for an inflammatory response to treatment, pts should be carefully monitored, and high-dose glucocorticoids should be used during treatment.

TABLE 109-1 DIAGNOSTIC CRITERIA FOR HUMAN CYSTICERCOSIS[a]

1. Absolute criteria
   a. Demonstration of cysticerci by histologic or microscopic examination of biopsy material
   b. Visualization of the parasite in the eye by funduscopy
   c. Neuroradiologic demonstration of cystic lesions containing a characteristic scolex
2. Major criteria
   a. Neuroradiologic lesions suggestive of neurocysticercosis
   b. Demonstration of antibodies to cysticerci in serum by enzyme-linked immunoelectrotransfer blot
   c. Resolution of intracranial cystic lesions spontaneously or after therapy with albendazole or praziquantel alone
3. Minor criteria
   a. Lesions compatible with neurocysticercosis detected by neuroimaging studies
   b. Clinical manifestations suggestive of neurocysticercosis
   c. Demonstration of antibodies to cysticerci or cysticercal antigen in cerebrospinal fluid by enzyme-linked immunosorbent assay
   d. Evidence of cysticercosis outside the central nervous system (e.g., cigar-shaped soft-tissue calcifications)
4. Epidemiologic criteria
   a. Residence in a cysticercosis-endemic area
   b. Frequent travel to a cysticercosis-endemic area
   c. Household contact with an individual infected with *Taenia solium*

[a]Diagnosis is confirmed by either one absolute criterion or a combination of two major criteria, one minor criterion, and one epidemiologic criterion. A probable diagnosis is supported by the fulfillment of (1) one major criterion plus two minor criteria; (2) one major criterion plus one minor criterion and one epidemiologic criterion; or (3) three minor criteria plus one epidemiologic criterion.
Source: Modified from OH Del Brutto et al: *Neurology* 57:177, 2001.

– Since glucocorticoids induce praziquantel metabolism, cimetidine should be given with praziquantel to inhibit this effect.
– Supportive measures include antiepileptic administration and treatment of hydrocephalus as indicated.

Echinococcosis

Microbiology and Epidemiology Humans are an intermediate host for *Echinococcus* larvae and acquire echinococcal disease by ingesting eggs spread by canine feces (for *E. granulosus*).

- After ingestion, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to many organs but particularly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts within which daughter cysts develop, as do germinating cystic structures (*brood capsules*). Cysts expand over years.

- Echinococcosis is prevalent on all continents, particularly in areas where livestock is raised in association with dogs.
- *E. multilocularis*, found in Arctic or sub-Arctic regions, is similar to *E. granulosus*, but wild canines (e.g., foxes) are the definitive hosts and rodents are the intermediate hosts. The parasite is multilocular, and vesicles progressively invade host tissue.

Clinical Manifestations Expanding cysts exert the effects of space-occupying lesions, causing symptoms in the affected organ (usually liver and lung); the liver is involved in two-thirds of *E. granulosus* infections and ~100% of *E. multilocularis* infections.

- Pts with hepatic disease most commonly present with abdominal pain or a palpable mass in the RUQ. Compression of a bile duct may mimic biliary disease, and rupture or leakage from a hydatid cyst may cause fever, pruritus, urticaria, eosinophilia, or anaphylaxis.
- Pulmonary cysts may rupture into the bronchial tree or pleural cavity and cause cough, salty phlegm, chest pain, or hemoptysis.
- Rupture of cysts may result in multifocal dissemination.
- *E. multilocularis* disease may present as a hepatic tumor, with destruction of the liver and extension into adjoining (e.g., lungs, kidneys) or distant (e.g., brain, spleen) organs.

Diagnosis Radiographic imaging is important in detecting and evaluating echinococcal cysts.

- Daughter cysts within a larger cyst are pathognomonic of *E. granulosus*. Eggshell or mural calcification on CT is also indicative of *E. granulosus* infection.
- Serologic testing yields positive results in ~90% of pts with hepatic disease, but results can be negative in up to half of pts with lung cysts.
- Aspiration of cysts usually is not attempted because leakage of cyst fluid can cause dissemination or anaphylactic reactions.

TREATMENT ECHINOCOCCOSIS

- Therapy is based on considerations of the size, location, and manifestations of cysts and the overall health of the pt. Ultrasound staging is recommended for *E. granulosus* infection.
- For some uncomplicated lesions, PAIR (*p*ercutaneous *a*spiration, *i*nfusion of scolicidal agents [95% ethanol or hypertonic saline], and *r*easpiration) is recommended.
  - Albendazole (7.5 mg/kg bid for 2 days before the procedure and for at least 4 weeks afterward) is given for prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during this treatment.
  - PAIR is contraindicated for superficial cysts, for cysts with multiple thick internal septal divisions, and for cysts communicating with the biliary tree.
- Surgical resection is the treatment of choice for complicated *E. granulosus* cysts.
  - Albendazole should also be given prophylactically, as just described. Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of protoscolices.
  - Medical therapy alone with albendazole for 12 weeks to 6 months results in cure in ~30% of cases and in clinical improvement in another 50%.
- *E. multilocularis* infection is treated surgically, and albendazole is given for at least 2 years after presumptively curative surgery. If surgery is not curative, albendazole should be continued indefinitely.

Diphyllobothriasis

Diphyllobothrium latum, the longest tapeworm (up to 25 m), attaches to the ileal and occasionally the jejunal mucosa. Humans are infected by consumption of infected

raw or smoked fish. Symptoms are rare and usually mild, but infection, particularly in Scandinavia, can cause vitamin B_{12} deficiency because the tapeworm absorbs large amounts of vitamin B_{12} and interferes with ileal B_{12} absorption. Up to 2% of infected pts, especially the elderly, have megaloblastic anemia resembling pernicious anemia and can suffer neurologic sequelae due to B_{12} deficiency. The diagnosis is made by detection of eggs in the stool. Praziquantel (5–10 mg/kg once) is highly effective.

ECTOPARASITES

Ectoparasites are arthropods or helminths that infest the skin or hair of animals, from which they derive sustenance and shelter. These organisms can inflict direct injury, elicit hypersensitivity, or inoculate toxins or pathogens.

Scabies

Etiology and Epidemiology Scabies is caused by the human itch mite *Sarcoptes scabiei* var. *hominis*, which infests ~300 million people worldwide.

- Gravid female mites burrow within the stratum corneum, deposit eggs that mature in ~8 days, and emerge as adults to reinvade the same or another host.
- Scabies transmission is facilitated by direct skin-to-skin contact with an infested person and by crowding, uncleanliness, or contact with multiple sexual partners.

Clinical Manifestations Itching, which is due to a sensitization reaction against excreta of the mite, is worst at night and after a hot shower. Burrows appear as dark wavy lines (3–15 mm in length), with most lesions located along the digital web spaces or on the volar wrists, elbows, scrotum, and penis. *Crusted* scabies (formerly termed *Norwegian* scabies)—hyperinfestation with thousands of mites—is associated with glucocorticoid use and immunodeficiency diseases.

Diagnosis Scrapings from unroofed burrows reveal the mite, its eggs, or fecal pellets.

TREATMENT SCABIES

- Permethrin cream (5%) should be applied thinly behind the ears and from the neck down after bathing and removed 8–14 h later with soap and water. A dose of ivermectin (200 μg/kg) is also effective but has not yet been approved by the FDA for scabies treatment.
- For crusted scabies, first a keratolytic agent (e.g., 6% salicylic acid) and then scabicides are applied to the scalp, face, and ears in addition to the rest of the body. Two doses of ivermectin, separated by an interval of 1–2 weeks, may be required for pts with crusted scabies.
- Itching and hypersensitivity may persist for weeks or months in scabies and should be managed with symptom-based treatment. Bedding and clothing should be washed in hot water and dried in a heated dryer, and close contacts (regardless of symptoms) should be treated to prevent reinfestations.
- Scabies infestations become noncommunicable within 1 day of effective treatment.

Pediculiasis

Etiology and Epidemiology Nymph and adult forms of human lice—*Pediculus capitis* (the head louse), *P. humanus* (the body louse), and *Pthirus pubis* (the pubic louse)—feed at least once a day and ingest human blood exclusively. The saliva of these lice produces an irritating rash in sensitized persons. Eggs are cemented firmly to hair or clothing, and empty eggs (nits) remain affixed for months after hatching. Lice are generally transmitted from person to person. Head lice are transmitted among

schoolchildren and body lice among disaster victims and indigent people; pubic lice are usually transmitted sexually. The body louse is a vector for the transmission of diseases such as louse-borne typhus, relapsing fever, and trench fever.

Diagnosis The diagnosis can be suspected if nits are detected, but confirmatory measures should include the demonstration of a live louse.

TREATMENT PEDICULIASIS

- If live lice are found, treatment with 1% permethrin (two 10-min applications 10 days apart) is usually adequate. If this course fails, treatment for ≤12 h with 0.5% malathion may be indicated. Eyelid infestations should be treated with petrolatum applied for 3–4 days.
- Body lice usually are eliminated by bathing and by changing to laundered clothes.
  - Pediculicides applied from head to foot may be needed in hirsute pts to remove body lice.
  - Clothes and bedding should be deloused by placement in a hot dryer for 30 min or by heat pressing.

Myiasis

In this infestation, maggots invade living or necrotic tissue or body cavities and produce clinical syndromes that vary with the species of fly. Certain flies are attracted to blood and pus, and newly hatched larvae enter wounds or diseased skin. Treatment consists of maggot removal and tissue debridement.

Leech Infestations

Medicinal leeches can reduce venous congestion in surgical flaps or replanted body parts. Pts occasionally develop sepsis from *Aeromonas hydrophila*, which colonizes the gullets of commercially available leeches.



For a more detailed discussion, see Reed SL, Davis CE: Laboratory Diagnosis of Parasitic Infections, Chap. 245e; Moore TA: Agents Used to Treat Parasitic Infections, Chap. 246e; Weller PF: Trichinellosis and Other Tissue Nematode Infections, Chap. 256, p. 1410; Weller PF, Nutman TB: Intestinal Nematode Infections, Chap. 257, p. 1413; Nutman TB, Weller PF: Filarial and Related Infections, Chap. 258, p. 1417; King CH, Mahmoud AAF: Schistosomiasis and Other Trematode Infections, Chap. 259, p. 1423; White AC Jr, Weller PF: Cestode Infections, Chap. 260, p. 1430; Pollack RJ, Norton SA: Ectoparasite Infestations and Arthropod Injuries, Chap. 475, p. 2744, in HPIM-19.

This page intentionally left blank

110 Physical Examination of the Heart

General examination of a pt with suspected heart disease should include vital signs (respiratory rate, pulse, blood pressure) and observation of skin color (e.g., cyanosis, pallor, jaundice), clubbing, edema, evidence of decreased perfusion (cool and diaphoretic skin), and hypertensive changes in optic fundi. Examine abdomen for evidence of hepatomegaly, ascites, or abdominal aortic aneurysm. An ankle-brachial index (systolic bp at ankle divided by arm systolic bp) <0.9 indicates lower extremity arterial obstructive disease. Important findings on cardiovascular examination include:

CAROTID ARTERY PULSE (FIG. 110-1)

- *Pulsus parvus:* Weak upstroke due to decreased stroke volume (hypovolemia, LV failure, aortic or mitral stenosis [MS])
- *Pulsus tardus:* Delayed upstroke (aortic stenosis)
- *Bounding (hyperkinetic) pulse:* Hyperkinetic circulation, aortic regurgitation, patent ductus arteriosus, marked vasodilation
- *Pulsus bisferiens:* Double systolic pulsation (aortic regurgitation, hypertrophic cardiomyopathy)
- *Pulsus alternans:* Regular alteration in pulse pressure amplitude (severe LV dysfunction)
- *Pulsus paradoxus:* Exaggerated inspiratory fall (>10 mmHg) in systolic bp (pericardial tamponade, severe obstructive lung disease)

JUGULAR VENOUS PULSATION (JVP)

Jugular venous distention develops in right-sided heart failure, constrictive pericarditis, pericardial tamponade, obstruction of superior vena cava. JVP normally falls with inspiration but may rise (Kussmaul sign) in constrictive pericarditis. Abnormalities in examination include:

- *Large "a" wave:* Tricuspid stenosis (TS), pulmonic stenosis (PS), atrioventricular (AV) dissociation (right atrium contracts against closed tricuspid valve)
- *Large "v" wave:* Tricuspid regurgitation, atrial septal defect
- *Steep "y" descent:* Constrictive pericarditis
- *Slow "y" descent:* TS

PRECORDIAL PALPATION

Cardiac apical impulse is normally localized at the fifth intercostal space, midclavicular line. Abnormalities include:

- *Forceful apical thrust:* Left ventricular hypertrophy
- *Lateral and downward displacement of apex impulse:* Left ventricular dilatation
- *Prominent presystolic impulse:* Hypertension, aortic stenosis, hypertrophic cardiomyopathy
- *Double systolic apical impulse:* Hypertrophic cardiomyopathy

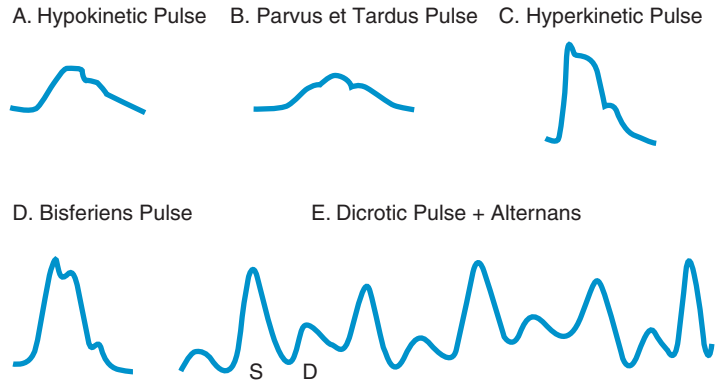


FIGURE 110-1 Carotid artery pulse patterns.

- *Sustained "lift" at lower left sternal border:* Right ventricular hypertrophy
- *Dyskinetic (outward bulge) impulse:* Ventricular aneurysm, large dyskinetic area post MI, cardiomyopathy

AUSCULTATION

HEART SOUNDS (FIG. 110-2)

S_1

Loud: Mitral stenosis (MS), short PR interval, hyperkinetic heart, thin chest wall. *Soft:* Long PR interval, heart failure, mitral regurgitation, thick chest wall, pulmonary emphysema.

S_2

Normally A_2 precedes P_2 and splitting increases with inspiration; abnormalities include:

- *Widened* splitting: Right bundle branch block, PS, mitral regurgitation
- *Fixed* splitting (no respiratory change in splitting): Atrial septal defect
- *Narrow* splitting: Pulmonary hypertension
- *Paradoxical* splitting (splitting narrows with inspiration): Aortic stenosis, left bundle branch block, heart failure
- *Loud* A_2: Systemic hypertension
- *Soft* A_2: Aortic stenosis (AS)
- *Loud* P_2: Pulmonary arterial hypertension
- *Soft* P_2: Pulmonic stenosis (PS)

S_3

Low-pitched, heard best with bell of stethoscope at apex, following S_2; normal in children; after age 30–35, indicates LV failure or volume overload.

S_4

Low-pitched, heard best with bell at apex, preceding S_1; reflects atrial contraction into a noncompliant ventricle; found in AS, hypertension, hypertrophic cardiomyopathy, and coronary artery disease (CAD).

Opening Snap (OS)

High-pitched; follows S_2 (by 0.06–0.12 s), heard at lower left sternal border and apex in MS; the more severe the MS, the shorter the S_2–OS interval.

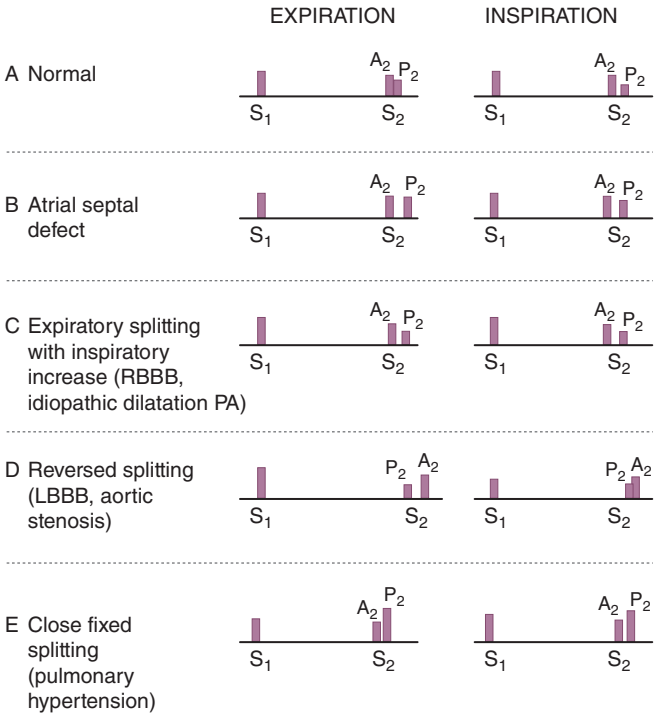


FIGURE 110-2 Heart sounds. **A.** Normal. S_1, first heart sound; S_2, second heart sound; A_2, aortic component of the second heart sound; P_2, pulmonic component of the second heart sound. **B.** Atrial septal defect with fixed splitting of S_2. **C.** Physiologic but wide splitting of S_2 with right bundle branch block. **D.** Reversed or paradoxical splitting of S_2 with left bundle branch block. **E.** Narrow splitting of S_2 with pulmonary hypertension. *(From NO Fowler: Diagnosis of Heart Disease. New York, Springer-Verlag, 1991, p 31.)*

Ejection Clicks

High-pitched sounds following S_1 typically loudest at left sternal border; observed in dilation of aortic root or pulmonary artery, congenital AS or PS; when due to the latter, click decreases with inspiration.

Midsystolic Clicks

At lower left sternal border and apex, often followed by late systolic murmur in mitral valve prolapse.

HEART MURMURS (FIG. 110-3; TABLES 110-1 AND 110-2)

Systolic Murmurs

May be "crescendo-decrescendo" ejection type, pansystolic, or late systolic; right-sided murmurs (e.g., tricuspid regurgitation) typically increase with inspiration.

Diastolic Murmurs

- *Early diastolic murmurs:* Begin immediately after S_2, are high-pitched, and are usually caused by aortic or pulmonary regurgitation.

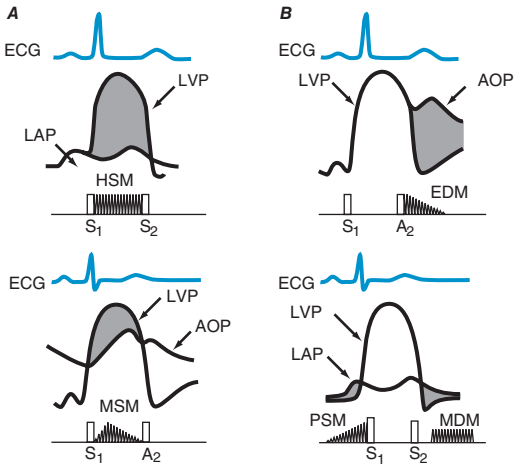


FIGURE 110-3 A. Schematic representation of ECG, aortic pressure (AOP), left ventricular pressure (LVP), and left atrial pressure (LAP). The gray areas indicated a transvalvular pressure difference during systole. HSM, holosystolic murmur; MSM, midsystolic murmur. **B.** Graphic representation of ECG, AOP, LVP, and LAP with gray areas indicating transvalvular diastolic pressure difference. EDM, early diastolic murmur; MDM, middiastolic murmur; PSM, presystolic murmur.

TABLE 110-1 HEART MURMURS

Systolic Murmurs	
Ejection-type	Aortic outflow tract
	Aortic valve stenosis
	Hypertrophic obstructive cardiomyopathy
	Aortic flow murmur
	Pulmonary outflow tract
	Pulmonic valve stenosis
	Pulmonic flow murmur
Holosystolic	Mitral regurgitation
	Tricuspid regurgitation
	Ventricular septal defect
Late-systolic	Mitral or tricuspid valve prolapse
Diastolic Murmurs	
Early diastolic	Aortic valve regurgitation
	Pulmonic valve regurgitation
Mid-to-late diastolic	Mitral or tricuspid stenosis
	Flow murmur across mitral or tricuspid valves
Continuous	Patent ductus arteriosus
	Coronary AV fistula
	Ruptured sinus of Valsalva aneurysm

Abbreviation: AV, atrioventricular.

TABLE 110-2 EFFECTS OF PHYSIOLOGIC AND PHARMACOLOGIC INTERVENTIONS ON THE INTENSITY OF HEART MURMURS AND SOUNDS

Respiration
Systolic murmurs due to TR or pulmonic blood flow through a normal or stenotic valve and diastolic murmurs of TS or PR generally increase with inspiration, as do right-sided S_3 and S_4. Left-sided murmurs and sounds usually are louder during expiration, as is the pulmonic ejection sound.
Valsalva Maneuver
Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. Following release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than left-sided murmurs.
After VPB or AF
Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle following a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation either do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).
Positional Changes
With *standing*, most murmurs diminish, two exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.
Exercise
Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise. However, the murmur of HCM often decreases with near maximum handgrip exercise. Left-sided S_4 and S_3 are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AR, aortic regurgitation; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

- *Mid-to-late diastolic murmurs:* Low-pitched, heard best with bell of stethoscope; observed in MS or TS; less commonly due to atrial myxoma.
- *Continuous murmurs:* Present in systole and diastole (envelops S_2); found in patent ductus arteriosus and sometimes in coarctation of aorta; less common causes are systemic or coronary AV fistula, aortopulmonary septal defect, ruptured aneurysm of sinus of Valsalva.



For a more detailed discussion, see O'Gara PT, Loscalzo J: Physical Examination of the Cardiovascular System, Chap. 267, p. 1442, in HPIM-19.

111 Electrocardiography

STANDARD APPROACH TO THE ECG

Normally, voltage standardization is 1.0 mV per 10 mm, and paper speed is 25 mm/s (each horizontal small box = 0.04 s).

Heart Rate

Beats/min = 300 divided by the number of *large* boxes (each 5 mm apart) between consecutive QRS complexes. For faster heart rates, divide 1500 by number of *small* boxes (1 mm apart) between each QRS.

Rhythm

Sinus rhythm is present if every P wave is followed by a QRS, PR interval ≥0.12 s, every QRS is preceded by a P wave, and the P wave is upright in leads I, II, and III. Arrhythmias are discussed in Chaps. 122 and 123.

Mean Axis

If QRS is primarily positive in limb leads I and II, then axis is *normal*. Otherwise, find limb lead in which QRS is most isoelectric (R = S). The mean axis is perpendicular to that lead (Fig. 111-1). If the QRS complex is *positive* in that perpendicular lead, then

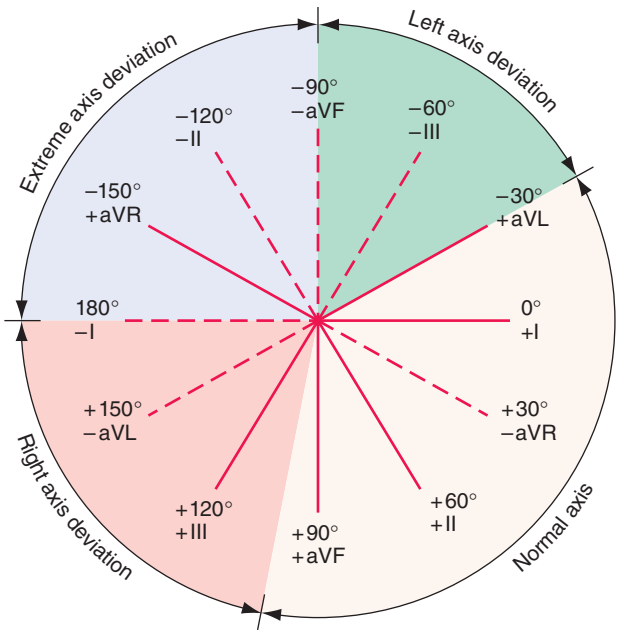


FIGURE 111-1 Electrocardiographic lead systems: The hexaxial frontal plane reference system to estimate electrical axis. Determine leads in which QRS deflections are maximum and minimum. For example, a maximum positive QRS in I which is isoelectric in aVF is oriented to 0°. Normal axis ranges from −30° to +90°. An axis > +90° is right-axis deviation and <30° is left-axis deviation.

mean axis is in the direction of that lead; if *negative*, then mean axis points directly away from that lead.

Left-axis deviation (more negative than –30°) occurs in diffuse left ventricular disease, inferior MI, and in left anterior hemiblock (small R, deep S in leads II, III, and aVF).

Right-axis deviation (>90°) occurs in right ventricular hypertrophy (R > S in V_1) and left posterior hemiblock (small Q and tall R in leads II, III, and aVF). Mild right-axis deviation is common in thin, healthy individuals (up to 110°).

INTERVALS (NORMAL VALUES IN PARENTHESES)

PR (0.12–0.20 s)

- *Short:* (1) preexcitation syndrome (look for slurred QRS upstroke due to "delta" wave), (2) nodal rhythm (inverted P in aVF).
- *Long:* first-degree atrioventricular (AV) block (Chap. 122).

QRS (0.06–0.10 s)

Widened: (1) ventricular premature beats, (2) bundle branch blocks: *right* (RsR′ in V_1, deep S in V_6) and *left* (RR′ in V_6 [Fig. 111-2]), (3) toxic levels of certain drugs (e.g., flecainide, propafenone, quinidine), (4) severe hypokalemia.

QT (<50% of RR interval; corrected QT ≤0.44 s)

Prolonged: congenital, hypokalemia, hypocalcemia, drugs (e.g., class IA and class III antiarrhythmics, tricyclics).

HYPERTROPHY

- *Right atrium:* P wave ≥2.5 mm in lead II.

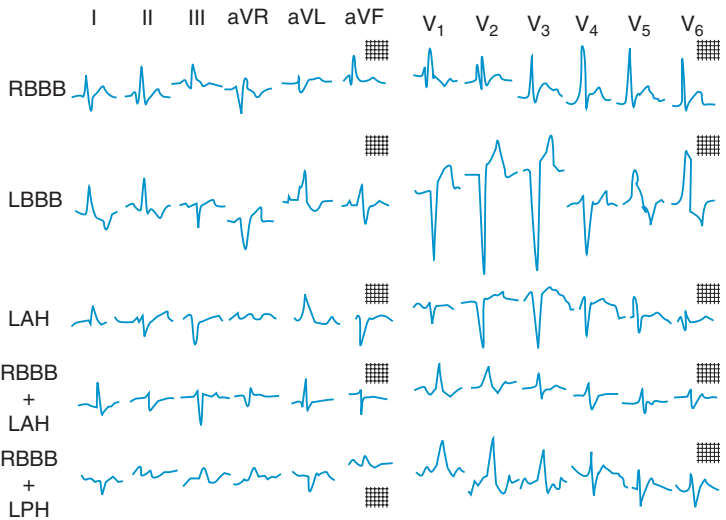


FIGURE 111-2 Intraventricular conduction abnormalities. Illustrated are right bundle branch block (RBBB); left bundle branch block (LBBB); left anterior hemiblock (LAH); right bundle branch block with left anterior hemiblock (RBBB + LAH); and right bundle branch block with left posterior hemiblock (RBBB + LPH).

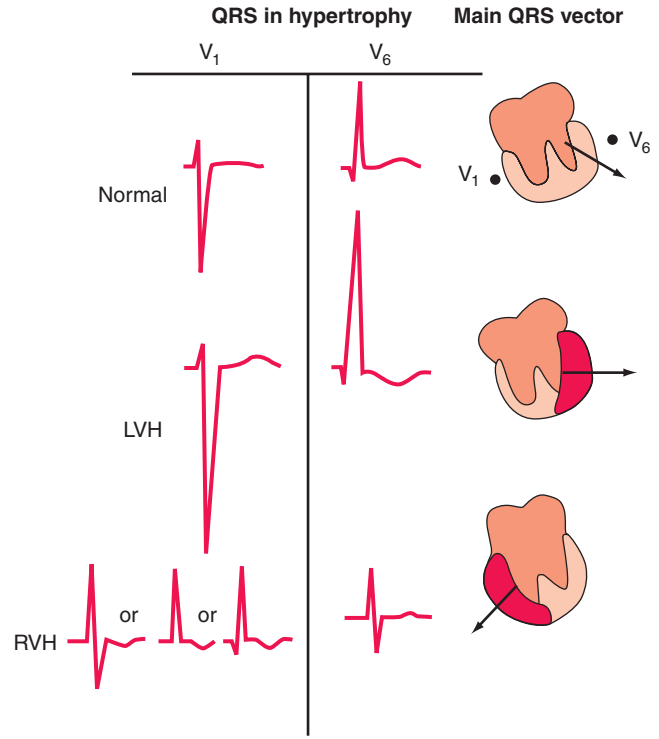


FIGURE 111-3 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V_1. T-wave inversions may be present in the right precordial leads.

- *Left atrium:* P biphasic (positive, then negative) in V_1, with terminal negative force wider than 0.04 s.
- *Right ventricle:* R > S in V_1 and R in V_1 > 5 mm; deep S in V_6; right-axis deviation (Fig. 111-3).
- *Left ventricle:* S in V_1 plus R in V_5 or V_6 ≥35 mm or R in aVL >11 mm (**Fig. 111-3**).

Infarction (Fig. 111-4)

Following acute ST-segment elevation MI without successful reperfusion: *Pathologic Q waves* (≥0.04 s and ≥25% of total QRS height) in leads shown in Table 111-1; acute *non-ST-segment elevation MI* shows ST-T changes in these leads without Q-wave development. A number of conditions (other than acute MI) can cause Q waves (Table 111-2).

ST-T WAVES

- *ST elevation:* Acute MI, coronary spasm, pericarditis (concave upward) (see Fig. 116-1 and Table 116-2), LV aneurysm, Brugada pattern (RBBB with ST elevation in V_1–V_2).

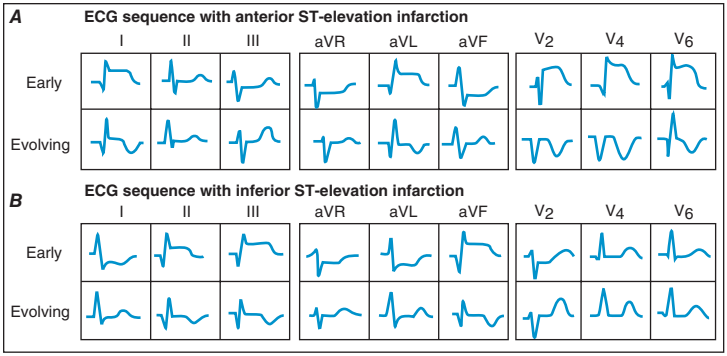


FIGURE 111-4 Sequence of depolarization and repolarization changes with **A.** acute anterior and **B.** acute inferior ST-elevation infarctions (in the absence of successful early reperfusion). With anterior infarcts, ST elevation in leads I, aVL, and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterior) infarcts may be associated with reciprocal ST depressions in leads V_1–V_3. (*Modified from AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia Elsevier, 2013.*)

TABLE 111-1 LEADS WITH ABNORMAL Q WAVES IN MI

Leads with Abnormal Q Waves	Site of Infarction
V_1–V_2	Anteroseptal
V_3–V_4	Apical
I, aVL, V_5–V_6	Anterolateral
II, III, aVF	Inferior
V_1–V_2 (tall R, *not* deep Q)	True posterior

TABLE 111-2 DIFFERENTIAL DIAGNOSIS OF Q WAVES (WITH SELECTED EXAMPLES)

Physiologic or positional factors
1. Normal "septal" Q waves
2. Left pneumothorax or dextrocardia
Myocardial injury or infiltration
1. Acute processes: myocardial infarction, myocarditis, hyperkalemia
2. Chronic processes: cardiomyopathy, amyloid, sarcoid, scleroderma, myocardial tumor
Ventricular hypertrophy/enlargement
1. Left ventricular (poor R-wave progression)[a]
2. Right ventricular (reversed R-wave progression)
3. Hypertrophic cardiomyopathy
Conduction abnormalities
1. Left bundle branch block
2. Wolff-Parkinson-White patterns

[a]Small or absent R waves in the right to midprecordial leads.
Source: Modified from AL Goldberger: *Myocardial Infarction: Electrocardiographic Differential Diagnosis*, 4th ed. St. Louis, Mosby-Year Book, 1991.

- *ST depression:* Digitalis effect, strain (due to ventricular hypertrophy), ischemia, or nontransmural MI.
- *Tall peaked T*: Hyperkalemia; acute MI ("hyperacute T").
- *Inverted T*: Non-Q-wave MI, ventricular "strain" pattern, drug effect (e.g., digitalis), hypokalemia, hypocalcemia, increased intracranial pressure (e.g., subarachnoid bleed).

For a more detailed discussion, see Goldberger AL: Electrocardiography, Chap. 268, p. 1450 in HPIM-19.

112 Noninvasive Examination of the Heart

ECHOCARDIOGRAPHY (TABLE 112-1 AND FIG. 112-1)

Visualizes heart in real time with ultrasound; Doppler recordings noninvasively assess hemodynamics and abnormal flow patterns. Imaging may be compromised in pts with chronic obstructive lung disease, thick chest wall, or narrow intercostal spaces.

Chamber Size and Ventricular Performance

Assessment of atrial and ventricular dimensions, global and regional systolic wall motion abnormalities, ventricular hypertrophy/infiltration, evaluation for pulmonary hypertension: RV systolic pressure (RVSP) is calculated from maximum velocity of tricuspid regurgitation (TR):

$$\text{RVSP} = 4 \times (\text{TR velocity})^2 + \text{RA pressure}$$

TABLE 112-1 CLINICAL USES OF ECHOCARDIOGRAPHY

2-D Echo	Transesophageal Echocardiography
Cardiac chambers: size, hypertrophy, wall motion abnormalities	Superior to 2-D echo to identify: Infective endocarditis
Valves: morphology and motion	Cardiac source of embolism
Pericardium: effusion, tamponade	Prosthetic valve dysfunction
Aorta: aneurysm, dissection	Aortic dissection
Assess intracardiac masses	
Doppler Echocardiography	**Stress Echocardiography**
Valvular stenosis and regurgitation Intracardiac shunts Diastolic filling/dysfunction Approximate intracardiac pressures	Assess myocardial ischemia and viability

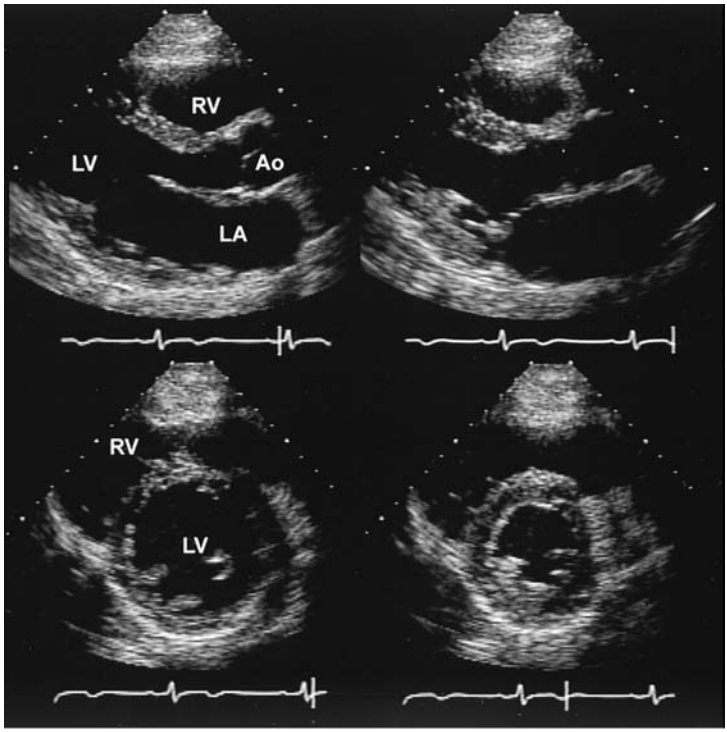


FIGURE 112-1 Two-dimensional echocardiographic still-frame images of a normal heart. *Upper:* Parasternal long axis view during systole and diastole (*left*) and systole (*right*). During systole, there is thickening of the myocardium and reduction in the size of the left ventricle (LV). The valve leaflets are thin and open widely. *Lower:* Parasternal short axis view during diastole (*left*) and systole (*right*) demonstrating a decrease in the left ventricular cavity size during systole as well as an increase in wall thickness. Ao, aorta. (*Reproduced from RJ Myerburg: HPIM-12.*)

(RA pressure is same as JVP estimated by physical examination.) In absence of RV outflow obstruction, RVSP = pulmonary artery systolic pressure.

LV diastolic function is assessed by transmitral Doppler (see Fig. 270e-8, in HPIM-19) and Doppler tissue imaging, which measures velocity of myocardial relaxation.

Valvular Abnormalities

Thickness, mobility, calcification, and regurgitation of each cardiac valve can be assessed. Severity of valvular stenosis is calculated by Doppler [peak gradient = 4 × (peak velocity)^2]. Structural lesions (e.g., flail leaflet, vegetation) resulting in regurgitation may be identified, and Doppler (Fig. 112-2) estimates severity of regurgitation.

Pericardial Disease

Echo is noninvasive modality of choice to rapidly identify pericardial effusion and assess its hemodynamic significance; in tamponade there is diastolic RA and RV

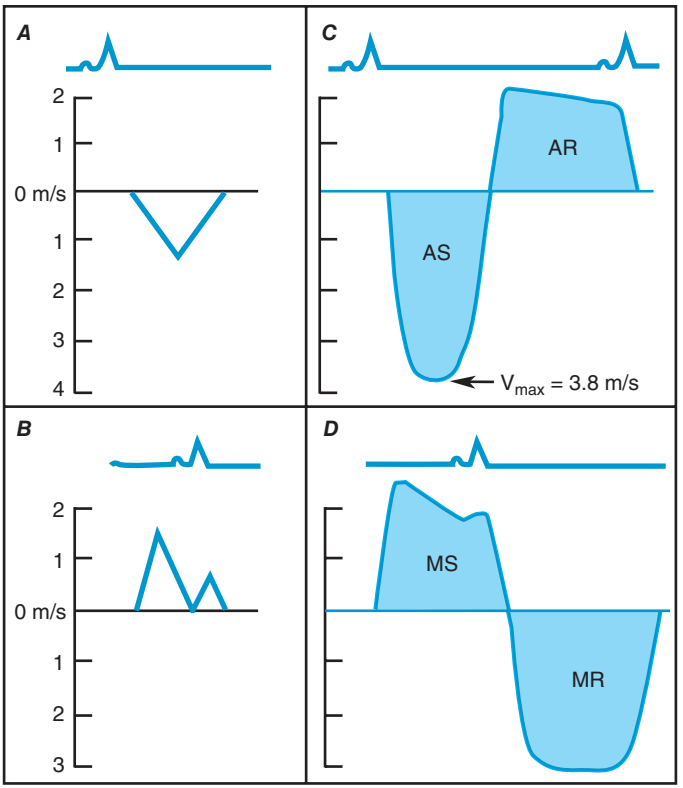


FIGURE 112-2 Schematic presentation of normal Doppler flow across the aortic **(A)** and mitral **(B)** valves**.** Abnormal continuous wave Doppler profiles: **C.** Aortic stenosis (AS) [peak transaortic gradient = $4 \times V_{max}^{2} = 4 \times (3.8)^2 = 58$ mmHg] and regurgitation (AR). **D.** Mitral stenosis (MS) and regurgitation (MR).

collapse, dilatation of IVC, exaggerated respiratory alterations in transvalvular Doppler velocities. Actual thickness of pericardium (e.g., in suspected constrictive pericarditis) is better measured by CT or MRI.

Intracardiac Masses

May visualize atrial or ventricular thrombus, intracardiac tumors, and valvular vegetations. Yield of identifying cardiac source of embolism is low in the absence of cardiac history or physical findings. Transesophageal echocardiography (TEE) is more sensitive than standard transthoracic study for masses <1 cm in diameter.

Aortic Disease

Aneurysm and dissection of the aorta may be evaluated and complications (aortic regurgitation, tamponade) assessed (Chap. 125) by standard transthoracic echo. TEE is more sensitive and specific for aortic dissection.

Congenital Heart Disease (See Chap. 113)

Echo, Doppler, and IV saline contrast echo are useful to identify congenital lesions and shunts.

Stress Echocardiography

Echo performed prior to, and after, treadmill or bicycle exercise identifies regions of prior MI and inducible myocardial ischemia (↓ regional contraction with exercise). Dobutamine pharmacologic stress echo can be substituted for pts who cannot exercise.

NUCLEAR CARDIOLOGY

Uses nuclear isotopes to assess LV perfusion and contractile function.

Ventricular Function Assessment

Contractile function can be assessed during gated single-photon emission computed tomography (SPECT) myocardial perfusion exercise test imaging (see below). Occasionally, blood pool imaging is obtained by injecting IV ^{99m} Tc-labeled albumin or RBCs to quantify LV ejection fraction.

Nuclear Myocardial Perfusion Assessment

SPECT imaging, most commonly using ^{99m} Tc-labeled compounds (sestamibi or tetrofosmin), or PET imaging (^{82}Rb or $^{13}NH_3$), obtained at peak stress and at rest, depicts zones of prior infarction as fixed defects and regions of inducible myocardial ischemia as reversible defects. Nuclear imaging is more sensitive, but less specific, than stress echocardiography for detection of ischemia.

For pts who cannot exercise, pharmacologic perfusion imaging with adenosine, regadenoson, dipyridamole, or dobutamine is used instead (Chap. 121). For pts with LBBB, perfusion imaging with adenosine or dipyridamole is preferred to avoid artifactual septal defects that are common with exercise imaging.

Pharmacologic PET scanning is especially useful in imaging obese pts and to assess myocardial viability. Thallium-201 SPECT imaging can also be utilized to assess viability.

MAGNETIC RESONANCE IMAGING

Delineates cardiac structures with high resolution without ionizing radiation. Excellent technique to quantitate LV mass, to characterize the pericardium, great vessels, anatomic relationships in congenital heart disease, abnormal cardiac masses, and to evaluate valvular heart disease as a complement to echocardiography. MRI with delayed gadolinium enhancement (avoid in pts with renal insufficiency) differentiates ischemic from nonischemic cardiomyopathy and is useful in assessing myocardial viability. Pharmacologic stress testing with MR identifies significant CAD and detects subendocardial ischemia with higher sensitivity than SPECT imaging.

COMPUTED TOMOGRAPHY

Provides high-resolution images of cardiac structures (including the pericardium and cardiac masses) and detects coronary calcification in atherosclerosis with high sensitivity. CT angiography (CTA) delineates abnormalities of the great vessels, including aortic aneurysms and dissection, and pulmonary embolism. Multislice spiral CT provides high-resolution images of coronary anatomy. It is most useful in evaluation of suspected coronary anatomic anomalies and to exclude high-grade coronary stenoses in pts with chest pain and intermediate pretest probability of coronary artery disease. Its greatest accuracy is in detection of left main and proximal

TABLE 112-2 SELECTION OF IMAGING TESTS

	Echo	Nuclear	CT	MRI[a]
LV size/ function	Initial modality of choice Low cost, portable Provides ancillary structural and hemodynamic information	Available from gated SPECT stress imaging	Best resolution High cost	Best resolution High cost
Valve disease	Initial modality of choice Valve motion Doppler hemodynamics			Visualize valve motion Delineate abnormal flow
Pericardial disease	Pericardial effusion Doppler hemodynamics		Pericardial thickening	Pericardial thickening
Aortic disease	TEE rapid diagnosis of acute dissection[c]		Image entire aorta Aortic aneurysms Aortic dissection	Image entire aorta Aortic aneurysms Chronic dissection
Cardiac masses	TTE—large intracardiac masses TEE—smaller intracardiac masses[b]		Extracardiac masses Myocardial masses	Extracardiac masses Myocardiac masses

[a]Relative contraindication: pacemakers, metallic objects, claustrophobic.
[b]When not seen on TTE.
Abbreviations: Echo, echocardiography; SPECT, single-photon emission CT; TEE, transesophageal echocardiography; TTE, transthoracic echocardiogram.

LAD and circumflex disease. CTA is also helpful in assessing the patency of bypass grafts.

Table 112-2 summarizes key diagnostic features of the noninvasive imaging modalities. Figure 112-3 provides an algorithm for diagnostic imaging assessment of suspected CAD.



For a more detailed discussion, see DiCarli MF, Kwong RY, Solomon SD: Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging, Chap. 270e, in HPIM-19.

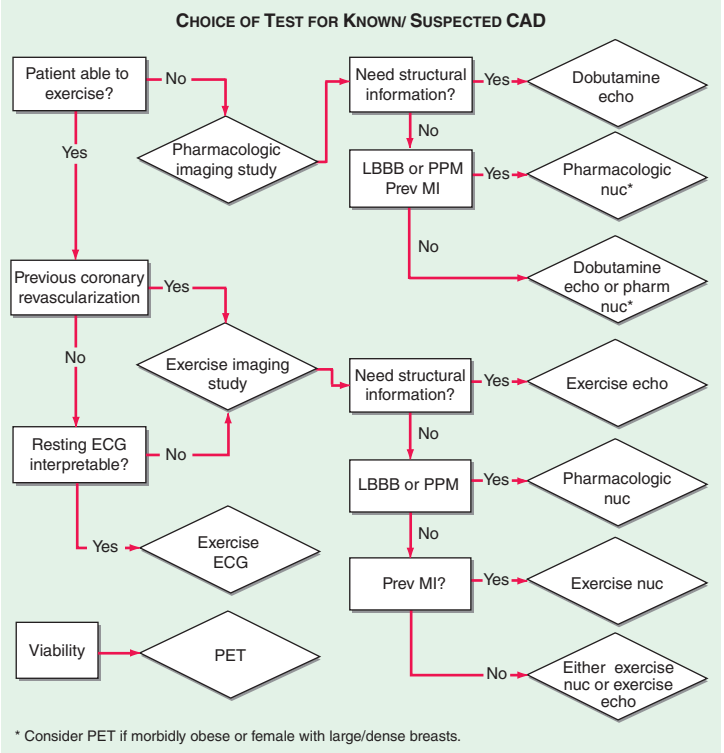


FIGURE 112-3 Flow diagram showing selection of initial stress test in a pt with chest pain. LBBB, left bundle branch block; Prev MI-Reg ischemia, previous MI with a need to detect regional ischemia; Nuc, SPECT nuclear imaging study; Pharm, pharmacologic.

113 Congenital Heart Disease in the Adult

ACYANOTIC CONGENITAL HEART LESIONS WITH LEFT-TO-RIGHT SHUNT

ATRIAL SEPTAL DEFECT (ASD)

Most common is *ostium secundum* ASD, located at mid interatrial septum. *Sinus venosus* type ASD involves the high atrial septum and may be associated with anomalous pulmonary venous connection to the right heart. *Ostium primum* ASDs (e.g., typical of Down syndrome) appear at lower atrial septum, adjacent to atrioventricular (AV) valves.

History

Usually asymptomatic until third or fourth decades, when exertional dyspnea, fatigue, and palpitations may occur. Onset of symptoms may be associated with development of pulmonary hypertension (see below).

Physical Examination

Prominent right ventricular (RV) impulse, wide fixed splitting of S_2, systolic murmur from flow across pulmonic valve, diastolic flow rumble across tricuspid valve, prominent jugular venous *v* wave.

ECG

Incomplete RBBB (rSR' in right precordial leads) common. Left axis deviation frequently present with ostium primum defect. Ectopic atrial pacemaker or first degree AV block occur in sinus venosus defects.

CXR

Increased pulmonary vascular markings, prominence of right atrium (RA), RV, and main pulmonary artery (LA enlargement *not* usually present).

Echocardiogram

RA, RV, and pulmonary artery enlargement; Doppler shows abnormal turbulent transatrial flow. Echo contrast (agitated saline injection into peripheral systemic vein) may visualize transatrial shunt. Transesophageal echo usually diagnostic if transthoracic echo is ambiguous.

TREATMENT **ATRIAL SEPTAL DEFECT**

In the absence of contraindications an ASD with a significant pulmonary-to-systemic flow (PF:SF) ratio (≥1.5:1.0) should be considered for surgical or percutaneous transcatheter closure. Closure is usually contraindicated with significant pulmonary hypertension and is not undertaken for small defects with trivial left-to-right shunt flow.

VENTRICULAR SEPTAL DEFECT (VSD)

Congenital VSDs may close spontaneously during childhood. Symptoms relate to size of the defect and pulmonary vascular resistance.

History

CHF may develop in infancy. Adults may be asymptomatic or develop fatigue and reduced exercise tolerance.

Physical Examination

Holosystolic murmur at lower left sternal border, which may be accompanied by a palpaple thrill, loud P_2; diastolic flow murmur across mitral valve.

ECG

Normal with small defects. Large shunts result in LA and LV enlargement.

CXR

Enlargement of main pulmonary artery, LA, and LV, with increased pulmonary vascular markings.

Echocardiogram

LA and LV enlargement; defect may be directly visualized. Color Doppler demonstrates flow across the defect.

TREATMENT **VENTRICULAR SEPTAL DEFECT**

Fatigue and mild dyspnea are treated with diuretics and afterload reduction (Chap. 124). Surgical closure is indicated if PF:SF >1.5:1 in absence of very high pulmonary vascular resistance.

PATENT DUCTUS ARTERIOSUS (PDA)

Abnormal communication between the descending aorta and pulmonary artery; associated with birth at high altitudes and maternal rubella.

History

Asymptomatic or fatigue and dyspnea on exertion.

Physical Examination

Hyperactive LV impulse; loud continuous "machinery" murmur at upper left sternal border. If pulmonary hypertension develops, diastolic component of the murmur may disappear.

ECG

LV hypertrophy is common; RV hypertrophy if pulmonary hypertension develops.

CXR

Increased pulmonary vascular markings: enlarged main pulmonary artery, LV, ascending aorta; occasionally, calcification of ductus.

Echocardiography

Hyperdynamic, enlarged LV; the PDA can often be visualized on two-dimensional echo; Doppler demonstrates abnormal flow through it.

TREATMENT **PATENT DUCTUS ARTERIOSUS**

In absence of pulmonary hypertension, PDA should be surgically ligated or divided to prevent infective endocarditis, LV dysfunction, and pulmonary hypertension. Transcatheter device closure is frequently possible.

PROGRESSION TO PULMONARY HYPERTENSION (PHT)

Pts with large, uncorrected left-to-right shunts (e.g., ASD, VSD, or PDA) may develop progressive, irreversible PHT with reverse shunting of desaturated blood into the arterial circulation (right-to-left direction), resulting in *Eisenmenger syndrome*. Fatigue, lightheadedness, and chest pain due to RV ischemia are common, accompanied by cyanosis, clubbing of digits, loud P_2, murmur of pulmonary valve regurgitation, and signs of RV failure. ECG and echocardiogram show RV hypertrophy. Therapeutic options are limited and include pulmonary artery vasodilators (see Chap. 127) and consideration of single lung transplant with repair of the cardiac defect, or heart-lung transplantation.

ACYANOTIC CONGENITAL HEART LESIONS WITHOUT A SHUNT

PULMONIC STENOSIS (PS)

A transpulmonary valve gradient < 30 mmHg indicates mild PS, 30–50 mmHg is moderate PS, and >50 mmHg is considered severe PS. Mild to moderate PS rarely causes symptoms, and progression tends not to occur. Pts with higher gradients may manifest dyspnea, fatigue, light-headedness, chest pain (RV ischemia).

Physical Examination

Jugular venous distention with prominent *a* wave, RV parasternal impulse, wide splitting of S_2 with soft P_2, ejection click followed by "diamond-shaped" systolic murmur at upper left sternal border, right-sided S_4.

ECG

Normal in mild PS; RA and RV enlargement in advanced PS.

CXR

Often shows poststenotic dilatation of the pulmonary artery and RV enlargement.

Echocardiography

RV hypertrophy and systolic "doming" of the pulmonic valve. Doppler accurately measures transvalvular gradient.

TREATMENT **PULMONIC STENOSIS**

Symptomatic or severe stenosis requires balloon valvuloplasty or surgical correction.

CONGENITALLY BICUSPID AORTIC VALVE

One of the most common congenital heart malformations (up to 1.4% of the population); rarely results in childhood aortic stenosis (AS), but is a cause of AS and/or regurgitation later in life. May go undetected in early life or suspected by the presence of a systolic ejection click; often identified during echocardiography that was obtained for another reason. See Chap. 114 for typical history, physical findings, and treatment of subsequent clinical aortic valve disease.

COARCTATION OF THE AORTA

Aortic constriction just distal to the origin of the left subclavian artery is a surgically correctable form of hypertension (Chap. 117). Usually asymptomatic, but may cause headache, fatigue, or claudication of lower extremities. Often accompanied by bicuspid aortic valve.

Physical Examination

Hypertension in upper extremities; delayed femoral pulses with decreased pressure in lower extremities. Pulsatile collateral arteries may be palpated in the intercostal spaces. Systolic (and sometimes also diastolic) murmur is best heard over the upper back at the left interscapular space.

ECG

LV hypertrophy.

CXR

Notching of the ribs due to collateral arteries; "figure 3" appearance of distal aortic arch.

Echocardiography

Can delineate site and length of coarctation, and Doppler determines the pressure gradient across it. MR or CT angiography also visualizes the site of coarctation and can identify associated collateral vessel formation.

TREATMENT **COARCTATION OF THE AORTA**

Surgical correction (or percutaneous transcatheter stent dilation in selected pts), although hypertension may persist. Recoarctation after surgical repair may be amenable to percutaneous balloon dilatation.

COMPLEX CONGENITAL HEART LESIONS

Such lesions are often accompanied by cyanosis. Examples include:

TETRALOGY OF FALLOT

The four main components are (1) malaligned VSD, (2) obstruction to RV outflow, (3) aorta that overrides the VSD, and (4) RV hypertrophy (RVH). Degree of RV outflow obstruction largely determines clinical presentation; when severe, the large right-to-left shunt causes cyanosis and systemic hypoxemia. *ECG* shows RVH. *CXR* demonstrates "boot-shaped" heart with prominent RV. *Echocardiography* delineates VSD, overriding aorta, and RVH and quantitates degree of RV outflow obstruction.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Accounts for 10% of pts with cyanotic congenital heart disease. Aorta and pulmonary artery arise abnormally from the right and left ventricles respectively, creating two separate parallel circulations; a communication must exist between the two sides (ASD, PDA, or VSD) to sustain life. Development of RV dysfunction and heart failure are common by the third decade. *Echocardiography* reveals the aberrant anatomy.

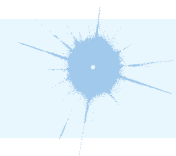
EBSTEIN ANOMALY

Abnormal downward placement of tricuspid valve within the RV; tricuspid regurgitation, hypoplasia of RV, and a right-to-left shunt are common. *Echocardiography* shows apical displacement of tricuspid septal leaflet, abnormal RV size, and quantitates degree of tricuspid regurgitation.

ENDOCARDITIS PROPHYLAXIS IN CONGENITAL HEART DISEASE

American Heart Association 2007 Guidelines recommend antibiotic prophylaxis only in specific pts with congenital heart disease, i.e., those who are to undergo a dental procedure associated with bacteremia who have:

1. Unrepaired cyanotic congenital heart disease (e.g., tetralogy of Fallot)
2. Repaired congenital heart disease with residual defects adjacent to site of a prosthetic patch or transcatheter device
3. A history of complete repair of congenital defects with prosthetic material or a transcatheter device within the previous 6 months



For a more detailed discussion, see Aboulhosn JA, Child JS: Congenital Heart Disease in the Adult, Chap. 282, p. 1519, in HPIM-19.

114 Valvular Heart Disease

MITRAL STENOSIS (MS)

Etiology

Most commonly rheumatic, although history of acute rheumatic fever is now uncommon; rare causes include congenital MS and calcification of the mitral annulus with extension onto the leaflets.

History

Symptoms most commonly begin in the fourth decade, but MS often causes severe disability at earlier ages in developing nations. Principal symptoms are dyspnea and pulmonary edema precipitated by exertion, excitement, fever, anemia, tachycardia, pregnancy, sexual intercourse, etc.

Physical Examination

Right ventricular lift; palpable S_1; opening snap (OS) follows A_2 by 0.06–0.12 s; OS–A_2 interval inversely proportional to severity of obstruction. Diastolic rumbling murmur with presystolic accentuation when in sinus rhythm. Duration of murmur correlates with severity of obstruction.

Complications

Hemoptysis, pulmonary embolism, pulmonary infection, systemic embolization; endocarditis is uncommon in pure MS.

Laboratory ECG

Typically shows atrial fibrillation (AF) or left atrial (LA) enlargement when sinus rhythm is present. Right-axis deviation and RV hypertrophy in the presence of pulmonary hypertension.

CXR

Shows LA and RV enlargement and Kerley B lines.

Echocardiogram

Most useful noninvasive test; shows reduced separation, calcification and thickening of valve leaflets and subvalvular apparatus, and LA enlargement. Doppler flow recordings provide estimation of transvalvular gradient, mitral valve area, and degree of pulmonary hypertension (Chap. 112).

TREATMENT MITRAL STENOSIS (SEE FIG. 114-1)

At-risk pts should receive prophylaxis for recurrent rheumatic fever (penicillin V 250–500 mg PO bid or benzathine penicillin G 1–2 M units IM monthly). In the presence of dyspnea, sodium restriction and oral diuretic therapy; beta blockers, rate-limiting calcium channel antagonists (i.e., verapamil or diltiazem), or digoxin to slow ventricular rate in AF. Warfarin (with target INR 2.0–3.0) for pts with AF or history of thromoembolism. For AF of recent onset, consider conversion (chemical or electrical) to sinus rhythm, ideally after ≥3 weeks of anticoagulation. Mitral valvotomy in the presence of symptoms and mitral orifice ≤ ~1.5 cm^2. In uncomplicated MS, percutaneous balloon valvuloplasty is the procedure of choice; if not feasible, then open surgical valvotomy (Fig. 114-1).

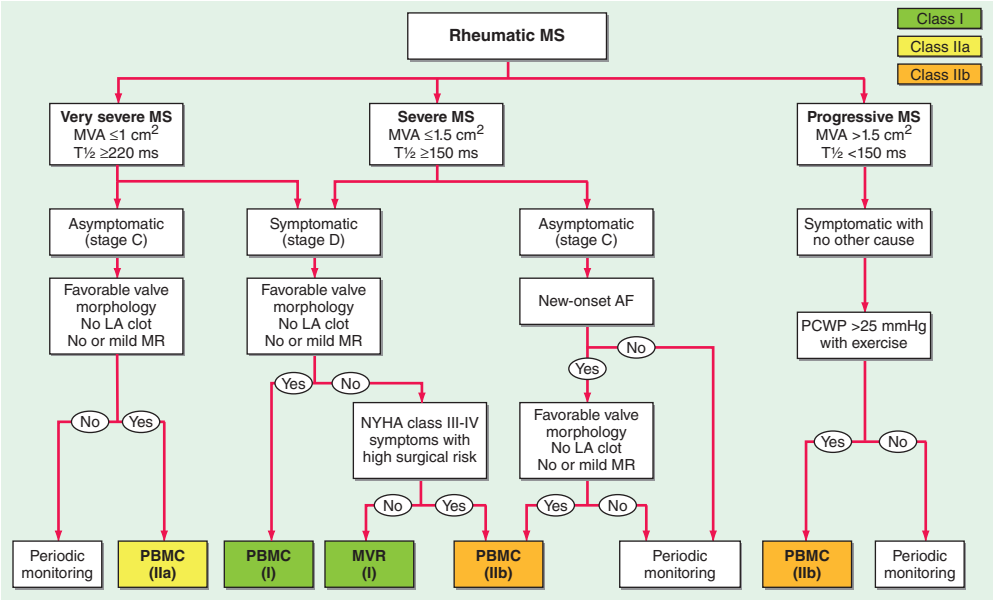


FIGURE 114-1 Management of rheumatic mitral stenosis. MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

MITRAL REGURGITATION (MR)

Etiology

Mitral valve prolapse (see below), rheumatic heart disease, ischemic heart disease with papillary muscle dysfunction, LV dilatation of any cause, mitral annular calcification, hypertrophic cardiomyopathy, infective endocarditis, congenital.

Clinical Manifestations

Fatigue, weakness, and exertional dyspnea. Physical examination: sharp low-volume upstroke of carotid arterial pulse, LV lift, S_1 diminished: wide splitting of S_2; S_3 common; loud holosystolic murmur at the apex (less than holosystolic in acute severe MR) and often a brief early-mid-diastolic murmur due to increased transvalvular flow.

Echocardiogram

Enlarged LA, hyperdynamic LV, identifies mechanism of MR; Doppler analysis helpful in diagnosis and assessment of severity of MR and degree of pulmonary hypertension.

TREATMENT MITRAL REGURGITATION (SEE FIG. 114-2)

For severe/decompensated MR, treat as for heart failure (Chap. 124). IV vasodilators (e.g., nitroprusside) are beneficial for acute, severe MR. Anticoagulation is indicated in the presence of atrial fibrillation. For chronic primary MR, surgical treatment, either valve repair or replacement, is appropriate if pt has symptoms or evidence of progressive LV dysfunction (e.g., LV ejection fraction [LVEF] ≤60% or end-systolic LV diameter by echo ≥40 mm). Operation should be carried out before development of chronic heart failure symptoms. Pts with functional ischemic MR may require coronary artery revascularization along with valve repair. Functional nonischemic MR due to LV enlargement with impaired contractile function should be treated with aggressive heart failure therapies and consideration of cardiac resynchronization therapy (Chap. 124).

MITRAL VALVE PROLAPSE (MVP)

Etiology

Most commonly idiopathic; may accompany Marfan syndrome, Ehlers-Danlos syndrome.

Pathology

Redundant mitral valve tissue with myxedematous degeneration and elongated chordae tendineae.

Clinical Manifestations

More common in females. Most pts are asymptomatic and remain so. Potential symptoms include vague chest pain and supraventricular and ventricular arrhythmias. Most important complication is progressive MR. Rarely, systemic emboli from platelet-fibrin deposits on valve. Sudden death is a very rare outcome.

Physical Examination

Mid or late systolic click(s) followed by late systolic murmur at the apex; exaggeration by Valsalva maneuver, reduced by squatting and isometric exercise (Chap. 110).

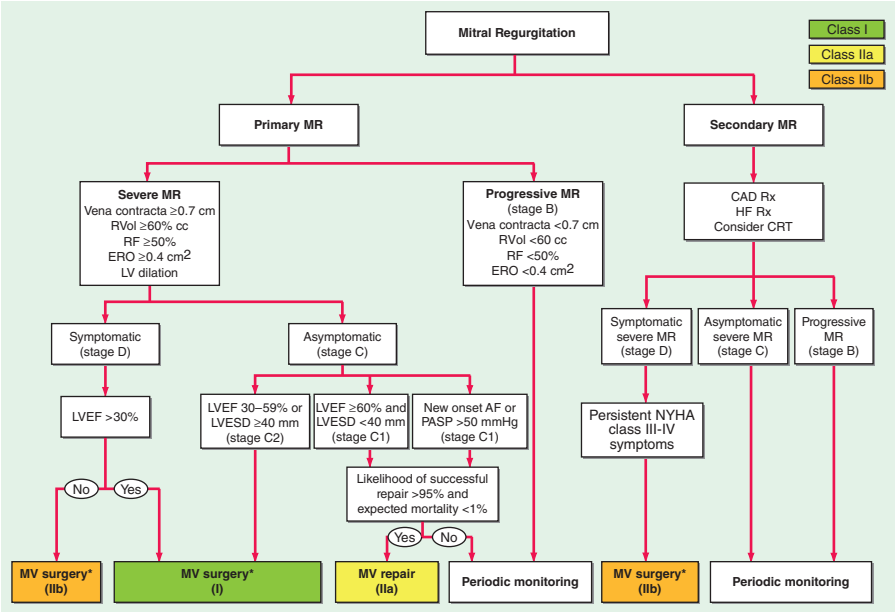


FIGURE 114-2 Management of mitral regurgitation. CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. Mitral valve repair preferred over MVR when possible. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

Echocardiogram

Shows posterior displacement of one or both mitral leaflets late in systole.

TREATMENT **MITRAL VALVE PROLAPSE**

Asymptomatic pts should be reassured. Beta blockers may lessen chest discomfort and palpitations. Prophylaxis for infective endocarditis is indicated only if prior history of endocarditis. Valve repair or replacement for pts with severe mitral regurgitation; aspirin or anticoagulants for pts with history of TIA or embolization.

AORTIC STENOSIS (AS)

Etiologies

Most common are (1) degenerative calcification of a congenitally bicuspid valve, (2) chronic deterioration and calcification of a trileaflet valve, and (3) rheumatic disease (almost always associated with rheumatic *mitral* disease).

Symptoms

Exertional dyspnea, angina, and syncope are cardinal symptoms; they occur late, after years of obstruction and aortic valve area ≤1.0 cm^2.

Physical Examination

Weak and delayed (parvus et tardus) arterial pulses with carotid thrill. A_2 soft or absent; S_4 common. Crescendo-decrescendo systolic murmur, often with systolic thrill. Murmur is typically loudest at second right intercostal space, with radiation to carotids and sometimes to the apex (*Gallavardin effect*).

ECG

Often shows LV hypertrophy, but not useful for predicting gradient.

Echocardiogram

Shows LV hypertrophy, calcification and thickening of aortic valve cusps with reduced systolic opening. Dilatation and reduced contraction of LV indicate poor prognosis. Doppler quantitates systolic gradient and allows calculation of valve area.

TREATMENT **AORTIC STENOSIS (SEE FIG. 114-3)**

Avoid strenuous activity in severe AS, even in asymptomatic phase. Treat heart failure in standard fashion (Chap. 124), but use vasodilators with caution in pts with advanced disease. Valve replacement is indicated in adults with symptoms resulting from AS and hemodynamic evidence of severe obstruction. Transcatheter aortic valve implantation (TAVI) is an alternative approach for pts at excessive or prohibitive surgical risk.

AORTIC REGURGITATION (AR)

Etiology

Valvular: Rheumatic (especially if rheumatic mitral disease is present), bicuspid valve, endocarditis. *Dilated aortic root:* dilatation due to cystic medial necrosis, aortic dissection, ankylosing spondylitis, syphilis. Three-fourths of pts are male.

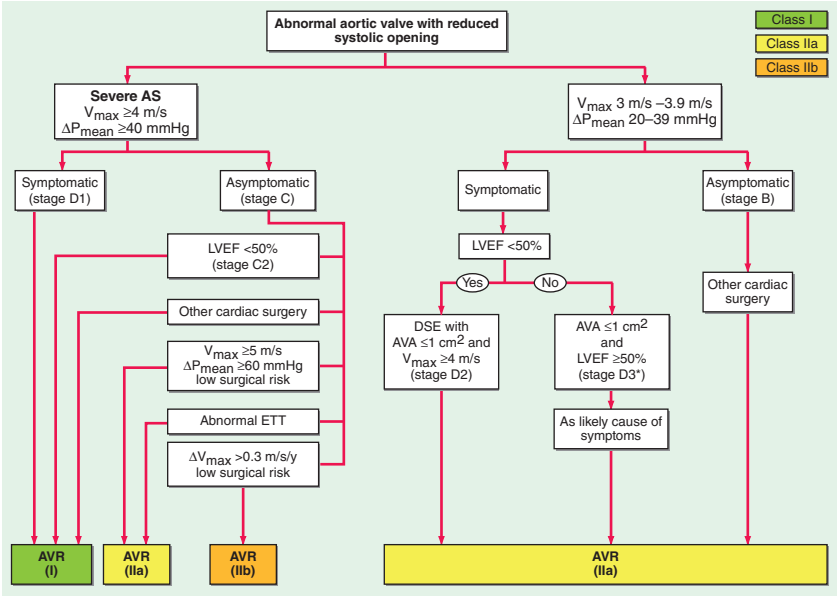


FIGURE 114-3 Algorithm for the management of aortic stenosis (AS). See Figure 283-2, p. 1533, in HPIM 19 for explanation of specific stages A-D of disease progression. AS, aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; and V_{max}, maximum velocity. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57, 2014.)*

Clinical Manifestations

Exertional dyspnea and awareness of forceful heartbeat, angina pectoris, and signs of LV failure. Wide pulse pressure, "water hammer" pulse, capillary pulsations (Quincke's sign), A_2 soft or absent, S_3 may be present. Blowing, decrescendo diastolic murmur along left sternal border (along right sternal border when due to aortic dilatation). In acute severe AR, the pulse pressure is typically not widened and the diastolic murmur is often short (i.e., occurring only in early diastole) and soft.

Laboratory ECG and CXR

LV enlargement.

Echocardiogram

LA enlargement, LV enlargement, high-frequency diastolic fluttering of mitral valve. Failure of coaptation of aortic valve leaflets may be present. Doppler studies useful in detection and quantification of AR. Cardiac magnetic resonance imaging helpful if echo is inadequate.

TREATMENT AORTIC REGURGITATION

Standard therapy for LV failure (Chap. 124). Vasodilators (ACE inhibitor or long-acting nifedipine) are recommended if hypertension present. Avoid beta blockers, which prolong diastolic filling. Surgical valve replacement should be carried out in pts with severe AR when symptoms develop or in asymptomatic pts with LV dysfunction (e.g., LVEF <50%, end-systolic diameter >50 mm, or LV diastolic dimension >65 mm) by imaging studies.

TRICUSPID STENOSIS (TS)

Etiology

Usually rheumatic; most common in females; almost invariably associated with MS.

Clinical Manifestations

Hepatomegaly, ascites, edema, jaundice, jugular venous distention with slow *y* descent (Chap. 110). Diastolic rumbling murmur along left sternal border increased by inspiration with loud presystolic component. Right atrial and superior vena caval enlargement on chest x-ray. Doppler echocardiography demonstrates thickened valve and impaired separation of leaflets and provides estimate of transvalvular gradient.

TREATMENT TRICUSPID STENOSIS

In severe TS, surgical relief is indicated, with valvular repair or replacement.

TRICUSPID REGURGITATION (TR)

Etiology

Usually functional and secondary to marked RV dilatation of any cause and often associated with pulmonary hypertension.

Clinical Manifestations

Severe RV failure, with edema, hepatomegaly, and prominent *v* waves in jugular venous pulse with rapid *y* descent (Chap. 110). Systolic murmur along lower left sternal edge is increased by inspiration. Doppler echocardiography confirms diagnosis and estimates severity.

TREATMENT **TRICUSPID REGURGITATION**

Intensive diuretic therapy when right-sided heart failure signs are present. In severe cases (in absence of severe pulmonary hypertension), surgical treatment consists of tricuspid annuloplasty or valve replacement.

For a more detailed discussion, see O'Gara PT, Loscalzo J: Aortic Valve Disease, Chap. 283, p. 1528; Mitral Valve Disease, Chap. 284, p. 1539; Tricuspid and Pulmonary Valve Disease, Chap. 285, p. 1547; Multiple and Mixed Valvular Disease, Chap. 286, p. 1550 in HPIM-19.

115 Cardiomyopathies and Myocarditis

Cardiomyopathies are primary diseases of heart muscle. Table 115-1 summarizes distinguishing presenting features of the three major types of cardiomyopathy. Table 115-2 details the comprehensive initial evaluation of suspected cardiomyopathies.

DILATED CARDIOMYOPATHY (CMP)

Symmetrically dilated left ventricle (LV), with poor systolic contractile function; right ventricle (RV) commonly involved.

Etiology

Approximately one-third of pts have a familial form, including those cases due to mutations in genes encoding sarcomeric proteins. Other causes include previous myocarditis, toxins (ethanol, certain antineoplastic agents [doxorubicin, trastuzumab, imatinib]), connective tissue disorders, hemochromatosis, sarcoidosis, muscular dystrophies, "peripartum." Impaired LV function owing to severe coronary disease/infarction or chronic aortic/mitral regurgitation may behave similarly.

Symptoms

Congestive heart failure (Chap. 124); tachyarrhythmias and peripheral emboli from LV mural thrombus occur.

Physical Examination

Jugular venous distention (JVD), rales, diffuse and dyskinetic LV apex, S_3, hepatomegaly, peripheral edema; murmurs of mitral and tricuspid regurgitation are common.

Laboratory ECG

Left bundle branch block and ST-T-wave abnormalities common.

CXR

Cardiomegaly, pulmonary vascular redistribution, pulmonary effusions common.

TABLE 115-1 PRESENTATION WITH SYMPTOMATIC CARDIOMYOPATHY

	Dilated	Restrictive	Hypertrophic
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased	Increased; may be massive	Increased
Valvular regurgitation	Related to annular dilation	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early	Exertional intolerance; may have chest pain
Congestive symptoms[a]	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion may develop late
Arrhythmia	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

[a]Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic versus congestion: discomfort on bending, hepatic and abdominal distention, peripheral edema.

Echocardiogram, CT, and Cardiac MRI

LV and RV enlargement with globally impaired contraction. *Regional* wall motion abnormalities suggest coronary artery disease rather than primary cardiomyopathy.

B-Type Natriuretic Peptide (BNP)

Level elevated in heart failure/cardiomyopathy but not in pts with dyspnea due to lung disease.

TREATMENT DILATED CARDIOMYOPATHY

Standard therapy of heart failure (Chap. 124): Diuretic for volume overload, vasodilator therapy with ACE inhibitor (preferred), angiotensin receptor blocker or hydralazine-nitrate combination shown to limit disease progression and improve longevity. Add beta blocker in most pts. Consider aldosterone antagonist

TABLE 115-2 INITIAL EVALUATION OF CARDIOMYOPATHY

Clinical Evaluation
Thorough history and physical examination to identify cardiac and noncardiac disorders[a]
Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders and tachyarrhythmias, sudden death
History of alcohol, illicit drugs, chemotherapy, or radiation therapy[a]
Assessment of ability to perform routine and desired activities[a]
Assessment of volume status, orthostatic blood pressure, body mass index[a]
Laboratory Evaluation
Electrocardiogram[a]
Chest radiograph[a]
Two-dimensional and Doppler echocardiogram[a]
Magnetic resonance imaging to assess myocardial inflammation and fibrosis
Chemistry:
Serum sodium,[a] potassium,[a] calcium,[a] magnesium[a]
Fasting glucose (glycohemoglobin in DM)
Creatinine, [a] blood urea nitrogen[a]
Albumin,[a] total protein,[a] liver function tests[a]
Lipid profile
Thyroid-stimulating hormone[a]
Serum iron, transferrin saturation
Urinalysis
Hematology:
Hemoglobin/hematocrit[a]
White blood cell count with differential,[a] including eosinophils
Erythrocyte sedimentation rate
Initial Evaluation Only in Pts Selected for Possible Specific Diagnosis
Titers for infection in presence of clinical suspicion:
Acute viral (e.g., coxsackievirus, echovirus, influenza virus)
Human immunodeficiency virus,
Chagas' disease, Lyme disease, toxoplasmosis
Catheterization with coronary angiography in pts with angina who are candidates for intervention[a]
Serologies for active rheumatologic disease
Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
Screening for sleep-disordered breathing

[a]Level I Recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the adult.
Source: From SA Hunt et al: *Circulation* 112: 2005.

therapy for pts with class II–IV heart failure, and chronic anticoagulation if there is accompanying atrial fibrillation (AF), prior embolism, or recent large anterior MI. Antiarrhythmic drugs (e.g., amiodarone or dofetilide) may be useful to maintain sinus rhythm in pts with AF. Consider implanted cardioverter defibrillator for pts with ≥ class III heart failure and LVEF <35%. For those with persistent class III–IV heart failure, LVEF <35%, and QRS duration >120 ms, consider biventricular

pacing. Possible trial of immunosuppressive drugs, if active myocarditis present on RV biopsy (controversial as long-term efficacy has not been demonstrated). In selected pts, consider cardiac transplantation.

RESTRICTIVE CARDIOMYOPATHY

Increased myocardial stiffness impairs ventricular relaxation; diastolic ventricular pressures are elevated. Etiologies include infiltrative disease (amyloid, sarcoid, hemochromatosis, eosinophilic disorders), endomyocardial fibrosis, Fabry's disease, and prior mediastinal irradiation.

Symptoms

Typically presents with heart failure, often predominantly right-sided.

Physical Examination

Especially signs of right-sided heart failure: JVD, hepatomegaly, peripheral edema, murmur of tricuspid regurgitation. S_4 is common.

Laboratory ECG

Low limb lead voltage, sinus tachycardia, ST-T-wave abnormalities.

CXR

Mild LV enlargement.

Echocardiogram, CT, Cardiac MRI

Bilateral atrial enlargement; increased ventricular thickness ("speckled pattern") in infiltrative disease, especially amyloidosis. Systolic function is usually normal but may be mildly reduced.

Cardiac Catheterization

Increased LV and RV diastolic pressures with "dip and plateau" pattern; RV biopsy useful in detecting infiltrative disease (rectal or fat pad biopsy useful in diagnosis of amyloidosis).

Note: Must distinguish restrictive cardiomyopathy from constrictive pericarditis, which is surgically correctable. Thickening of pericardium on CT or MR imaging is apparent in >80% of pts with constrictive pericarditis.

TREATMENT RESTRICTIVE CARDIOMYOPATHY

Salt restriction and diuretics ameliorate pulmonary and systemic congestion. ***Note:*** Increased sensitivity to digitalis in amyloidosis. Anticoagulation often indicated, particularly in pts with eosinophilic endomyocarditis. For specific therapy of hemochromatosis and sarcoidosis, see Chaps. 428 and 390, respectively, in HPIM-19.

HYPERTROPHIC CARDIOMYOPATHY

Marked LV hypertrophy; often asymmetric, without underlying hypertension or valvular disease. Systolic function is usually normal; increased LV stiffness results in elevated diastolic filling pressures. Typically results from mutations in sarcomeric proteins (autosomal dominant transmission).

Symptoms

Secondary to elevated diastolic pressure, dynamic LV outflow obstruction (if present), and arrhythmias; dyspnea on exertion, angina, and presyncope; sudden death may occur.

Physical Examination

Brisk carotid upstroke with pulsus bisferiens; S_4, harsh systolic murmur along left sternal border, blowing murmur of mitral regurgitation at apex; murmur enhances with Valsalva and other maneuvers that decrease LV filling (Chap. 110).

Laboratory ECG

LV hypertrophy with prominent "septal" Q waves in leads I, aVL, $V_{5–6}$. Periods of AF or ventricular tachycardia (VT) are often detected by Holter monitor.

Echocardiogram

LV hypertrophy, often with asymmetric involvement, especially of the septum or apex; LV contractile function typically excellent with small end-systolic volume. If LV outflow tract obstruction is present, systolic anterior motion (SAM) of mitral valve and midsystolic partial closure of aortic valve are present. Doppler shows early systolic accelerated blood flow through LV outflow tract.

TREATMENT HYPERTROPHIC CARDIOMYOPATHY

Strenuous exercise should be avoided. Beta blockers, verapamil, or disopyramide used individually to reduce symptoms. Digoxin, other inotropes, diuretics, and vasodilators are generally *contraindicated*. Endocarditis antibiotic prophylaxis (Chap. 80) is necessary only in pts with a prior history of endocarditis. Antiarrhythmic agents, especially amiodarone, may suppress atrial and ventricular arrhythmias. However, consider implantable cardioverter defibrillator for pts with high-risk profile, e.g., history of syncope or aborted cardiac arrest, nonsustained VT, marked LVH (>3 cm), exertional hypotension, or family history of sudden death. In selected pts, LV outflow gradient can be reduced by controlled septal infarction by ethanol injection into the septal artery. Surgical myectomy may be useful in pts refractory to medical therapy.

MYOCARDITIS

Inflammation of the myocardium that may progress to chronic dilated cardiomyopathy, most commonly due to acute viral infection (e.g., parvovirus B19, human herpesvirus 6, Epstein-Barr virus, coxsackievirus, adenovirus). Myocarditis may also develop in pts with HIV infection, hepatitis C or Lyme disease. Chagas' disease is a common cause of myocarditis in endemic areas, typically Central and South America. Noninfective causes of myocarditis include granulomatous disease (e.g., sarcoid, giant cell myocarditis), which should be considered if VT or conduction blocks dominate the presentation of heart failure in the absence of CAD.

History

Fever, fatigue, palpitations; if LV dysfunction develops, symptoms of heart failure are present. Viral myocarditis may be preceded by URI.

Physical Examination

Fever, tachycardia, soft S_1; S_3 common.

Laboratory

CK-MB isoenzyme and cardiac troponins may be elevated in absence of MI. Convalescent antiviral antibody titers may rise.

ECG

Transient ST-T-wave abnormalities.

CXR

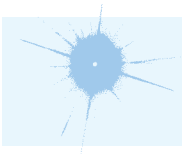
Cardiomegaly

Echocardiogram, Cardiac MRI

Depressed LV function; pericardial effusion present if accompanying pericarditis present. MRI demonstrates mid-wall gadolinium enhancement.

TREATMENT MYOCARDITIS

Rest; treat as heart failure (Chap. 124); efficacy of immunosuppressive therapy (e.g., steroids) has not been demonstrated except in isolated conditions such as sarcoidosis and giant cell myocarditis. In fulminant cases, cardiac transplantation may be indicated.



For a more detailed discussion, see Lakdawala NK, Stevenson LW, Loscalzo J: Cardiomyopathy and Myocarditis, Chap. 287, p. 1553, in HPIM-19.

116 Pericardial Disease

ACUTE PERICARDITIS

Etiologies (See Table 116-1)

History

Chest pain, which may be intense, mimicking acute MI, but characteristically sharp, pleuritic, and positional (relieved by leaning forward); fever and palpitations are common. Typical pain may not be present in slowly developing pericarditis (e.g., tuberculous, post-irradiation, neoplastic, uremic).

Physical Examination

Rapid or irregular pulse, coarse pericardial friction rub, which may vary in intensity and is loudest with pt sitting forward.

Laboratory ECG (See Table 116-2 and Fig. 116-1)

Diffuse ST elevation (concave upward) usually present in all leads except aVR and V_1; PR-segment depression (and/or PR elevation in lead aVR) may be present; *days* later (unlike acute MI), ST returns to baseline and T-wave inversion develops. Atrial premature beats and atrial fibrillation may appear. Differentiate from ECG of early repolarization (ER) (ratio of ST elevation/T wave height <0.25 in ER, but >0.25 in pericarditis).

TABLE 116-1 ETIOLOGIES OF PERICARDITIS

"Idiopathic"
Infections (particularly viral)
Connective tissue disease (e.g., rheumatoid arthritis, SLE)
Post-cardiac injury (i.e., following heart surgery or myocardial infarction)
Uremia
Neoplasms
Mediastinal radiation therapy
Drug reaction (e.g., procainamide, hydralazine)

CXR

Symmetrically increased size of cardiac silhouette if large (>250 mL) pericardial effusion is present.

Echocardiogram

Most readily available test for detection of pericardial effusion, which commonly accompanies acute pericarditis.

TREATMENT ACUTE PERICARDITIS

Aspirin 650–975 mg qid or other NSAIDs (e.g., ibuprofen 400–600 mg tid or indomethacin 25–50 mg tid); addition of colchicine 0.6 mg bid may be beneficial and reduces frequency of recurrences. For *severe*, *refractory* pain, glucocorticoids (e.g., prednisone) can be prescribed. Intractable, prolonged pain or frequently recurrent episodes may require pericardiectomy. Anticoagulants are relatively contraindicated in acute pericarditis because of risk of pericardial hemorrhage.

CARDIAC TAMPONADE

Life-threatening condition resulting from accumulation of pericardial fluid under pressure; impaired filling of cardiac chambers and decreased cardiac output.

TABLE 116-2 ECG IN ACUTE PERICARDITIS VS ACUTE ST-ELEVATION MI

ST-Segment Elevation	ECG Lead Involvement	Evolution of ST and T Waves	PR-Segment Deviation
Pericarditis			
Concave upward	All leads involved except aVR and V_1	ST remains elevated for several days; after ST returns to baseline, T waves invert	Yes, in majority
Acute ST elevation MI			
Convex upward	ST elevation over infarcted region only; reciprocal ST depression in opposite leads	In absence of successful reperfusion therapies: T waves invert within hours, while ST still elevated; followed by Q-wave development	No

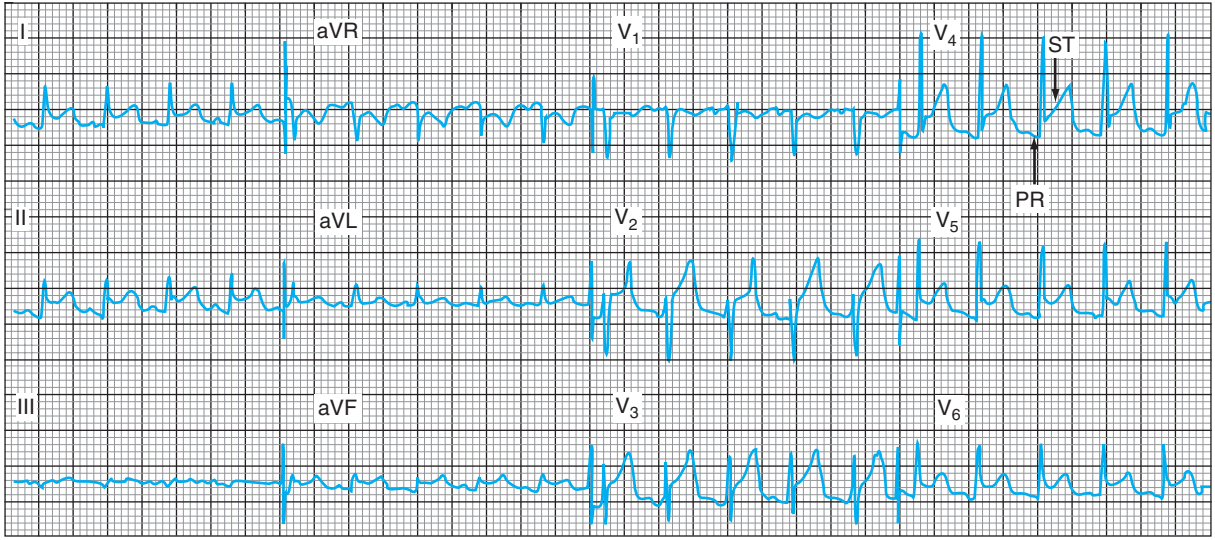


FIGURE 116-1 Electrocardiogram in acute pericarditis. Note diffuse ST-segment elevation and PR-segment depression.

Etiology

Previous pericarditis (most commonly metastatic tumor, uremia, viral or idiopathic pericarditis), cardiac trauma, or myocardial perforation during intravascular procedures.

History

Hypotension may develop suddenly; subacute symptoms include dyspnea, weakness, confusion.

Physical Examination

Tachycardia, hypotension, pulsus paradoxus (inspiratory fall in systolic blood pressure >10 mmHg), jugular venous distention with preserved *x* descent but loss of *y* descent; heart sounds distant. If tamponade develops subacutely, peripheral edema, hepatomegaly, and ascites may be present.

Laboratory ECG

Low limb lead voltage; large effusions may cause electrical alternans (alternating size of QRS complex due to swinging of heart).

CXR

Enlarged cardiac silhouette if large (>250 mL) effusion present.

Echocardiogram

Swinging motion of heart within large effusion; prominent respiratory alteration of RV dimension with RA and RV collapse during diastole. Doppler shows marked respiratory variation of transvalvular flow velocities.

Cardiac Catheterization

Confirms diagnosis; shows elevated pericardial pressure with equalization of diastolic pressures in all cardiac chambers.

TREATMENT **CARDIAC TAMPONADE**

Immediate pericardiocentesis and IV volume expansion.

CONSTRICTIVE PERICARDITIS

Condition in which a rigid pericardium impairs cardiac filling, causing elevation of systemic and pulmonary venous pressures, and decreased cardiac output. Results from healing and scar formation in some pts with previous pericarditis. Viral, tuberculosis (mostly in developing nations), previous cardiac surgery, collagen vascular disorders, uremia, neoplastic, and radiation-associated pericarditis are potential causes.

History

Gradual onset of dyspnea, fatigue, pedal edema, abdominal swelling; symptoms of LV failure uncommon.

Physical Examination

Tachycardia, jugular venous distention (with prominent *y* descent) that increases further on inspiration (Kussmaul sign); hepatomegaly, ascites, peripheral edema are common; sharp diastolic sound, pericardial knock following S_2 sometimes present.

Laboratory ECG

Low limb lead voltage; atrial arrhythmias are common.

TABLE 116-3 NONINVASIVE FEATURES THAT HELP DIFFERENTIATE CONSTRICTIVE PERICARDITIS FROM RESTRICTIVE CARDIOMYOPATHY

	Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical examination		
Kussmaul sign	Present	May be present
Pericardial knock	May be present	Absent
Chest X-ray		
Pericardial calcification	May be present	Absent
Echocardiography		
Thickened pericardium	Present	Absent
Thickened myocardium	Absent	Often present
Exaggerated variation in transvalvular velocities	Present	Absent
CT or MRI		
Thickened pericardium	Present	Absent

CXR

Rim of pericardial calcification is most common in tuberculous pericarditis.

Echocardiogram

Thickened pericardium, normal ventricular contraction; abrupt halt in ventricular filling in early diastole. Dilatation of IVC is common. Dramatic effects of respiration are typical: During inspiration the ventricular septum shifts to the left with prominent reduction of blood flow velocity across mitral valve; pattern reverses during expiration.

CT or MRI

More precise than echocardiogram for demonstrating thickened pericardium (present in >80% of pts with constrictive pericarditis).

Cardiac Catheterization

Equalization of diastolic pressures in all chambers; ventricular pressure tracings show "dip and plateau" appearance. Differentiate from restrictive cardiomyopathy (Table 116-3).

TREATMENT CONSTRICTIVE PERICARDITIS

Surgical stripping of the pericardium. Progressive improvement ensues over several months.

APPROACH TO THE PATIENT: Asymptomatic Pericardial Effusion of Unknown Cause

If careful history and physical examination do not suggest etiology, the following may lead to diagnosis:

- Testing for tuberculosis (Chap. 94)
- Serum albumin and urine protein measurement (nephrotic syndrome)
- Serum creatinine and BUN (uremia)

- Thyroid function tests (myxedema)
- Antineutrophil antibodies (SLE and other collagen-vascular disease)
- Search for a primary tumor (especially lung and breast)

For a more detailed discussion, see Braunwald E: Pericardial Disease, Chap. 288, p. 1571, in HPIM-19.

117 Hypertension

DEFINITION

Chronic elevation in bp (systolic ≥140 mmHg or diastolic ≥90 mmHg); etiology unknown in 80–95% of pts ("essential hypertension"). Always consider a secondary correctable form of hypertension, especially in pts under age 30 or those who become hypertensive after 55. Isolated systolic hypertension (systolic ≥140, diastolic <90) most common in elderly pts, due to reduced vascular compliance.

SECONDARY HYPERTENSION

Renal Artery Stenosis (Renovascular Hypertension)

Due to either atherosclerosis (older men) or fibromuscular dysplasia (young women). Presents with recent onset of hypertension, refractory to usual antihypertensive therapy. Abdominal bruit is present in 50% of cases; hypokalemia due to activation of the renin-angiotensin-aldosterone system may be present.

Renal Parenchymal Disease

Elevated serum creatinine and/or abnormal urinalysis, containing protein, cells, or casts.

Coarctation of Aorta

Presents in children or young adults (including 35% of pts with Turner syndrome); constriction is usually present in aorta at origin of left subclavian artery. Examination shows diminished, delayed femoral pulsations; late systolic murmur loudest over the midback. CXR shows indentation of the aorta at the level of the coarctation and rib notching (due to development of collateral arterial flow).

Pheochromocytoma

A catecholamine-secreting tumor, typically of the adrenal medulla or extraadrenal paraganglion tissue, that presents as paroxysmal or sustained hypertension in young to middle-aged pts. Sudden episodes of headache, palpitations, and profuse diaphoresis are common. Associated findings include chronic weight loss, orthostatic *hypotension*, and impaired glucose tolerance. Pheochromocytomas may be localized

to the bladder wall and may present with micturition-associated symptoms of catecholamine excess. Diagnosis is suggested by elevated plasma metanephrine level or urinary catecholamine metabolites in a 24-h urine collection (see below); the tumor is then localized by CT scan or MRI.

Hyperaldosteronism

Usually due to aldosterone-secreting adenoma or bilateral adrenal hyperplasia. Should be suspected when hypokalemia is present in a hypertensive pt off diuretics (Chap. 171).

Other Causes

Oral contraceptive usage, obstructive sleep apnea (Chap. 137), Cushing's and adrenogenital syndromes (Chap. 171), thyroid disease (Chap. 170), hyperparathyroidism, and acromegaly (Chap. 168). In pts with systolic hypertension and wide pulse pressure, consider thyrotoxicosis, aortic regurgitation (Chap. 114), and systemic AV fistula.

APPROACH TO THE PATIENT: **Hypertension**

History: Most pts are asymptomatic. Severe hypertension may lead to headache, dizziness, or blurred vision.

Clues to specific forms of secondary hypertension: Use of medications (e.g., birth control pills, glucocorticoids, decongestants, erythropoietin, NSAIDs, cyclosporine); paroxysms of headache, sweating, or tachycardia (pheochromocytoma); history of renal disease or abdominal trauma (renal hypertension); daytime somnolence and snoring (sleep apnea).

Physical examination: Measure bp with appropriate-sized cuff (large cuff for large arm). Measure bp in both arms as well as a leg (to evaluate for aortic coarctation). Signs of hypertension include retinal arteriolar changes (narrowing/nicking); left ventricular lift, loud A_2, S_4. Clues to secondary forms of hypertension include cushingoid appearance, thyromegaly, abdominal bruit (renal artery stenosis), delayed femoral pulses (coarctation of aorta).

LABORATORY WORKUP

Screening tests for secondary hypertension: Should be carried out on all pts with documented hypertension: (1) serum creatinine, BUN, and urinalysis (renal parenchymal disease); (2) serum K^+ measured off diuretics (hypokalemia prompts workup for hyperaldosteronism or renal artery stenosis); (3) CXR (rib notching or indentation of distal aortic arch in coarctation of the aorta); (4) ECG (LV hypertrophy suggests chronicity of hypertension); (5) other useful screening blood tests including CBC, glucose, lipid levels, calcium, uric acid; (6) thyroid-stimulating hormone if thyroid disease suspected.

Further workup: Indicated for specific diagnoses if screening tests are abnormal or bp is refractory to antihypertensive therapy: (1) *renal artery stenosis:* magnetic resonance angiography, captopril radionuclide scan, renal duplex ultrasound, renal arteriography; (2) *Cushing's syndrome:* dexamethasone suppression test (Chap. 171); (3) *pheochromocytoma:* 24-h urine collection for catecholamines, metanephrines, and vanillylmandelic acid and/or measurement of plasma metanephrine; (4) *primary hyperaldosteronism:* depressed plasma renin activity and hypersecretion of aldosterone, both of which fail to change with volume expansion; (5) *renal parenchymal disease* (Chap. 139).

TREATMENT HYPERTENSION

Helpful lifestyle modifications include weight reduction (to attain BMI <25 kg/m^2); sodium restriction; diet rich in fruits, vegetables, and low-fat dairy products; regular exercise; and moderation of alcohol consumption.

DRUG THERAPY OF ESSENTIAL HYPERTENSION (SEE TABLE 117-1 AND FIG. 117-1)

Goal is to control hypertension with minimal side effects. A combination of medications with complementary actions is often required. First-line agents include diuretics, ACE inhibitors, angiotensin receptor antagonists, calcium channel antagonists, and sometimes beta blockers. On-treatment blood pressure goal is <135–140 systolic, <80–85 diastolic.

Diuretics Often the cornerstone of antihypertensive regimes. Thiazides preferred over loop diuretics because of longer duration of action; however, the latter are more potent when serum creatinine >2.5 mg/dL. Major side effects include hypokalemia, hyperglycemia, and hyperuricemia, which can be minimized by using low dosage (e.g., hydrochlorothiazide 6.25–50 mg qd). Diuretics are particularly effective in elderly and African-American pts. Prevention of hypokalemia is especially important in pts on digitalis glycosides.

ACE Inhibitors and Angiotensin II Receptor Blockers (ARBs) ACE inhibitors and ARBs are well tolerated with low frequency of side effects. May be used as monotherapy or in combination with a diuretic, calcium antagonist, or beta blocker. Side effects are uncommon and include angioedema (<1% of pts; more common with ACE inhibitors than ARBs), hyperkalemia, and azotemia (particularly in pts with elevated baseline serum creatinine). A nonproductive cough may develop in the course of therapy in up to 15% of pts on an ACE inhibitor, prompting substitution with an ARB (cough is not common side effect) or alternate antihypertensives. Note that renal function may deteriorate rapidly as a result of inhibition of the renin-angiotensin system in pts with bilateral renal artery stenosis.

Potassium supplements and potassium-sparing diuretics should be used cautiously with ACE inhibitors or ARBs to prevent hyperkalemia.

Calcium Antagonists Direct arteriolar vasodilators; all have negative inotropic effects (particularly verapamil) and should be used cautiously if LV dysfunction is present. Verapamil and, to a lesser extent, diltiazem can result in bradycardia and AV block, so combination with beta blockers is generally avoided. Use sustained-release formulations, as short-acting dihydropyridine calcium channel blockers may increase incidence of coronary events. Common side effects include peripheral edema and constipation.

If bp proves refractory to drug therapy, work up for secondary forms of hypertension, especially renal artery stenosis and pheochromocytoma.

Beta Blockers May be useful in young pts with "hyperkinetic" circulation. Begin with low dosage (e.g., metoprolol succinate 25–50 mg daily). Relative contraindications: bronchospasm, CHF, AV block, bradycardia, and "brittle" insulin-dependent diabetes.

Table 117-2 lists compelling indications for specific initial drug treatment.

SPECIAL CIRCUMSTANCES

Pregnancy Most commonly used antihypertensives include methyldopa (250–1000 mg PO bid-tid), labetalol (100–200 mg bid), and hydralazine (10–150 mg PO bid-tid). Calcium channel blockers (e.g., nifedipine, long-acting, 30–90 mg daily) also appear to be safe in pregnancy. Beta blockers should be used cautiously; fetal hypoglycemia and low birth weights have been reported. ACE inhibitors and ARBs are *contraindicated* in pregnancy.

TABLE 117-1 ORAL DRUGS COMMONLY USED IN TREATMENT OF HYPERTENSION

Drug Class	Examples	Usual Total Daily Dose (Dosing Frequency/Day)	Potential Adverse Effects
Diuretics			
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)	Hypokalemia, hyperuricemia, hyperglycemia, ↑ cholesterol, ↑ triglycerides
Thiazide-like	Chlorthalidone	25–50 mg (1)	same as above
Loop diuretics	Furosemide	40–80 mg (2–3)	Hypokalemia, hyperuricemia
	Ethacrynic acid	50–100 mg (2-3)	
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	Hyperkalemia, gynecomastia
	Eplerenone	50–100 mg (1–2)	Hyperkalemia
K^+-retaining	Amiloride	5–10 mg (1–2)	
	Triamterene	50–100 mg (1–2)	
Beta blockers			
β_1-selective	Atenolol	25–100 mg (1–2)	Bronchospasm, bradycardia, heart block, fatigue, sexual dysfunction, ↑ triglycerides, ↓ HDL
	Metoprolol	25–100 mg (1–2)	same as above
Nonselective	Propranolol	40–160 mg (2)	same as above
	Propranolol LA	60–180 mg (1)	same as above
Combined alpha/beta	Labetolol	200–800 mg (2)	Bronchospasm, bradycardia, heart block
	Carvedilol	12.5–50 mg (2)	

ACE inhibitors	Captopril	25–200 mg (2)	Cough, hyperkalemia, azotemia, angioedema
	Lisinopril	10–40 mg (1)	
	Ramipril	2.5–20 mg (1–2)	
Angiotensin II receptor blockers	Losartan	25–100 mg (1–2)	Hyperkalemia, azotemia
	Valsartan	80–320 mg (1)	
	Candesartan	2–32 mg (1–2)	
Calcium channel antagonists			
Dihydropyridines	Nifedipine long-acting	30–60 mg (1)	Edema, constipation
Nondihydropyridines	Verapamil long-acting	120–360 mg (1–2)	Edema, constipation, bradycardia, heart block
	Diltiazem long-acting	180–420 mg (1)	

TABLE 117-2 GUIDELINES FOR SELECTING INITIAL DRUG TREATMENT OF HYPERTENSION

Class of Drug	Compelling Indications	Possible Indications	Compelling Contraindications	Possible Contraindications
Diuretics	Heart failure Elderly pts Systolic hypertension		Gout	
Beta blockers	Angina After MI Tachyarrhythmias	Heart failure Pregnancy	Uncontrolled asthma and COPD Heart block[a]	Athletes and physically active pts Peripheral vascular disease
ACE inhibitors	Heart failure LV dysfunction After MI Diabetic nephropathy	Chronic renal parenchymal disease	Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Angiotensin receptor blockers	ACE inhibitor cough Heart failure Diabetic nephropathy	Chronic renal parenchymal disease	Pregnancy Bilateral renal artery stenosis Hyperkalemia	
Calcium channel blockers	Angina Elderly pts Systolic hypertension	Peripheral vascular disease	Heart block[b]	Congestive heart failure[c]

[a]Second- or third-degree atrioventricular block.
[b]Second- or third-degree atrioventricular block with verapamil or diltiazem.
[c]Verapamil or diltiazem.
Abbreviations: ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease.

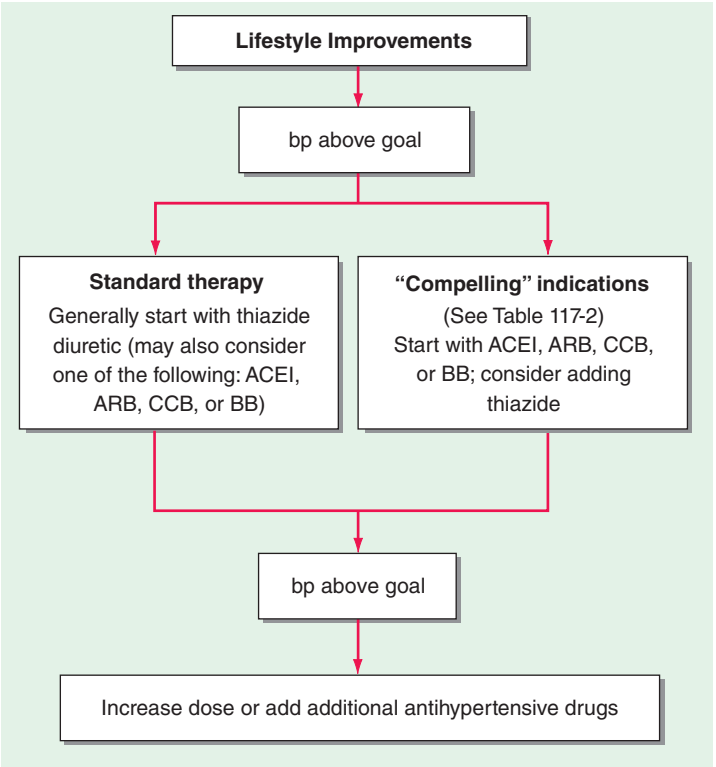


FIGURE 117-1 Initiation of therapy in pts with hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta blocker.

Renal Disease Standard thiazide diuretics may not be effective. Consider metolazone, furosemide, or bumetanide, alone or in combination.

Diabetes Goal bp <130/80. Consider ACE inhibitors and angiotensin receptor blockers as first-line therapy to control bp and slow renal function deterioration.

Malignant Hypertension Defined as an abrupt increase in bp in pt with chronic hypertension or sudden onset of severe hypertension; a medical emergency. Immediate therapy is mandatory if there is evidence of cardiac decompensation (CHF, angina), encephalopathy (headache, seizures, visual disturbances), or deteriorating renal function. Inquire about use of cocaine, amphetamines, or monoamine oxidase inhibitors. Drugs to treat hypertensive crisis are listed in Table 117-3. Replace with PO antihypertensive as pt becomes asymptomatic and bp improves.

TABLE 117-3 USUAL INTRAVENOUS DOSES OF ANTIHYPERTENSIVE AGENTS USED IN HYPERTENSIVE EMERGENCIES[a]

Antihypertensive Agent	IV Dose
Nitroprusside	Initial 0.3 (mg/kg)/min; usual 2–4 (mg/kg)/min; maximum 10 (mg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h
Esmolol	Initial 80–500 mg/kg over 1 min, then 50–300 (mg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 mcg/min, then titrate by 5 mcg/min at 3–5 min intervals; if no response is seen at 20 mcg/min, incremental increases of 10–20 mcg/min may be used
Hydralazine	10–50 mg at 30-min intervals

[a]Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

For a more detailed discussion, see Kotchen TA: Hypertensive Vascular Disease, Chap. 298, p. 1611, in HPIM-19.

118 Metabolic Syndrome

The *metabolic syndrome* (*insulin resistance syndrome*, *syndrome X*) is an important risk factor for cardiovascular disease and type 2 diabetes; it consists of a constellation of metabolic abnormalities that includes central obesity, insulin resistance, hypertension, and dyslipidemia, high triglycerides, and low HDL. The prevalence of metabolic syndrome varies among ethnic groups; it increases with age, degree of obesity, and propensity to type 2 diabetes.

ETIOLOGY

Overweight/obesity (especially central adiposity), sedentary lifestyle, increasing age, and lipodystrophy are all risk factors for the metabolic syndrome. The exact cause is not known and may be multifactorial. Insulin resistance is central to the

development of the metabolic syndrome. Increased intracellular fatty acid metabolites contribute to insulin resistance by impairing insulin-signaling pathways and accumulating as triglycerides in skeletal and cardiac muscle, while stimulating hepatic glucose and triglyceride production. Excess adipose tissue leads to increased production of proinflammatory cytokines.

CLINICAL FEATURES

There are no specific symptoms of the metabolic syndrome. The major features include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension (Table 118-1). Associated conditions include cardiovascular disease, type 2 diabetes, nonalcoholic fatty liver disease, hyperuricemia/gout, polycystic ovary syndrome, and obstructive sleep apnea.

DIAGNOSIS

The diagnosis of the metabolic syndrome relies on satisfying the criteria listed in Table 118-1. Screening for associated conditions should be undertaken.

TABLE 118-1 NCEP:ATPIII[a] 2001 AND HARMONIZING DEFINITION CRITERIA FOR THE METABOLIC SYNDROME

NCEP:ATPIII 2001	Harmonizing Definition[b]
Three or more of the following:	**Three of the following:**
• Central obesity: waist circumference >102 cm (M), >88 cm (F)	Waist circumference (cm) **Men** / **Women** / **Ethnicity** ≥94 / ≥80 / Europid, sub-Saharan African, Eastern and Middle Eastern ≥90 / ≥80 / South Asian, Chinese, and ethnic South and Central American ≥85 / ≥90 / Japanese
• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication	• Fasting triglyceride level >150 mg/dL or specific medication
Low HDL[c] cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication	• HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication	• Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication
• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes	• Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)

[a]National Cholesterol Education Program and Adult Treatment Panel III.
[b]In this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used.
[c]High-density lipoprotein.

TREATMENT **METABOLIC SYNDROME**

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to this disorder. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. Weight loss drugs or bariatric surgery are adjuncts that may be considered for obesity management (Chap. 172). Hypertension (Chap. 117), impaired fasting glucose or diabetes (Chap. 173), and lipid abnormalities (Chap. 178) should be managed according to current guidelines. The antihypertensive regimen should include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker when possible.

For a more detailed discussion, see Eckel RH: The Metabolic Syndrome, Chap. 422, p. 2449, in HPIM-19.

119 ST-Segment Elevation Myocardial Infarction

Early recognition and immediate treatment of acute ST-segment elevation myocardial infarction (STEMI) are essential; diagnosis is based on characteristic history, ECG, and serum cardiac markers.

Symptoms

Chest pain similar to angina (Chap. 31) but more intense and persistent; not fully relieved by rest or nitroglycerin, often accompanied by nausea, sweating, apprehension. However, ~25% of MIs are clinically silent.

Physical Examination

Pallor, diaphoresis, tachycardia, S_4, dyskinetic cardiac impulse may be present. If CHF exists, rales and S_3 are present. Jugular venous distention is common in right ventricular infarction.

ECG

ST elevation, followed (if acute reperfusion is not achieved) by T-wave inversion, then Q-wave development over several hours.

Cardiac Biomarkers

Cardiac-specific troponins T and I are highly specific for myocardial injury and are the preferred biochemical markers for diagnosis of acute MI. They remain elevated for 7–10 days. Creatine phosphokinase (CK) level rises within 4–8 h, peaks at 24 h, and returns to normal by 48–72 h. CK-MB isoenzyme is more specific for MI but may also be elevated with myocarditis or after electrical cardioversion. Serum cardiac markers should be measured at presentation, 6–9 h later, and then at 12–24 h.

Noninvasive Imaging Techniques

Useful when diagnosis of MI is not clear. *Echocardiography* detects infarct-associated regional wall motion abnormalities (but cannot distinguish acute MI from a previous myocardial scar). Echo is also useful in detecting RV infarction, LV aneurysm, and LV thrombus. *MRI with delayed gadolinium enhancement* accurately indicates regions of infarction, but is technically difficult to obtain in acutely ill pts.

TREATMENT STEMI

INITIAL THERAPY

Initial goals are to (1) quickly identify if pt is candidate for reperfusion therapy, (2) relieve pain, and (3) prevent/treat arrhythmias and mechanical complications.

- Aspirin should be administered immediately (162–325 mg chewed at presentation, then 75–162 mg PO qd), unless pt is aspirin-intolerant.
- Perform targeted history, examination, and ECG to identify STEMI (>1 mm ST elevation in two contiguous limb leads, ≥2 mm ST elevation in two contiguous precordial leads, or new LBBB) and appropriateness of reperfusion therapy (percutaneous coronary intervention [PCI] or IV fibrinolytic agent), which reduces infarct size, LV dysfunction, and mortality.
- Primary PCI is generally more effective than fibrinolysis and is preferred at experienced centers capable of performing the procedure rapidly (**Fig. 119-1**), especially when diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for >3 h.
- Proceed with IV fibrinolysis if PCI is not available or if logistics would delay PCI >1 h longer than fibrinolysis could be initiated (Fig. 119-1). Door-to-needle time should be <30 min for maximum benefit. Ensure absence of contraindications (**Fig. 119-2**) before administering fibrinolytic agent. Those treated within 1–3 h benefit most; can still be useful up to 12 h if chest pain is persistent or ST remains elevated in leads that have not developed new Q waves. Complications include bleeding, reperfusion arrhythmias, and, in case of streptokinase (SK), allergic reactions. Enoxaparin or heparin (60 U/kg [maximum 4000 U], then 12 [U/kg]/h [maximum 1000 U/h]) should be initiated with fibrinolytic agents (Fig. 119-2); maintain activated partial thromboplastin time (aPTT) at 1.5–2.0 × control (~50–70 s).
- If chest pain or ST elevation persists >90 min after fibrinolysis, consider referral for rescue PCI. Coronary angiography after fibrinolysis should also be considered for pts with recurrent angina or high-risk features (**Fig. 119-2**) including extensive ST elevation, signs of heart failure (rales, S_3, jugular venous distension, left ventricular ejection fraction [LVEF] ≤35%), or systolic bp <100 mmHg.

The initial management of NSTEMI (non-Q MI) is different (**Chap. 120**). In particular, fibrinolytic therapy should not be administered.

ADDITIONAL STANDARD TREATMENT

(Whether or not reperfusion therapy is undertaken):

- *Hospitalize in CCU* with continuous ECG monitoring.
- *IV line* for emergency arrhythmia treatment.
- *Pain control:* (1) Morphine sulfate 2–4 mg IV q5–10 min until pain is relieved or side effects develop (nausea, vomiting, respiratory depression [treat with naloxone 0.4–1.2 mg IV], hypotension [if bradycardic, treat with atropine 0.5 mg IV; otherwise use careful volume infusion]); (2) nitroglycerin 0.3 mg SL if systolic bp >100 mmHg; for refractory pain: IV nitroglycerin (begin at 10 μg/min, titrate upward to maximum of 200 μg/min, monitoring bp closely); do not administer

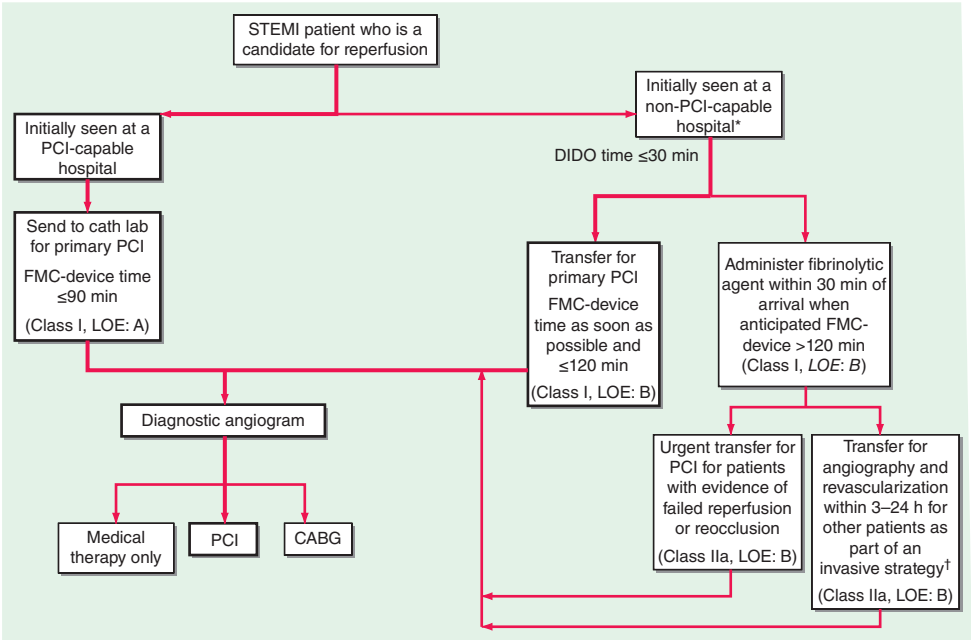


FIGURE 119-1 Reperfusion strategies in STEMI. DIDO, door-in-door-out; FMC, first medical contact; LOC, level of evidence. *(Adapted from P O'Gara, et al: Circulation 127:e362, 2013.)*

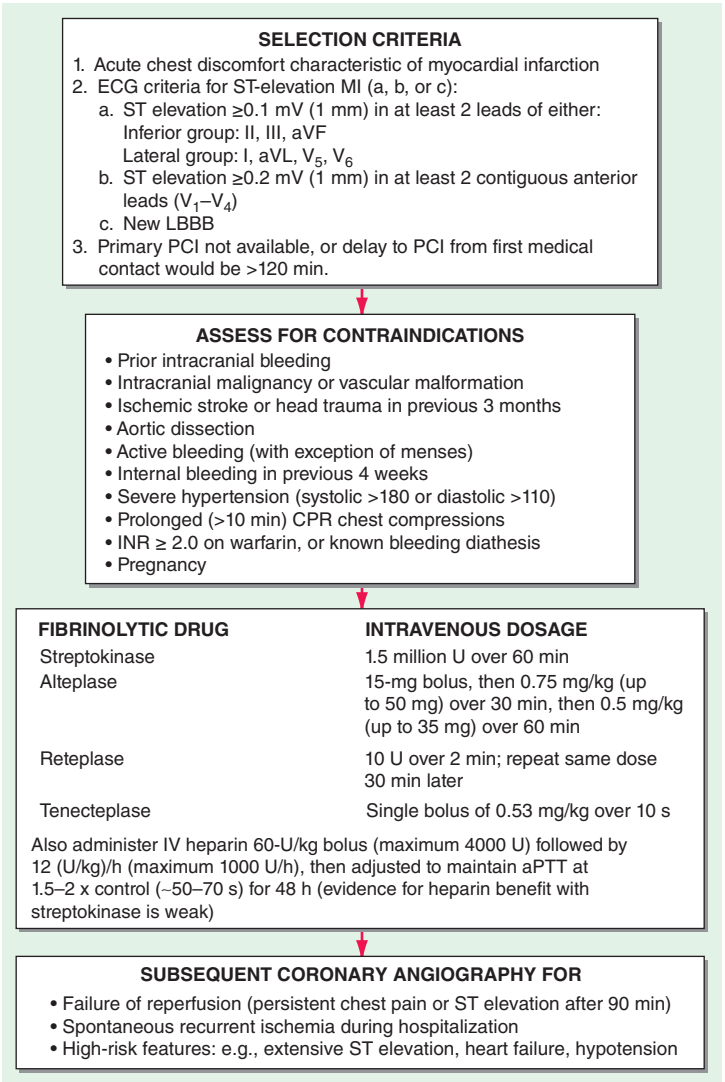


FIGURE 119-2 Algorithm for fibrinolytic therapy of acute STEMI.

nitrates within 24 h of sildenafil or within 48 h of tadalafil (used for erectile dysfunction); (3) β-adrenergic antagonists (see below).

- *Oxygen:* 2–4 L/min by nasal cannula (if needed to maintain O_2 saturation >90%).
- Mild *sedation* (e.g., diazepam 5 mg, oxazepam 15–30 mg, or lorazepam 0.5–2 mg PO three to four times daily).
- *Soft diet* and stool softeners (e.g., docusate sodium 100–200 mg/d).

- β-*Adrenergic blockers* (Chap. 117) reduce myocardial O_2 consumption, limit infarct size, and reduce mortality. Especially useful in pts with hypertension, tachycardia, or persistent ischemic pain; contraindications include active CHF, systolic bp <95 mmHg, heart rate <50 beats/min, AV block, or history of bronchospasm. Consider IV (e.g., metoprolol 5 mg q2–5min to total dose of 15 mg) if pt is hypertensive. Otherwise, begin PO regimen (e.g., metoprolol tartrate 25–50 mg four times daily).
- *Anticoagulants:* Most pts with STEMI should receive an anticoagulant (typically unfractionated heparin [UFH] or bivalirudin for those undergoing PCI [discontinued at end of procedure or shortly thereafter]; enoxaparin [for up to 8 days, or until discharge, whichever is earlier] or UFH [for ≥2 days] for those receiving fibrinolysis or no reperfusion therapy). Continued full-dose IV heparin (PTT 1.5–2 × control) or LMWH (e.g., enoxaparin 1 mg/kg SC q12h) followed by warfarin is recommended for pts with high risk of thromboembolism (severe LV dysfunction, presence of ventricular thrombus, large dyskinetic region in acute anterior MI, or pulmonary embolism). If used, warfarin is continued for 3–6 months.
- *Antiplatelet agents:* Continue aspirin 162–325 md daily and an oral $P2Y_{12}$ platelet receptor antagonist after STEMI (e.g., ticagrelor, clopidogrel, or prasugrel [the latter only if PCI is undertaken]).
- *ACE inhibitors* reduce mortality in pts following acute MI and should be prescribed within 24 h of hospitalization for pts with STEMI—e.g., captopril (6.25 mg PO test dose advanced to 50 mg PO tid). ACE inhibitors should be continued indefinitely after discharge in pts with heart failure or those with asymptomatic LV dysfunction (ejection fraction ≤40%); if pt is ACE inhibitor intolerant, use ARB (e.g., valsartan or candesartan).
- *Aldosterone antagonists (spironolactone or eplerenone 25–50 mg daily)* further reduce mortality in pts with LVEF ≤40% and either symptomatic heart failure or diabetes; do not use in pts with advanced renal insufficiency (e.g., creatinine ≥2.5 mg/dL) or hyperkalemia.
- *Serum magnesium* level should be measured and repleted if necessary to reduce risk of arrhythmias.

COMPLICATIONS

(For arrhythmias, see also Chaps. 122 and 123)

Ventricular Arrhythmias

Isolated ventricular premature beats (VPBs) occur frequently. Precipitating factors should be corrected (hypoxemia, acidosis, hypokalemia, hypomagnesemia, CHF, arrhythmogenic drugs). Routine beta blocker administration (see above) diminishes ventricular ectopy. Other in-hospital antiarrhythmic therapy should be reserved for pts with sustained ventricular arrhythmias.

Ventricular Tachycardia

If hemodynamically unstable, perform immediate electrical countershock (unsynchronized discharge of 200–300 J or 50% less if using biphasic device). If hemodynamically tolerated, use IV amiodarone (bolus of 150 mg over 10 min, then infusion of 1.0 mg/min for 6 h, then 0.5 mg/min).

Ventricular Fibrillation

VF requires immediate defibrillation (200–400 J). If unsuccessful, initiate cardiopulmonary resuscitation (CPR) and standard resuscitative measures (Chap. 10). Ventricular arrhythmias that appear several days or weeks following MI often reflect

pump failure and may warrant invasive electrophysiologic study and implantation of a cardioverter defibrillator (ICD).

Accelerated Idioventricular Rhythm

Wide QRS complex, regular rhythm, rate 60–100 beats/min, is common and usually benign; if it causes hypotension, treat with atropine 0.6 mg IV.

Supraventricular Arrhythmias

Sinus tachycardia may result from heart failure, hypoxemia, pain, fever, pericarditis, hypovolemia, administered drugs. If no cause is identified, suppressive beta blocker therapy may be beneficial to reduce myocardial oxygen demand. Other *supraventricular arrhythmias* (paroxysmal supraventricular tachycardia, atrial flutter, and fibrillation) are often secondary to heart failure. If hemodynamically unstable, proceed with electrical cardioversion. In absence of acute heart failure, suppressive alternatives include beta blockers, verapamil, or diltiazem (Chap. 123).

Bradyarrhythmias and AV Block

(See Chap. 122) In *inferior MI*, usually represent heightened vagal tone or discrete AV nodal ischemia. If hemodynamically compromised (CHF, hypotension, emergence of ventricular arrhythmias), treat with atropine 0.5 mg IV q5min (up to 2 mg). If no response, use temporary external or transvenous pacemaker. Isoproterenol should be avoided. In *anterior MI*, AV conduction defects usually reflect extensive tissue necrosis. Consider temporary external or transvenous pacemaker for (1) complete heart block, (2) Mobitz type II block (Chap. 122), (3) new bifascicular block (LBBB, RBBB + left anterior hemiblock, RBBB + left posterior hemiblock), (4) any bradyarrhythmia associated with hypotension or CHF.

Heart Failure

CHF may result from systolic "pump" dysfunction, increased LV diastolic "stiffness," and/or acute mechanical complications.

Symptoms Dyspnea, orthopnea, tachycardia.

Examination Jugular venous distention, S_3 and S_4 gallop, pulmonary rales; systolic murmur if acute mitral regurgitation or ventricular septal defect (VSD) has developed.

TREATMENT HEART FAILURE (SEE CHAPS. 13 AND 124)

Initial therapy includes diuretics (begin with furosemide 10–20 mg IV), inhaled O_2, and vasodilators, particularly nitrates (PO, topical, or IV [Chap. 124] unless pt is hypotensive [systolic bp <100 mmHg]); digitalis is usually of little benefit in acute MI. Diuretic, vasodilator, and inotropic therapy (Table 119-1) may be guided by invasive hemodynamic monitoring (Swan-Ganz pulmonary artery catheter, arterial line), particularly in pts with accompanying hypotension (Table 119-2; Fig. 119-3). In acute MI, an acceptable pulmonary capillary wedge (PCW) pressure is 15–20 mmHg; in the absence of hypotension, PCW >20 mmHg is treated with diuretic plus vasodilator therapy (IV nitroglycerin [begin at 10 μg/min] or nitroprusside [begin at 0.5 μg/kg per min]) and titrated to optimize bp, PCW, and systemic vascular resistance (SVR).

$$\text{SVR} = \frac{(\text{mean arterial pressure} - \text{mean RA pressure}) \times 80}{\text{cardiac output}}$$

Normal SVR = 900 – 1350 dyne • s/cm^5. If PCW >20 mmHg and pt is hypotensive (Table 119-2 and Fig. 119-3), evaluate for VSD or acute mitral regurgitation,

TABLE 119-1 IV VASODILATORS AND INOTROPIC DRUGS USED IN ACUTE MI

Drug	Usual Dosage Range	Comment
Nitroglycerin	5–100 μg/min	May improve coronary blood flow to ischemic myocardium
Nitroprusside	0.5–10 (μg/kg)/min	More potent vasodilator, but improves coronary blood flow less than nitroglycerin With therapy >24 h or in renal failure, watch for thiocyanate toxicity (blurred vision, tinnitus, delirium)
Dobutamine	2–20 (μg/kg)/min	Results in ↑ cardiac output, ↓ PCW, but does not raise bp
Dopamine	2–20 (μg/kg)/min	More appropriate than dobutamine if hypotensive Hemodynamic effect depends on dose: (μg/kg)/min <5: ↑ renal blood flow 2.5–10: positive inotrope >10: vasoconstriction
Norepinephrine	0.5–30 μg/min	Less likely than dopamine to cause arrhythmias in cardiogenic shock

consider dobutamine (begin at 1–2 [μg/kg]/min), titrate upward to maximum of 10 (μg/kg)/min; beware of drug-induced tachycardia or ventricular ectopy.

After stabilization on parenteral vasodilator therapy, oral therapy follows with an ACE inhibitor or an ARB (Chap. 124). Consider addition of long-term aldosterone antagonist (spironolactone 25–50 mg daily or eplerenone 25–50 mg daily) to ACE inhibitor if LVEF ≤40% or symptomatic heart failure or diabetes are present—do not use if renal insufficiency or hyperkalemia are present.

Cardiogenic Shock

(See Chap. 11) Severe LV failure with hypotension (bp <90 mmHg), elevated PCW (>20 mmHg), cardiac index <2.2 L/min/m^2, accompanied by oliguria, peripheral vasoconstriction, dulled sensorium, and metabolic acidosis.

TREATMENT CARDIOGENIC SHOCK (FIG. 119-3)

Swan-Ganz catheter and intraarterial bp monitoring are not always essential but may be helpful; aim for mean PCW of 18–20 mmHg with adjustment of volume (diuretics or infusion) as needed. Vasopressors (e.g., norepinephrine or dopamine [Table 119-1]) and/or intraaortic balloon counterpulsation may be necessary to maintain systolic bp >90 mmHg and reduce PCW. Administer high concentration of O_2 by mask; if pulmonary edema coexists, consider bilateral positive airway pressure (BiPAP) or intubation and mechanical ventilation. Acute mechanical complications (see below) should be sought and promptly treated.

If cardiogenic shock develops within 36 h of acute STEMI, reperfusion by PCI or coronary artery bypass grafting (CABG) may markedly improve LV function.

Hypotension

May also result from *right ventricular MI*, which should be suspected in inferior or posterior MI, if jugular venous distention and elevation of right-heart pressures

TABLE 119-2 HEMODYNAMIC COMPLICATIONS IN ACUTE MI

Condition	Cardiac Index, (L/min)/m²	PCW, mmHg	Systolic bp, mmHg	Treatment
Uncomplicated	>2.5	≤18	>100	—
Hypovolemia	<2.5	<15	<100	Successive boluses of normal saline In setting of inferior wall MI, consider RV infarction (esp. if RA pressure >10)
Volume overload	>2.5	>20	>100	Diuretic (e.g., furosemide 10–20 mg IV) Nitroglycerin, topical paste or IV (Table 119-1)
LV failure	<2.5	>20	>100	Diuretic (e.g., furosemide 10–20 mg IV) IV nitroglycerin (or if hypertensive, use IV nitroprusside)
Severe LV failure	<2.5	>20	<100	If bp ≥90: IV dobutamine ± IV nitroglycerin or sodium nitroprusside If bp <90: IV dopamine If accompanied by pulmonary edema: attempt diuresis with IV furosemide; may be limited by hypotension If new systolic murmur present, consider acute VSD or mitral regurgitation
Cardiogenic shock	<2.2	>20	<90 with oliguria and confusion	IV norepinephrine or dopamine Intraaortic balloon pump Reperfusion by PCI or CABG may be life-saving

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PCW, pulmonary capillary wedge pressure; RA, right atrium; VSD, ventricular septal defect.

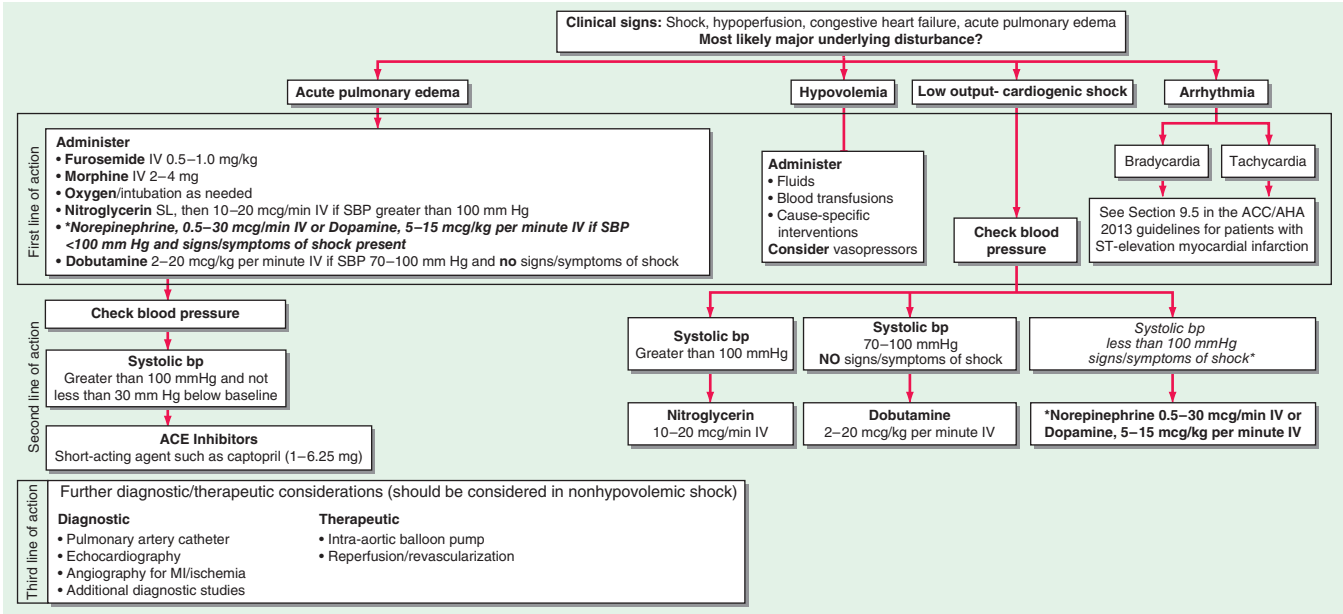


FIGURE 119-3 Emergency management of cardiogenic shock and pulmonary edema. *(Modified from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7: The era of reperfusion: Section 1: Acute coronary syndromes [acute myocardial infarction]. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:1172, 2000.)*

predominate (rales are typically absent and PCW may be normal); right-sided ECG leads typically show ST elevation, and echocardiography may confirm diagnosis. *Treatment* consists of volume infusion. Noncardiac causes of hypotension should be considered: hypovolemia, acute arrhythmia, or sepsis.

Acute Mechanical Complications

Ventricular septal rupture and acute mitral regurgitation due to papillary muscle ischemia/infarct develop during the first week following MI and are characterized by sudden onset of CHF and new systolic murmur. Echocardiography and Doppler interrogation can confirm presence of these complications. PCW tracings may show large *v* waves in either condition, but an oxygen "step-up" as the catheter is advanced from right atrium to right ventricle suggests septal rupture.

Acute medical therapy of these conditions includes vasodilator therapy (IV nitroprusside: begin at 10 μg/min and titrate to maintain systolic bp ~100 mmHg); intraaortic balloon pump may be required to maintain cardiac output. Mechanical correction is the definitive therapy. Acute ventricular free-wall rupture presents with sudden loss of bp, pulse, and consciousness, while ECG shows an intact rhythm (pulseless electrical activity); emergent surgical repair is crucial, and mortality is high.

Pericarditis

Characterized by *pleuritic*, *positional* pain, and pericardial rub (Chap. 116); atrial arrhythmias are common; must be distinguished from recurrent angina. Often responds to aspirin, 650 mg PO qid. Anticoagulants should be avoided when pericarditis is suspected to avoid development of pericardial bleeding/tamponade.

Ventricular Aneurysm

Localized "bulge" of LV chamber due to infarcted myocardium. *True aneurysms* consist of scar tissue and do not rupture. However, complications include CHF, ventricular arrhythmias, and thrombus formation. Typically an aneurysm is confirmed by echocardiography or by left ventriculography. The presence of thrombus within the aneurysm, or a large aneurysmal segment due to anterior MI, warrants consideration of oral anticoagulation with warfarin for 3–6 months.

Pseudoaneurysm is a form of cardiac rupture contained by a local area of pericardium and organized thrombus; direct communication with the LV cavity is present; surgical repair usually necessary to prevent rupture.

Recurrent Angina

Usually associated with transient ST-T wave changes; signals high incidence of reinfarction; when it occurs in early post-MI period, proceed directly to coronary arteriography, to identify those who would benefit from revascularization.

SECONDARY PREVENTION

For pts who have not already undergone coronary angiography and PCI, submaximal exercise testing should be performed prior to or soon after discharge. A positive test in certain subgroups (angina at a low workload, a large region of provocable ischemia, or provocable ischemia with a reduced LVEF) suggests need for cardiac catheterization to evaluate myocardium at risk of recurrent infarction. *Beta blockers* (e.g., metoprolol, 25–200 mg daily) should be prescribed routinely for at least 2 years following acute MI, unless contraindications present (asthma, active heart failure, bradycardia). Continue oral antiplatelet agents (e.g., aspirin 81–325 mg daily and a P2Y12 platelet receptor antagonist) to reduce incidence of reinfarction. If LVEF ≤40%, an ACE inhibitor or ARB (if ACE inhibitor is not tolerated) should be used indefinitely. Consider addition of aldosterone antagonist (see "Heart Failure," above).

Modification of cardiac risk factors must be encouraged: discontinue smoking; control hypertension, diabetes, and serum lipids (typically atorvastatin 80 mg daily in immediate post-MI period—see Chap. 178); and pursue graduated exercise.

For a more detailed discussion, see Antman EM, Loscalzo J: ST-Segment Elevation Myocardial Infarction, Chap. 295, p. 1599; and Hochman JS, Ingbar DH: Cardiogenic Shock and Pulmonary Edema, Chap. 326, p. 1759, in HPIM-19.

120 Unstable Angina and Non-ST-Elevation Myocardial Infarction

Unstable angina (UA) and non-ST-elevation MI (NSTEMI) are acute coronary syndromes with similar mechanisms, clinical presentations, and treatment strategies.

Clinical Presentation

UA includes (1) new onset of severe angina, (2) angina at rest or with minimal activity, and (3) recent increase in frequency and intensity of chronic angina. NSTEMI is diagnosed when symptoms of UA are accompanied by evidence of myocardial necrosis (e.g., elevated cardiac biomarkers). Some pts with NSTEMI present with symptoms identical to STEMI—the two are differentiated by ECG findings.

Physical Examination

May be normal or include diaphoresis, pale cool skin, tachycardia, S_4, basilar rales; if large region of ischemia, may demonstrate S_3, hypotension.

Electrocardiogram

May include ST depression and/or T-wave inversion; unlike STEMI, there is no Q-wave development.

Cardiac Biomarkers

Cardiac-specific troponins (specific and sensitive markers of myocardial necrosis) and CK-MB (less sensitive marker) are elevated in NSTEMI. Small troponin elevations may also occur in pts with CHF, myocarditis, or pulmonary embolism.

TREATMENT UNSTABLE ANGINA AND NON-ST-ELEVATION MYOCARDIAL INFARCTION

First step is appropriate triage based on likelihood of coronary artery disease (CAD) and acute coronary syndrome (Fig. 120-1) as well as identification of higher-risk pts (Fig. 120-2). Pts with low likelihood of active ischemia are initially monitored by serial ECGs and serum cardiac biomarkers, and for recurrent chest discomfort; if these are negative, stress testing (or CT angiography if probability of CAD is low) can be used for further therapeutic planning.

Therapy of UA/NSTEMI is directed (1) against the inciting intracoronary thrombus, and (2) toward restoration of balance between myocardial oxygen supply and demand. Pts with the highest-risk scores (Fig. 120-2) benefit the most from aggressive interventions.

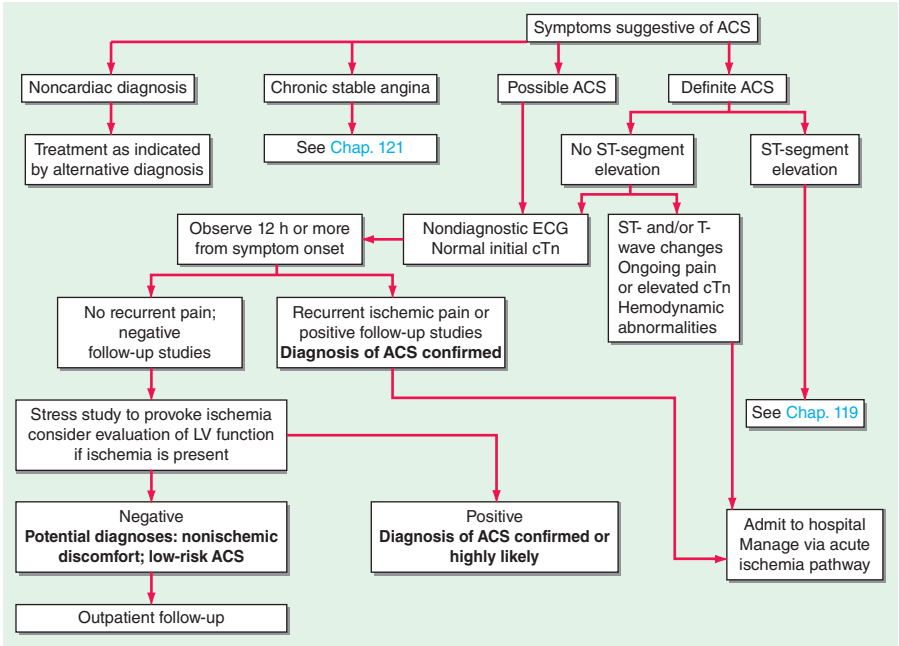


FIGURE 120-1 Algorithm for evaluation and treatment of pts with a suspected acute coronary syndrome. ACS, acute coronary syndrome; cTn, cardiac troponin. *(Adapted from JL Anderson et al: J Am Coll Cardiol 61:e179, 2013.)*

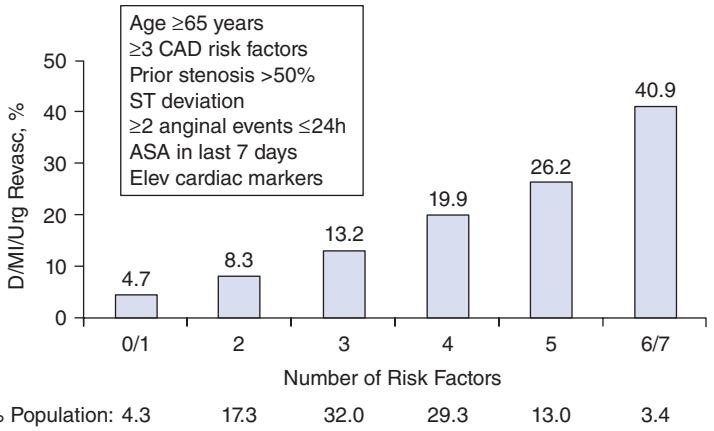


FIGURE 120-2 The TIMI Risk Score for UA/NSTEMI. The quantity of listed attributes correlates with risk of death, MI, or need for urgent revascularization over 14 days. *(Modified from E Antman et al: JAMA 284:835, 2000.)*

ANTITHROMBOTIC THERAPIES

- Aspirin (325 mg initially, then 75–100 mg/d).
- Platelet P2Y12 receptor antagonist (unless excessive risk of bleeding or immediate coronary artery bypass grafting [CABG] likely): Clopidogrel (300–600 mg PO load, then 75 mg/d), ticagrelor (180 mg PO, then 90 mg PO bid [chronic aspirin dose should not exceed 100 mg daily]) or prasugrel (60 mg PO, then 10 mg daily—use prasugrel only if PCI is planned).
- Anticoagulant: Unfractionated heparin (UFH) [70–100 U/kg (maximum 5000 U) then 12 (U/kg)/h (maximum 1000 U/h)] to achieve aPTT 1.5–2.5 × control, *or* low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg SC q12h), which is superior to UFH in reduction of future cardiac events. Alternatives include (1) the factor Xa inhibitor fondaparinux (2.5 mg SC daily), which is associated with lower bleeding risk, or (2) the direct thrombin inhibitor bivalirudin [0.75-mg/kg bolus, then 1.75 (mg/kg)/h], which causes less bleeding in pts undergoing catheterization compared with UFH plus a GP IIb/IIIa inhibitor.
- For high-risk unstable pts who undergo PCI, consider an IV GP IIb/IIIa antagonist [e.g., tirofiban, 25 (μg/kg)/min load, then 0.15 (μg/kg)/min for up to 18 h; or eptifibatide, 180-μg/kg bolus, then 2.0 (μg/kg)/min for 72–96 h].

ANTI-ISCHEMIC THERAPIES

- Nitroglycerin 0.3–0.6 mg sublingually or by buccal spray. If chest discomfort persists after three doses given 5 min apart, consider IV nitroglycerin (5–10 μg/min, then increase by 10 μg/min every 3–5 min until symptoms relieved or systolic bp <100 mmHg). Do not use nitrates in pts with recent use of phosphodiesterase-5 inhibitors for erectile dysfunction (e.g., not within 24 h of sildenafil or within 48 h of tadalafil).
- Beta blockers (e.g., metoprolol 25–50 mg PO q6h) targeted to a heart rate of 50–60 beats/min. In pts with contraindications to beta blockers (e.g., bronchospasm), consider long-acting verapamil or diltiazem (Table 166-1) if LV contractile function is not impaired.

TABLE 120-1 CLASS I RECOMMENDATIONS FOR USE OF AN EARLY INVASIVE STRATEGY

Recurrent angina/ischemia at rest or minimal exertion despite anti-ischemic therapy
Elevated cardiac TnT or TnI
New ST-segment depression
CHF symptoms, rales or worsening mitral regurgitation
Positive stress test
LVEF <0.40
Hemodynamic instability or hypotension
Sustained ventricular tachycardia
PCI within previous 6 months, or prior CABG
Diabetes
Renal dysfunction
High-risk score

Abbreviations: CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TnI, troponin I; TnT, troponin T.
Source: Modified from JL Anderson et al: *J Am Coll Cardiol* 61:e179, 2013.

ADDITIONAL RECOMMENDATIONS

- Admit to unit with continuous ECG monitoring, initially with bed rest.
- Consider morphine sulfate 2–5 mg IV q5–30min for refractory chest discomfort.
- Add HMG-CoA reductase inhibitor (initially at high dose, e.g., atorvastatin 80 mg daily) and consider ACE inhibitor (Chap. 119).

INVASIVE VS CONSERVATIVE STRATEGY

In highest-risk pts (Table 120-1), an early invasive strategy (coronary arteriography within ~48 h followed by percutaneous intervention or CABG) improves outcomes. In lower-risk pts, angiography can be deferred but should be pursued if myocardial ischemia recurs spontaneously (angina or ST deviations at rest or with minimal activity) or is provoked by stress testing.

LONG-TERM MANAGEMENT

- Stress importance of smoking cessation, achieving optimal weight, diet low in saturated and trans fats, regular exercise; these principles can be reinforced by encouraging pt to enter cardiac rehabilitation program.
- Continue aspirin (75–100 mg/d), a P2Y12 receptor antagonist (clopidogrel, prasugrel or ticagrelor), beta blocker, high-dose statin, and ACE inhibitor or angiotensin receptor blocker (especially if hypertensive, or diabetic, or LV ejection fraction is reduced).



For a more detailed discussion, see Cannon CP, Braunwald E: Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina), Chap. 294, p. 1593, in HPIM-19.

121 Chronic Stable Angina

ANGINA

Angina pectoris, the most common clinical manifestation of coronary artery disease (CAD), results from an imbalance between myocardial O_2 supply and demand, most often due to atherosclerotic coronary artery obstruction. Other major conditions that upset this balance and result in angina include aortic valve disease (Chap. 114), hypertrophic cardiomyopathy (Chap. 115), and coronary artery spasm (see below).

Symptoms

Angina is typically associated with exertion or emotional upset; relieved quickly by rest or nitroglycerin (Chap. 31). Major risk factors are cigarette smoking, hypertension, hypercholesterolemia (↑LDL; ↓HDL), diabetes, obesity, and family history of CAD before age 55.

Physical Examination

Often normal; arterial bruits or retinal vascular abnormalities suggest generalized atherosclerosis; S_4 is common. During acute anginal episode, other signs may appear: e.g., an S_4, diaphoresis, rales, and a transient murmur of mitral regurgitation due to papillary muscle ischemia.

Laboratory ECG

May be normal between anginal episodes or show old infarction (Chap. 111). During angina, ST- and T-wave abnormalities typically appear (ST-segment depression reflects subendocardial ischemia; ST-segment elevation may reflect acute infarction or transient coronary artery spasm). Ventricular arrhythmias frequently accompany acute ischemia.

Stress Testing

Enhances diagnosis of CAD (Fig. 121-1). Exercise is performed on treadmill or bicycle until target heart rate is achieved or pt becomes symptomatic (chest pain, lightheadedness, hypotension, marked dyspnea, ventricular tachycardia) or develops diagnostic ST-segment changes. Useful information includes duration of exercise achieved; peak heart rate and bp; depth, morphology, and persistence of ST-segment depression; and whether and at which level of exercise pain, hypotension, or ventricular arrhythmias develop. Exercise testing with radionuclide, echocardiographic, or magnetic resonance imaging increases sensitivity and specificity and is particularly useful if baseline ECG abnormalities prevent interpretation of test. ***Note:*** Exercise testing should not be performed in pts with acute MI, unstable angina, or severe aortic stenosis. If the pt is unable to exercise, pharmacologic stress with IV dipyridamole, adenosine, regadenoson, or dobutamine can be performed in conjunction with radionuclide or echocardiographic imaging. (Table 121-1). Pts with LBBB on baseline ECG should be referred for adenosine or dipyridamole radionuclide imaging, which is most specific for diagnosis of CAD in this setting.

The prognostic utility of coronary calcium detection (by electron-beam or multidetector CT) in the diagnosis and management of CAD has not yet been fully defined.

Some pts do not experience chest pain during ischemic episodes with exertion ("silent ischemia") but are identified by transient ST-T-wave abnormalities during stress (see below).

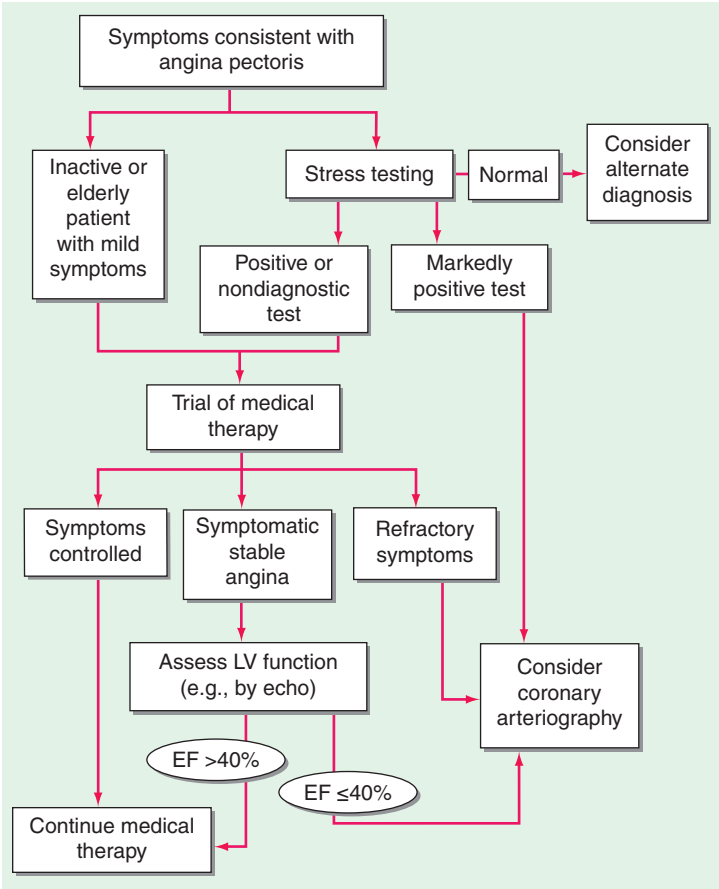


FIGURE 121-1 Role of exercise testing in management of CAD; EF, left ventricular ejection fraction. (*Modified from LS Lilly, in Textbook of Primary Care Medicine, 3rd ed., J Noble [ed.]. St. Louis, Mosby, 2001, p. 552.*)

Coronary Arteriography

The definitive test for assessing severity of CAD; major indications are (1) angina refractory to medical therapy, (2) markedly positive exercise test (≥2-mm ST-segment depression, onset of ischemia at low workload, or ventricular tachycardia or hypotension with exercise) suggestive of left main or three-vessel disease, (3) recurrent angina or positive exercise test after MI, (4) to assess for coronary artery spasm, and (5) to evaluate pts with perplexing chest pain in whom noninvasive tests are not diagnostic.

The role of newer *noninvasive* coronary imaging techniques (CT and MR angiography) continues to be defined.

TABLE 121-1 STRESS TESTING RECOMMENDATIONS

Subgroup	Recommended Study
Pt able to exercise	
If baseline ST-T on ECG is normal	Standard exercise test (treadmill, bicycle, or arm ergometry)
If baseline ST-T impairs test interpretation (e.g., LVH with strain, digoxin)	Standard exercise test (above) combined with *either* Perfusion scintigraphy (thallium-201, ^{99m}Tc-sestamibi) *or* Echocardiography
Pt *not* able to exercise (regardless of baseline ST-T abnormality)	Pharmacologic stress test (IV dobutamine, dipyridamole, or adenosine) combined with imaging: Perfusion scintigraphy [thallium 201, ^{99m}Tc-sestamibi, or PET (rubidium-82 or N-13 ammonia)] *or* Echocardiography *or* Cardiac MRI
LBBB on baseline ECG	Adenosine (or dipyridamole) ^{99m}Tc-sestamibi or PET scintigraphy

TREATMENT CHRONIC STABLE ANGINA

GENERAL

- Identify and treat risk factors: mandatory cessation of smoking; treatment of diabetes, hypertension, and lipid disorders (Chap. 178); advocate a diet low in saturated fat and trans fats.
- Correct exacerbating factors contributing to angina: morbid obesity, CHF, anemia, hyperthyroidism.
- Reassurance and pt education.

DRUG THERAPY

Sublingual nitroglycerin (TNG 0.3–0.6 mg); may be repeated at 5-min intervals; warn pts of possible headache or light-headedness; teach prophylactic use of TNG prior to activity that regularly evokes angina. If chest pain persists for >10 min despite 2–3 TNG, pt should report promptly to nearest medical facility for evaluation of possible acute coronary syndrome.

Long-Term Angina Suppression The following classes of drugs are used, frequently in combination.

Long-Acting Nitrates May be administered by many routes (Table 121-2); start at the lowest dose and frequency to limit tolerance and side effects of headache, light-headedness, tachycardia.

Beta Blockers (See Table 117-1) All have antianginal properties; β_1-selective agents are less likely to exacerbate airway or peripheral vascular disease. Dosage should be titrated to resting heart rate of 50–60 beats/min. *Contraindications* to beta blockers include CHF, AV block, bronchospasm, "brittle" diabetes. Side effects include fatigue, bronchospasm, depressed LV function, impotence, depression, and masking of hypoglycemia in diabetics.

Calcium Antagonists (See Table 117-1) Useful for stable and unstable angina, as well coronary vasospasm. Combination with other antianginal agents is beneficial,

TABLE 121-2 EXAMPLES OF COMMONLY USED NITRATES

	Usual Dose	Recommended Dosing Frequency
Short-acting agents		
Sublingual TNG	0.3–0.6 mg	As needed
Aerosol TNG	0.4 mg (1 inhalation)	As needed
Sublingual ISDN	2.5–10 mg	As needed
Long-acting agents		
ISDN		
Oral	5–30 mg	tid
Sustained-action	40 mg	bid (once in the A.M., then 7 h later)
TNG ointment (2%)	0.5–2	qid (with one 7- to 10-h nitrate-free interval)
TNG skin patches	0.1–0.6 mg/h	Apply in morning, remove at bedtime
ISMO		
Oral	20–40 mg	bid (once in the A.M., then 7 h later)
Sustained-action	30–240 mg	Daily

Abbreviations: TNG, nitroglycerin; ISDN, isosorbide dinitrate; ISMO, isosorbide mononitrate.

but verapamil should be administered cautiously to pts on beta blockers (additive effects on slowing heart rate). Use sustained-release, not short-acting, calcium antagonists; the latter are associated with increased coronary mortality.

Ranolazine For pts who continue to experience stable angina despite the above standard medications, consider addition of ranolazine (500–1000 mg PO bid), which reduces anginal frequency and improves exercise capacity without affecting blood pressure or heart rate. Ranolazine is contraindicated in hepatic impairment, in pts with prolongation of the QT_c interval, or in combination with drugs that inhibit its metabolism (e.g., ketoconazole, macrolide antibiotics, HIV protease inhibitors, diltiazem, and verapamil).

Aspirin 81–162 mg/d reduces the incidence of MI in chronic stable angina, following MI, and in asymptomatic men. It is recommended in pts with CAD in the absence of contraindications (GI bleeding or allergy). Consider clopidogrel (75 mg/d) for aspirin-intolerant individuals.

The addition of an ACE inhibitor is recommended in pts with CAD and LV ejection fraction <40%, hypertension, diabetes, or chronic kidney disease.

MECHANICAL REVASCULARIZATION

Used in conjunction with, not as replacement for, risk factor modification and medical therapies.

Percutaneous Coronary Intervention (PCI) Technique of balloon dilatation, usually with intracoronary stent implantation. Performed on anatomically suitable stenoses of native vessels and bypass grafts; more effective than medical therapy for relief of angina. Has not been shown to reduce risk of MI or death in chronic stable angina; should not be performed on asymptomatic or only mildly symptomatic individuals. With PCI initial relief of angina occurs in 95% of pts; however, restenosis develops in 30–45% following balloon dilatation alone, in ~20% after bare metal stenting, but in only <10% after drug-eluting stent (DES) implantation. Late

TABLE 121-3 COMPARISON OF REVASCULARIZATION PROCEDURES IN MULTIVESSEL DISEASE

Procedure	Advantages	Disadvantages
Percutaneous coronary revascularization	Less invasive Shorter hospital stay Lower initial cost Effective in relieving symptoms	Restenosis requiring repeat procedure Possible incomplete revascularization Limited to specific anatomic subsets
Coronary artery bypass grafting	Lower rate of recurrent angina Ability to achieve complete revascularization	Cost Risk of a repeat procedure due to late graft closure Morbidity and mortality of major surgery

Source: Modified from DP Faxon, in GA Beller (ed), Chronic Ischemic Heart Disease, in E Braunwald (series ed), *Atlas of Heart Disease*, Philadelphia, Current Medicine, 1994.

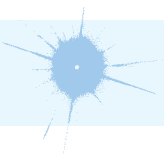
stent thrombosis may occur rarely in pts with DES; it is diminished by prolonged antiplatelet therapy (aspirin indefinitely and a platelet P2Y12 receptor antagonist for a minimum of 12 months).

Coronary Artery Bypass Graft (CABG) Appropriately used for angina refractory to medical therapy or when the latter is not tolerated (and when lesions are not amenable to PCI) or if severe CAD is present (e.g., left main, three-vessel disease with impaired LV function). In type 2 diabetics with multivessel CAD, CABG plus optimal medical therapy is superior to medical therapy alone in prevention of major coronary events.

The relative advantages of PCI and CABG are summarized in Table 121-3.

PRINZMETAL'S VARIANT ANGINA (CORONARY VASOSPASM)

Intermittent focal spasm of coronary artery; often associated with atherosclerotic lesion near site of spasm. Chest discomfort is similar to angina but more severe and occurs typically at rest, with transient ST-segment elevation. Acute infarction or malignant arrhythmias may develop during spasm-induced ischemia. Evaluation includes observation of ECG for transient ST elevation during discomfort; diagnosis confirmed at coronary angiography using provocative (e.g., IV acetylcholine) testing. Primary treatment consists of long-acting nitrates and calcium antagonists. Prognosis is better in pts with anatomically normal coronary arteries than in those with fixed coronary stenoses.



For a more detailed discussion, see Antman EM, and Loscalzo J: Ischemic Heart Disease, Chap. 293, p. 1578, in HPIM-19.

122 Bradyarrhythmias

Bradyarrhythmias arise from (1) failure of impulse initiation (sinoatrial node dysfunction) or (2) impaired electrical conduction (e.g., AV conduction blocks).

SINOATRIAL (SA) NODE DYSFUNCTION

Etiologies are either *intrinsic* (degenerative, ischemic, inflammatory, infiltrative [e.g., senile amyloid], or rare mutations in sodium channel or pacemaker current genes) or *extrinsic* (e.g., drugs [beta blockers, Ca^{++} channel blockers, digoxin], autonomic dysfunction, hypothyroidism).

Symptoms are due to *bradycardia* (fatigue, weakness, lightheadedness, syncope) and/or episodes of associated *tachycardia* (e.g., rapid palpitations, angina) in pts with sick sinus syndrome (SSS).

Diagnosis

Examine ECG for evidence of sinus bradycardia (sinus rhythm at <60 beats/min) or failure of rate to increase with exercise, sinus pauses, or exit block. In pts with SSS, periods of tachycardia (i.e., atrial fibrillation/flutter) occur. Prolonged ECG monitoring (24–48 h Holter, 30-day loop recorder, or long-term implanted monitor) aids in identifying these abnormalities. Invasive electrophysiologic testing is rarely necessary to establish diagnosis.

TREATMENT SINOATRIAL NODE DYSFUNCTION

Remove or treat extrinsic causes such as contributing drugs or hypothyroidism. Otherwise, symptoms of bradycardia respond to permanent pacemaker placement. In SSS, treat associated atrial fibrillation or flutter as indicated in Chap. 123.

AV BLOCK

Impaired conduction from atria to ventricles may be structural and permanent, or reversible (e.g., autonomic, metabolic, drug-related)—see Table 122-1.

First Degree (See Fig. 122-1A)

Prolonged, constant PR interval (>0.20 s). May be normal or secondary to increased vagal tone or drugs (e.g., beta blocker, diltiazem, verapamil, digoxin); treatment not usually required.

Second Degree (See Fig. 122-1B)

Mobitz I (Wenckebach)

Narrow QRS, progressive increase in PR interval until a ventricular beat is dropped, then sequence is repeated (Fig. 122-1D). Seen with drug intoxication (digitalis, beta blockers), increased vagal tone, inferior MI. Usually transient, no therapy required; if symptomatic, use atropine (0.6 mg IV, repeated × 3–4) or temporary pacemaker.

Mobitz II

Fixed PR interval with occasional dropped beats, in 2:1, 3:1, or 4:1 pattern; the QRS complex is usually wide. Seen with MI or degenerative conduction system disease; more serious than Mobitz I—may progress suddenly to complete AV block; permanent pacemaker is indicated.

TABLE 122-1 ETIOLOGIES OF ATRIOVENTRICULAR BLOCK

Autonomic	
Carotid sinus hypersensitivity	Vasovagal
Metabolic/Endocrine	
Hyperkalemia	Hypothyroidism
Hypermagnesemia	Adrenal insufficiency
Drug-Related	
Beta blockers	Adenosine
Calcium channel blockers	Antiarrhythmics (class I and III)
Digitalis	Lithium
Infectious	
Endocarditis	Tuberculosis
Lyme disease	Diphtheria
Chagas' disease	Toxoplasmosis
Syphilis	
Heritable/Congenital	
Congenital heart disease	Kearns-Sayre syndrome (OMIM #530000)
Maternal SLE	Myotonic dystrophy
Inflammatory	
SLE	MCTD
Rheumatoid arthritis	Scleroderma
Infiltrative	
Amyloidosis	Hemochromatosis
Sarcoidosis	
Neoplastic/Traumatic	
Lymphoma	Radiation
Mesothelioma	Catheter ablation
Melanoma	
Degenerative	
Lev disease	Lenégre disease
Coronary Artery Disease	
Acute MI	

Abbreviations: MCTD, mixed connective tissue disease; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database).

Third Degree (Complete AV Block) (See Fig. 122-1C)

Complete failure of conduction from atria to ventricles; atria and ventricles depolarize independently. May occur with MI, digitalis toxicity, or degenerative conduction system disease. Permanent pacemaker is usually indicated, except when reversible (e.g., drug-related or appears only transiently in MI without associated bundle branch block).



For a more detailed discussion, see Spragg DD, Tomaselli GF: The Bradyarrhythmias: Disorders of the Sinoatrial Node, Chap. 274, p. 1466; and Chap. 275, and Spragg DD, Tomaselli GF: The Bradyarrhythmias: Disorders of the Atrioventricular Node, p. 1470, in HPIM-19.

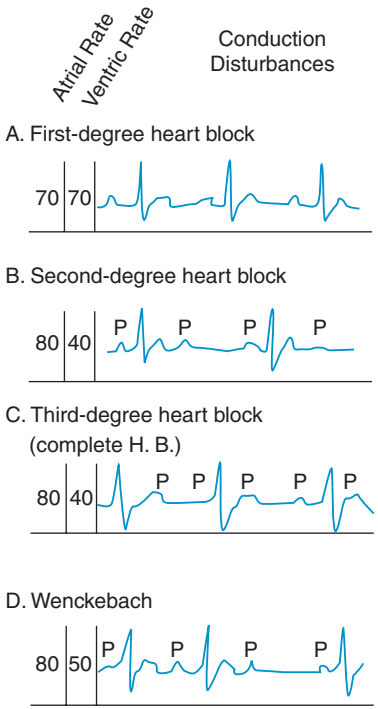


FIGURE 122-1 Bradyarrhythmias. (*Modified from BE Sobel, E Braunwald: HPIM-9, p. 1052.*)

123 Tachyarrhythmias

Tachyarrhythmias may appear in the presence or absence of structural heart disease; they are more serious in the former. Conditions that provoke arrhythmias include (1) myocardial ischemia, (2) heart failure, (3) hypoxemia, (4) hypercapnia, (5) hypotension, (6) electrolyte disturbances (e.g., hypokalemia and/or hypomagnesemia), (7) drug toxicity (digoxin, pharmacologic agents that prolong the QT interval), (8) caffeine consumption, (9) ethanol consumption.

Diagnosis

Examine ECG for evidence of ischemic changes (Chap. 111), prolonged or shortened QT interval, characteristics of Wolff-Parkinson-White (WPW) syndrome (see below), or ST elevation in leads V_1–V_3 typical of Brugada syndrome. See Table 123-1 for diagnosis of tachyarrhythmias; always identify atrial activity and relationship between P waves and QRS complexes. To aid the diagnosis:

TABLE 123-1 CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF COMMON ARRHYTHMIAS

Rhythm	Atrial Rate	Features	Carotid Sinus Massage	Precipitating Conditions	Initial Treatment
Narrow QRS complex					
Atrial premature beats	—	P wave abnormal; QRS width normal	—	Can be normal or due to anxiety, CHF, hypoxia, caffeine, abnormal electrolytes ($\downarrow K^+$ $\downarrow Mg^{2+}$)	Remove precipitating cause; if symptomatic: beta blocker
Sinus tachycardia	100–160	Normal P wave contour	Rate gradually slows	Fever, anxiety, dehydration, pain, CHF, hyperthyroidism, COPD	Remove precipitating cause; if symptomatic: beta blocker
AV nodal tachycardia (reentrant)	120–250	Absent or retrograde P wave	Abruptly converts to sinus rhythm (or no effect)	Can occur in healthy individuals	Vagal maneuvers; if unsuccessful: adenosine, verapamil, beta blocker, cardioversion (100–200 J). To prevent recurrence: beta blocker, verapamil, diltiazem, digoxin, class IC agent, or catheter ablation
Atrial tachycardia	130–200	P contour different from sinus P wave; AV block may occur; automatic form shows "warm-up" in rate in first several beats	AV block may ↑	Digitalis toxicity; pulmonary disease; scars from prior cardiac surgery	If digitalis toxic: hold digoxin, correct [K^+] In absence of digoxin toxicity: slow rate with beta blocker, verapamil, or diltiazem; can attempt conversion with IV procainamide or amiodarone; if unsuccessful, proceed to cardioversion or catheter ablation

Atrial flutter Atrial fibrillation	260–300 >350	"Sawtooth" flutter waves; 2:1, 4:1 block No discrete P; irregularly spaced QRS	↑ AV block with ↓ventricular rate ↓ Ventricular rate	Mitral valve disease, hypertension, pulmonary embolism, pericarditis, post–cardiac surgery, hyperthyroidism; obstructive lung disease, EtOH, idiopathic	1. Slow the ventricular rate: beta blocker, verapamil, diltiazem, or digoxin 2. Convert to NSR (after anticoagulation if chronic) electrically (50–100 J for atrial flutter, 100–200 J for atrial fibrillation) or chemically with IV ibutilide or oral class IC, III, or IA[a] agent Atrial flutter may respond to rapid atrial pacing, and radio frequency ablation highly effective to prevent recurrences; consider ablation for recurrences of atrial fibrillation
Multifocal atrial tachycardia	100–150	More than three different P wave shapes with varying PR intervals	No effect	Severe respiratory insufficiency	Treat underlying lung disease; verapamil or diltiazem may be used to slow ventricular rate; class IC agents or amiodarone may ↓ episodes
Wide QRS Complex					
Ventricular premature beats		Fully compensatory pause between normal beats	No effect	CAD, MI, CHF, hypoxia, hypokalemia, digitalis toxicity, prolonged QT interval (congenital or drug-related)	May not require therapy; if needed for symptomatic suppression, use beta blocker
Ventricular tachycardia		QRS rate 100–250; slightly irregular rate	No effect		If unstable: electrical conversion/defibrillation (≥200 J monophasic, or 100 J biphasic) Otherwise: acute (IV): amiodarone, lidocaine, procainamide; chronic management: usually ICD Pts without structural heart disease (e.g., focal outflow tract ventricular tachycardia) may respond to beta blockers or verapamil

(*Continued*)

TABLE 123-1 CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF COMMON ARRHYTHMIAS (*CONTINUED*)

Rhythm	Atrial Rate	Features	Carotid Sinus Massage	Precipitating Conditions	Initial Treatment
Accelerated idioventricular rhythm (AIVR)		Gradual onset and offset; QRS rate 40–120		Acute MI, myocarditis	Usually none; for symptoms, use atropine or atrial pacing
Ventricular fibrillation		Erratic electrical activity	No effect		Immediate defibrillation
Torsade de pointes		Ventricular tachycardia with sinusoidal oscillations of QRS height	No effect	Prolonged QT interval (congenital or drug-related)	IV magnesium (1- to 2-g bolus); overdrive pacing; isoproterenol for bradycardia-dependent torsades (unless CAD present); lidocaine Drugs that prolong QT interval are contraindicated
Supraventricular tachycardias with aberrant ventricular conduction		P wave typical of the supraventricular rhythm; wide QRS complex due to conduction through partially refractory pathways		Etiologies of the respective supraventricular rhythms listed above; atrial fibrillation with rapid, wide QRS may be due to preexcitation (WPW)	Same as treatment of respective supraventricular rhythm; if ventricular rate rapid (>200), treat as WPW (see text)

[a]Antiarrhythmic drug groups listed in Table 123-2.

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EtOH, ethyl alcohol; ICD, implantable cardioverter defibrillator; NSR, normal sinus rhythm; WPW, Wolff-Parkinson-White.

TABLE 123-2 EXAMPLES OF ANTIARRHYTHMIC DRUGS

Drug	Loading Dose	Maintenance Dose	Side Effects	Excretion
Class IA				
Quinidine		PO: 300–600 mg q6h	Diarrhea, tinnitus, QT prolongation, hypotension, anemia, thrombocytopenia	Hepatic
Procainamide	IV: 15 mg/kg over 60 min	IV: 1–4 mg/min PO: 500–1000 mg q4h	Nausea, lupus-like syndrome, agranulocytosis, QT prolongation	Renal and hepatic
Sustained-release		PO: 1000–2500 mg q12h		
Disopyramide		PO: 100–300 mg q6–8h	Myocardial depression, AV block, QT prolongation anticholinergic effects	Renal and hepatic
Sustained-release		PO: 200–400 mg q12h		
Class IB				
Lidocaine	IV: 1-mg/kg bolus followed by 0.5-mg/kg bolus q8–10 min to total 3 mg/kg	IV: 1–4 mg/min	Confusion, seizures, respiratory arrest	Hepatic
Mexiletine		PO: 150–300 mg q8–12h	Nausea, tremor, gait disturbance	Hepatic
Class IC				
Flecainide		PO: 50–200 mg q12h	Nausea, exacerbation of ventricular arrhythmia, prolongation of PR and QRS intervals	Hepatic and renal
Propafenone		PO: 150–300 mg q8h		Hepatic
Class II				
Metoprolol	IV: 5–10 mg q5min × 3	PO: 25–100 mg q6h	Bradycardia, AV block, CHF, bronchospasm	Hepatic
Esmolol	IV: 500 μg/kg over 1 min	IV: 50 (μg/kg)/min		

(*Continued*)

TABLE 123-2 EXAMPLES OF ANTIARRHYTHMIC DRUGS (*CONTINUED*)

Drug	Loading Dose	Maintenance Dose	Side Effects	Excretion
Class III				
Amiodarone	PO: 800–1600 mg qd × 1–2 weeks, then 400–600 mg/d × 3 weeks IV: 150 mg over 10 min	PO: 100–400 mg qd IV: 1 mg/min × 6 h, then 0.5 mg/min	Thyroid abnormalities, pulmonary fibrosis, transaminitis, bluish skin	Hepatic
Ibutilide	IV (≥60 kg): 1 mg over 10 min, can repeat after 10 min	—	Torsade de pointes, hypotension, nausea	Hepatic
Dofetilide		PO: 125–500 μg bid	Torsade de pointes, headache, dizziness	Renal
Sotalol		PO: 80–160 mg q12h	Fatigue, bradycardia, exacerbation of ventricular arrhythmia	Renal
Dronedarone		PO: 400 mg q12h	Bradycardia, AV block, prolonged QT, exacerbation of heart failure, GI discomfort	Hepatic
Class IV				
Verapamil	IV: 2.5–10 mg over 3–5 min	IV: 2.5–10 mg/h PO: 80–120 mg q6–8 h	AV block, CHF, hypotension, constipation	Hepatic
Diltiazem	IV: 0.25 mg/kg over 3–5 min (maximum 20 mg)	IV: 5–15 mg/h PO: 30–60 mg q6h		Hepatic
Other				
Digoxin	IV, PO: 0.75–1.5 mg over 24 h	IV, PO: 0.125–0.25 mg qd	Nausea, AV block, ventricular and supraventricular arrhythmias	Renal
Adenosine	IV: 6-mg rapid bolus; if no effect then 12-mg bolus	—	Transient hypotension or atrial standstill	—

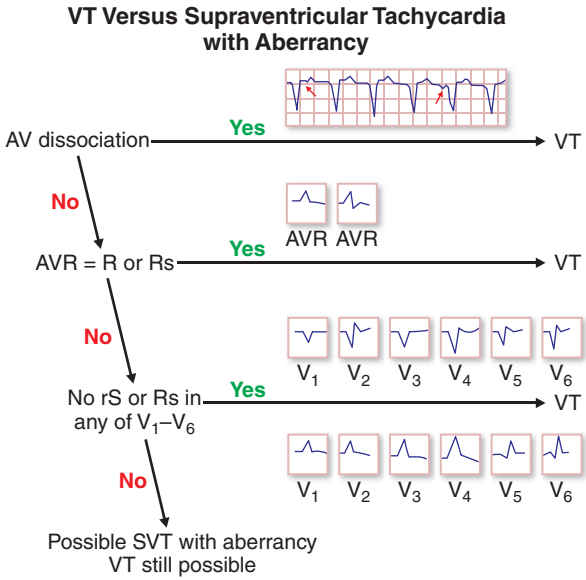


FIGURE 123-1 Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT).

- Obtain long rhythm strip of lead II, aVF, or V_1. P waves can be made more evident by intentionally doubling the ECG voltage.
- Place accessory ECG leads (e.g., right-sided chest leads) to help identify P waves. Record ECG during carotid sinus massage (Table 123-1). ***Note:*** Do not massage both carotids simultaneously.
- For intermittent symptoms, consider 24-h Holter monitor (if symptoms occur daily), a pt-activated or continuously recording event monitor over 2–4 weeks, or, if symptoms are very infrequent but severely symptomatic, an implanted loop monitor. A standard exercise test may be used to provoke arrhythmias for diagnostic purposes.

Tachyarrhythmias with wide QRS complex beats may represent ventricular tachycardia or supraventricular tachycardia with aberrant conduction. Factors favoring ventricular tachycardia include (1) AV dissociation, (2) monomorphic R or Rs in atrioventricular reentry (AVR), (3) concordance of QRS with monophasic R or S waves in V1–V6 (Figure 123-1).

TREATMENT TACHYARRHYTHMIAS (TABLES 123-1 AND 123-2)

Precipitating causes (listed above) should be corrected. If pt is hemodynamically compromised (angina, hypotension, CHF), proceed to immediate cardioversion.

Do not cardiovert sinus tachycardia; exercise caution if digitalis toxicity is suspected. Initiate drugs as indicated in the tables; follow ECG intervals (esp. QRS and QT). Reduce dosage for pts with hepatic or renal dysfunction as indicated in Table 123-2. Drug efficacy is confirmed by ECG (or Holter) monitoring, stress testing, and, in special circumstances, invasive electrophysiologic study.

Antiarrhythmic agents all have potential toxic side effects, including provocation of ventricular arrhythmias, esp. in pts with LV dysfunction or history of sustained ventricular arrhythmias. Drug-induced QT prolongation and associated torsades de pointes ventricular tachycardia (Table 123-1) is most common with class IA and III agents; the drug should be discontinued if the QTc interval (QT divided by square root of RR interval) increases by >25%. Antiarrhythmic drugs should be avoided in pts with asymptomatic ventricular arrhythmias after MI, since mortality risk increases.

CHRONIC ATRIAL FIBRILLATION (AF)

Evaluate potential underlying cause (e.g., thyrotoxicosis, mitral stenosis, excessive ethanol consumption, pulmonary embolism). Pts with rheumatic mitral valve disease or CHA_2DS_2-VASc score ≥2 (1 point each for CHF, hypertension, diabetes, vascular disease, age 65–75, female gender; 2 points each for age 75, history of stroke or TIA) should receive anticoagulation with either warfarin (INR 2.0–3.0) or, for AF not associated with valvular disease, newer oral anticoagulants that do not require prothrombin time monitoring—e.g., dabigatran 150 mg bid for creatinine clearance (CrCl) >30 mL/min (75 mg bid for CrCl 15–30 mL/min), rivaroxaban 20 mg daily with the evening meal (15 mg daily for CrCl 15–50 mL/min; avoid if CrCl <15), or apixaban 5 mg bid (2.5 mg bid for 2 of the following: age ≥80, weight ≤60 kg, serum creatinine ≥1.5 md/dL). Can also consider anticoagulation for CHA_2DS_2-VASc score of 1. Prescribe aspirin, up to 325 mg/d, for CHA_2DS_2-VASc of 0–1 or if contraindication to systemic anticoagulation exists.

Control ventricular rate (60–80 beats/min at rest, <100 beats/min with mild exercise) with beta blocker, calcium channel blocker (verapamil, diltiazem), or digoxin.

Consider cardioversion (100–200 J) after ≥3 weeks therapeutic anticoagulation, or acutely if no evidence of left atrial thrombus by transesophageal echo, especially if symptomatic despite rate control. Initiation of class IC, III, or IA agents prior to electrical cardioversion facilitates maintenance of sinus rhythm after successful procedure. Class IC (Table 123-2) drugs are preferred in pts without structural heart disease, and class III drugs are recommended in presence of left ventricular dysfunction or coronary artery disease. Anticoagulation should be continued for a minimum of 3 weeks after successful cardioversion.

Catheter-based ablation (pulmonary vein isolation) can be considered for recurrent symptomatic AF refractory to pharmacologic measures.

PREEXCITATION SYNDROME (WPW)

Conduction occurs through an accessory pathway between atria and ventricles. Baseline ECG typically shows a short PR interval and slurred upstroke of the QRS ("delta" wave). Associated tachyarrhythmias are of two types:

- Narrow QRS "orthodromic" tachycardia (antegrade conduction through AV node). Treat cautiously with IV adenosine or beta blocker, verapamil, or diltiazem (Table 123-2).
- Wide QRS complex "antidromic" tachycardia (antegrade conduction through accessory pathway); wide complex tachycardia may also be associated with AF with a very rapid (>250/min) ventricular rate, which can degenerate into VF. If hemodynamically compromised, immediate cardioversion is indicated; otherwise, treat with IV procainamide or ibutilide (Table 123-2), *not* digoxin, beta blocker, or verapamil.

Consider catheter ablation of accessory pathway for long-term prevention.

For a more detailed discussion, see Michaud GF, Stevenson WG: Supraventricular Tachyarrhythmias, Chap. 276, p. 1476 and John RM, Stevenson WG: Ventricular Arrhythmias, Chapter 277, p. 1489 in HPIM-19.

124 Heart Failure and Cor Pulmonale

HEART FAILURE

Definition

Abnormality of cardiac structure and/or function resulting in clinical symptoms (e.g., dyspnea, fatigue) and signs (e.g., edema, rales), hospitalizations, poor quality of life, and shortened survival. It is important to identify the underlying nature of the cardiac disease and the factors that precipitate acute CHF.

Underlying Cardiac Disease

Includes (1) states that depress systolic ventricular function with reduced ejection fraction (HFrEF; e.g., coronary artery disease [CAD], dilated cardiomyopathies, valvular disease, congenital heart disease); and (2) states of heart failure with preserved ejection fraction (HFpEF; e.g., restrictive cardiomyopathies, hypertrophic cardiomyopathy, fibrosis, endomyocardial disorders), also termed *diastolic failure*.

Acute Precipitating Factors

Include (1) excessive Na^+ intake, (2) noncompliance with heart failure medications, (3) acute MI (may be silent), (4) exacerbation of hypertension, (5) acute arrhythmias, (6) infections and/or fever, (7) pulmonary embolism, (8) anemia, (9) thyrotoxicosis, (10) pregnancy, (11) acute myocarditis or infective endocarditis, and (12) certain drugs (e.g., nonsteroidal anti-inflammatory agents, verapamil).

Symptoms

Due to inadequate perfusion of peripheral tissues (fatigue) and elevated intracardiac filling pressures (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema).

Physical Examination

Jugular venous distention, S_3 (in HFrEF/volume overload), pulmonary congestion (rales, dullness over pleural effusion), peripheral edema, hepatomegaly, and ascites. Sinus tachycardia is common.

In pts with HFpEF, S_4 is often present.

Laboratory

CXR may reveal cardiomegaly, pulmonary vascular redistribution, interstitial edema, pleural effusions. Left ventricular systolic and diastolic dysfunction can be assessed

by *echocardiography* with Doppler, and EF calculated or estimated. In addition, echo can identify underlying valvular, pericardial, or congenital heart disease, and regional wall motion abnormalities typical of CAD. Cardiac MR may be valuable in assessing ventricular structure, mass, volumes, and can help determine cause of heart failure (e.g., CAD, amyloid, hemochromatosis). Measurement of B-type natriuretic peptide (BNP) or N-terminal pro-BNP differentiates cardiac from pulmonary causes of dyspnea (elevated in the former).

Conditions that Mimic CHF

Pulmonary Disease: Chronic bronchitis, emphysema, and asthma (Chaps. 129 and 131); assess for sputum production and abnormalities on CXR and pulmonary function tests. *Other Causes of Peripheral Edema*: Obesity, varicose veins, and venous insufficiency do not cause jugular venous distention. Edema due to renal dysfunction is often accompanied by elevated serum creatinine and abnormal urinalysis (Chap. 36).

TREATMENT HEART FAILURE

Aimed at symptomatic relief, prevention of adverse cardiac remodeling, and prolonging survival. Overview of treatment shown in Table 124-1; notably, ACE inhibitors and beta blockers are cornerstones of therapy in pts with HFrEF. Once symptoms develop:

- *Control excess fluid retention*: (1) *Dietary sodium restriction* (eliminate salty foods, e.g., potato chips, canned soups, bacon, salt added at table); more stringent requirements (<2 g NaCl/d) in advanced CHF. If dilutional hyponatremia present, restrict fluid intake (<1000 mL/d). (2) *Diuretics: Loop diuretics* (e.g., furosemide or torsemide [Table 124-2]) are most potent and, unlike thiazides, remain effective when GFR <25 mL/min. Combine loop diuretic with thiazide or metolazone for augmented effect.

During acute diuresis, obtain daily weights, aiming for loss of 1–1.5 kg/d.

- *ACE inhibitors* (Table 124-2): Recommended as standard initial CHF therapy. They prolong life in pts with symptomatic CHF, delay the onset of CHF in pts with asymptomatic LV dysfunction, and lower mortality when begun soon after acute MI. ACE inhibitors may result in hypotension in pts who are volume depleted, so start at lowest dosage (e.g., captopril 6.25 mg PO tid). Angiotensin receptor blockers (ARBs) (Table 124-2) may be substituted if pt is intolerant of ACE inhibitor (e.g., because of cough or angioedema). Consider hydralazine plus an oral nitrate instead in pts who develop hyperkalemia or renal insufficiency on ACE inhibitor.
- *Beta blockers* (Table 124-2) administered in gradually augmented dosage improve symptoms and prolong survival in pts with heart failure and reduced EF <40%. Begin at low dosage and increase gradually (e.g., carvedilol 3.125 mg bid, double q2weeks as tolerated to maximum of 25 mg bid [for weight <85 kg] or 50 mg bid [weight >85 kg]).
- Aldosterone antagonist therapy (*spironolactone* or *eplerenone* [Table 124-2]), added to standard therapy in pts with advanced heart failure reduces mortality. Such therapy should be considered in pts with class II-IV heart failure symptoms and LVEF ≤35%. Should be used cautiously when combined with ACE inhibitor or ARB to avoid hyperkalemia.
- *Digoxin* may be useful in heart failure due to (1) marked systolic dysfunction (LV dilatation, low EF, S_3) and (2) heart failure with atrial fibrillation (AF) and rapid ventricular rates. Unlike ACE inhibitors and beta blockers, digoxin does not prolong survival in heart failure pts but reduces hospitalizations. Not indicated in CHF due to pericardial disease, restrictive cardiomyopathy, or mitral stenosis

TABLE 124-1 THERAPY FOR CHRONIC HEART FAILURE

1. General measures
   a. Restrict salt intake
   b. Avoid NSAIDs
   c. Immunize against influenza and pneumococcal pneumonia
2. Diuretics
   a. Use in volume-overloaded pts to achieve normal JVP and relief of edema
   b. Weigh daily to adjust dose
   c. For diuretic resistance, administer IV or use 2 diuretics in combination (e.g., furosemide plus metolazone)
3. ACE inhibitor or angiotensin receptor blocker
   a. For all pts with LV systolic heart failure or asymptomatic LV dysfunction
   b. Contraindications: Serum K^+ >5.5, advanced renal disease (e.g., creatinine >3 mg/dL), bilateral renal artery stenosis, pregnancy
4. Beta blocker
   a. For pts with symptomatic or asymptomatic heart failure and LVEF <40%, combined with ACE inhibitor and diuretics
   b. Contraindications: Bronchospasm, symptomatic bradycardia or advanced heart block, unstable heart failure
5. Aldosterone antagonist
   a. Consider for class II–IV heart failure and LVEF <35%
   b. Avoid if K^+ >5.0 or creatinine >2.5 mg/dL
6. Digitalis
   a. For persistently symptomatic pts with systolic heart failure (especially if atrial fibrillation present) added to ACE inhibitor, diuretics, beta blocker
7. Other measures
   a. Consider combination of hydralazine and oral nitrate if not tolerant of ACE inhibitor/ARB
   b. Consider ivabradine for LVEF ≤35%, if in sinus rhythm, rate > 70, already on maximum tolerated beta blocker, or if contraindication to beta-blocker
   c. Consider ventricular resynchronization (biventricular pacemaker) for pts with class III or IV heart failure, LVEF <35%, and QRS >120 ms
   d. Consider implantable cardioverter-defibrillator in pts with class II–III heart failure and ejection fraction <35%

(unless AF is present). Digoxin is contraindicated in hypertrophic cardiomyopathy and in pts with AV conduction blocks.

– Digoxin dosing (0.125–0.25 mg qd) depends on age, weight, and renal function and can be guided by measurement of serum digoxin level (maintain level <1.0 ng/mL).

– *Digitalis toxicity* may be precipitated by hypokalemia, hypoxemia, hypercalcemia, hypomagnesemia, hypothyroidism, or myocardial ischemia. Early signs of toxicity include anorexia, nausea, and lethargy. *Cardiac toxicity* includes ventricular and supraventricular dysrhythmias and all degrees of AV block. At first sign of digitalis toxicity, discontinue the drug; maintain serum K^+

TABLE 124-2 DRUGS FOR THE TREATMENT OF CHRONIC HEART FAILURE WITH REDUCED EF

	Initiating Dose	Maximal Dose
Diuretics		
Furosemide	20–40 mg qd or bid	400 mg/d
Torsemide	10–20 mg qd bid	200 mg/d
Bumetanide	0.5–1.0 mg qd or bid	10 mg/d
Hydrochlorothiazide	25 mg qd	100 mg/d
Metolazone	2.5–5.0 mg qd or bid	20 mg/d
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10–20 mg bid
Lisinopril	2.5–5.0 mg qd	20–40 mg qd
Ramipril	1.25–2.5 mg bid	2.5–5 mg bid
Trandolapril	0.5 mg qd	4 mg qd
Angiotensin receptor blockers		
Valsartan	40 mg bid	160 mg bid
Candesartan	4 mg qd	32 mg qd
Losartan	25–50 mg qd	150 mg qd
β receptor blockers		
Carvedilol	3.125 mg bid	25–50 mg bid
Bisoprolol	1.25 mg qd	10 mg qd
Metoprolol succinate CR	12.5–25 mg qd	200 mg qd
Aldosterone antagonists		
Spironolactone	12.5–25 mg qd	25–50 mg qd
Eplerenone	25 mg qd	50 mg qd
Additional therapies		
Combination of hydralazine/isosorbide dinitrate	10–25 mg/10 mg tid	75 mg/40 mg tid
Fixed dose of hydralazine/isosorbide dinitrate	37.5 mg/20 mg (one tablet) tid	75 mg/40 mg (two tablets) tid
Digoxin	0.125 mg qd	Guided by renal function and serum level

concentration between 4.0 and 5.0 mmol/L. Bradyarrhythmias and AV block may respond to atropine (0.6 mg IV); otherwise, a temporary pacemaker may be required. Antidigoxin antibodies are available for massive overdose.

- The combination of the oral vasodilators *hydralazine* (10–75 mg tid) and *isosorbide dinitrate* (10–40 mg tid) may be of benefit for chronic administration in pts intolerant of ACE inhibitors and ARBs and is also beneficial as part of standard therapy, along with ACE inhibitor and beta blocker, in African Americans with class II–IV heart failure.
- Ivabradine, an inhibitor of the sinoatrial nodal I_f current, has been shown to reduce hospitalizations and cardiovascular endpoints in heart failure and was recently approved for that purpose. It is a second line agent that can be prescribed (starting at 2.5–5.0 mg orally twice daily) to pts with left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with heart rate >70 bpm, already on maximally tolerated beta-blocker dose or have a contraindication to beta-blocker use.
- In sicker, hospitalized pts, IV vasodilator therapy (Table 124-3) is often necessary. *Nitroprusside* is a potent mixed vasodilator for pts with markedly elevated

TABLE 124-3 DRUGS FOR TREATMENT OF ACUTE HEART FAILURE

	Initiating Dose	Maximal Dose
Vasodilators		
Nitroglycerin	20 μg/min	40–400 μg/min
Nitroprusside	10 μg/min	up to 5 μg/kg/min
Nesiritide	Bolus 2 μg/kg	0.01 μg/kg per min[a]
Inotropes		
Dobutamine	1–2 μg/kg per min	2–20 μg/kg per min
Milrinone	Bolus 50 μg/kg slowly over 10 min	0.1–0.75 μg/kg per min
Dopamine	1–2 μg/kg per min	2–4 μg/kg per min
Levosimendan	Bolus 6–12 μg/kg over 10 min	0.1–0.2 μg/kg per min[a]

[a]Approved outside of the United States for the management of acute heart failure.

systemic vascular resistance. It is metabolized to thiocyanate, which is excreted via the kidneys. To avoid thiocyanate toxicity (seizures, altered mental status, nausea), follow thiocyanate levels in pts with renal dysfunction or if administered for >2 days. IV *nesiritide* (Table 124-3), a purified preparation of BNP, is a vasodilator that reduces pulmonary capillary wedge pressure in pts with acutely decompensated CHF, but has neutral effects on mortality or sense of dyspnea. It should be considered only in pts with refractory heart failure.

- IV inotropic agents (see Table 124-3) are administered to hospitalized pts for refractory symptoms or acute exacerbation of CHF to augment cardiac output. They are contraindicated in hypertrophic cardiomyopathy. *Dobutamine* augments cardiac output without significant peripheral vasoconstriction or tachycardia. *Dopamine* at low dosage (1–5 [μg/kg]/min) facilitates diuresis; at higher dosage (5–10 [μg/kg]/min) positive inotropic effects predominate; peripheral vasoconstriction is greatest at dosage >10 (μg/kg)/min. *Milrinone* (0.1–0.75 [μg/kg]/min after 50-μg/kg loading dose) is a nonsympathetic positive inotrope and vasodilator. The above vasodilators and inotropic agents may be used together for additive effect.
- The initial approach to treatment of acute decompensated heart failure can rely on the pt's hemodynamic profile (Fig. 124-1) based on clinical examination and, if necessary, invasive hemodynamic monitoring:

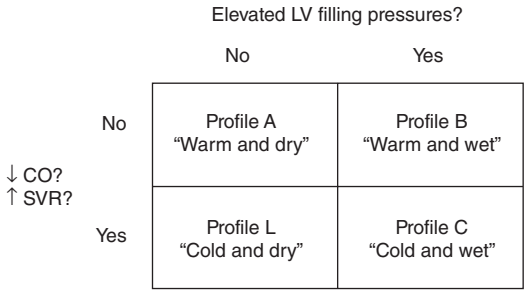


FIGURE 124-1 Hemodynamic profiles in pts with acute heart failure. CO, cardiac output; SVR, systemic vascular resistance. *(Modified from Grady KL et al: Circulation 102:2443, 2000.)*

  - *Profile A "Warm and dry":* Symptoms due to conditions other than heart failure (e.g., acute ischemia). Treat underlying condition.
  - *Profile B "Warm and wet":* Treat with diuretic and vasodilators.
  - *Profile C "Cold and wet":* Treat with IV vasodilators and inotropic agents.
  - *Profile L "Cold and dry":* If low filling pressure (PCW <12 mmHg) confirmed, consider trial of volume repletion.
- Consider implantable cardioverter defibrillator (ICD) prophylactically for chronic class II–III heart failure and LVEF <35%. Pts with an LVEF <35%, refractory CHF (NYHA class III–IV), and QRS >120 ms may be candidates for biventricular pacing (cardiac resynchronization therapy), typically in combination with an ICD. Pts with severe disease and very limited, short-term expected survival, and who meet stringent criteria, may be candidates for cardiac transplantation or prolonged-assisted mechanical circulation (see HPIM-19, **Chap. 281**, p. 1516).
- Pts with predominantly diastolic heart failure are treated with salt restriction and diuretics. Beta blockers and ACE inhibitors may be of benefit in blunting neurohormonal activation.

COR PULMONALE

RV enlargement and/or altered function resulting from primary lung disease; leads to RV hypertrophy and eventually to RV failure. Etiologies include:

- *Pulmonary parenchymal or airway disease* leading to hypoxemic vasoconstriction: e.g., chronic obstructive pulmonary disease (COPD), interstitial lung diseases, bronchiectasis, cystic fibrosis (**Chaps. 131** and **134**).
- *Diseases of the pulmonary vasculature*: e.g., recurrent pulmonary emboli, pulmonary arterial hypertension (PAH) (**Chap. 127**), vasculitis, sickle cell anemia.
- *Inadequate mechanical ventilation (chronic hypoventilation).* Kyphoscoliosis, neuromuscular disorders, marked obesity, sleep apnea (**Chap. 137**).

Symptoms

Depend on underlying disorder but include dyspnea, cough, fatigue, and sputum production (in parenchymal diseases).

Physical Examination

Tachypnea, RV impulse along left sternal border, loud P_2, right-sided S_4; cyanosis, clubbing are late findings. If RV failure develops, elevated jugular venous pressure, hepatomegaly with ascites, pedal edema; murmur of tricuspid regurgitation is common.

Laboratory ECG

RV hypertrophy and RA enlargement (**Chap. 111**); tachyarrhythmias are common.

Radiologic Studies

CXR shows RV and pulmonary artery enlargement; if PAH present, tapering of the pulmonary artery branches. Chest CT identifies emphysema, interstitial lung disease, and acute pulmonary embolism; V/Q scan is more reliable for diagnosis of chronic thromboemboli. Pulmonary function tests and ABGs characterize intrinsic pulmonary disease.

Echocardiogram

RV hypertrophy; LV function typically normal. RV systolic pressure can be estimated from Doppler measurement of tricuspid regurgitant flow. If imaging is

difficult because of air in distended lungs, RV volume and wall thickness can be evaluated by MRI.

Right-Heart Catheterization

Can confirm presence of pulmonary hypertension and exclude left-heart failure as cause.

TREATMENT **COR PULMONALE**

Aimed at underlying pulmonary disease and may include bronchodilators, antibiotics, oxygen administration, and noninvasive mechanical ventilation. For pts with PAH, pulmonary vasodilator therapy may be beneficial to reduce RV afterload (Chap. 127). See Chap. 133 for specific treatment of pulmonary embolism.

If RV failure is present, treat as heart failure, instituting low-sodium diet and diuretics; digoxin is of uncertain benefit and must be administered cautiously (toxicity increased due to hypoxemia, hypercapnia, acidosis). Loop diuretics must also be used with care to prevent significant metabolic alkalosis that blunts respiratory drive.

For a more detailed discussion, see Mann DL, Chakinala M: Heart Failure: Pathophysiology and Diagnosis, Chap. 279, p. 1500, and Mehra MR: Heart Failure: Management, Chap. 280, p. 1507, in HPIM-19.

125 Diseases of the Aorta

AORTIC ANEURYSM

Abnormal dilatation of the abdominal or thoracic aorta; in ascending aorta most commonly secondary to cystic medial necrosis (e.g., familial, Marfan's syndrome, Ehlers-Danlos syndrome type IV); aneurysms of descending thoracic and abdominal aorta are primarily atherosclerotic. Rare causes of aneurysms are infections (syphilitic, tuberculous, mycotic) and vasculitides (e.g., Takayasu's arteritis, giant cell arteritis).

History

May be clinically silent, but thoracic aortic aneurysms can result in deep, diffuse chest pain, dysphagia, hoarseness, hemoptysis, dry cough; abdominal aneurysms may result in abdominal pain or thromboemboli to the lower extremities.

Physical Examination

Abdominal aneurysms are often palpable, most commonly in periumbilical area. Pts with ascending thoracic aneurysms may show features of Marfan's syndrome (Chap. 427, HPIM-19).

Laboratory

Suspect thoracic aneurysm by abnormal *CXR* (enlarged aortic silhouette) and confirm by *echocardiography*, *contrast CT*, or *MRI*. Confirm abdominal aneurysm by *abdominal plain film* (rim of calcification), *ultrasound*, *CT*, *MRI*, or *contrast aortography*. If clinically suspected, obtain serologic test for syphilis, especially if ascending thoracic aneurysm shows thin shell of calcification. Screening abdominal ultrasound to assess for abdominal aortic aneurysm (AAA) is recommended for men aged 65–75 who have ever smoked, for individuals with a history of a thoracic aortic aneurysm, and for first degree relatives of pts with AAA.

TREATMENT AORTIC ANEURYSM

Pharmacologic control of hypertension (Chap. 117) is essential, usually including a beta blocker. Surgical resection for symptoms, for large aneurysms (ascending thoracic aortic aneurysms >5.5 cm, descending thoracic aortic aneurysms >6.0 cm, or abdominal aortic aneurysm >5.5 cm), for persistent pain despite bp control, or for evidence of rapid expansion. In pts with Marfan's syndrome thoracic aortic aneurysms >5 cm usually warrant repair. Less invasive endovascular repair is an option for some pts with descending thoracic or abdominal aortic aneurysms.

AORTIC DISSECTION (FIG. 125-1)

Potentially life-threatening condition in which disruption or aortic intima allows dissection of blood into vessel wall; may involve ascending aorta (type II), descending aorta (type III), or both (type I). Alternative classification: Type A—dissection involves ascending aorta; type B—limited to transverse and/or descending aorta. Involvement of the ascending aorta is most lethal form. Variant acute aortic syndromes include intramural hematoma without an intimal flap, and penetrating atherosclerotic ulcer.

Etiology

Ascending aortic dissection is associated with hypertension, cystic medial necrosis, Marfan's and Ehlers-Danlos syndromes; descending dissections are commonly associated with atherosclerosis or hypertension. Incidence is increased in pts with coarctation of aorta, bicuspid aortic valve, and rarely in third trimester of pregnancy in otherwise normal women.

Symptoms

Sudden onset of severe anterior or posterior chest pain, with "ripping" quality; maximal pain may travel if dissection propagates. Additional symptoms relate to obstruction of aortic branches (stroke, MI), dyspnea (acute aortic regurgitation), or symptoms of low cardiac output due to cardiac tamponade (dissection into pericardial sac).

Physical Examination

Sinus tachycardia common; if cardiac tamponade develops, hypotension, pulsus paradoxus, and pericardial rub appear. Asymmetry of carotid or brachial pulses, aortic regurgitation, and neurologic abnormalities associated with interruption of carotid artery flow are possible findings.

Laboratory

CXR: Widening of mediastinum; dissection can be confirmed by *CT*, *transesophageal echocardiography, or MRI*. Aortography is rarely required, as sensitivity of these noninvasive techniques is >90%.

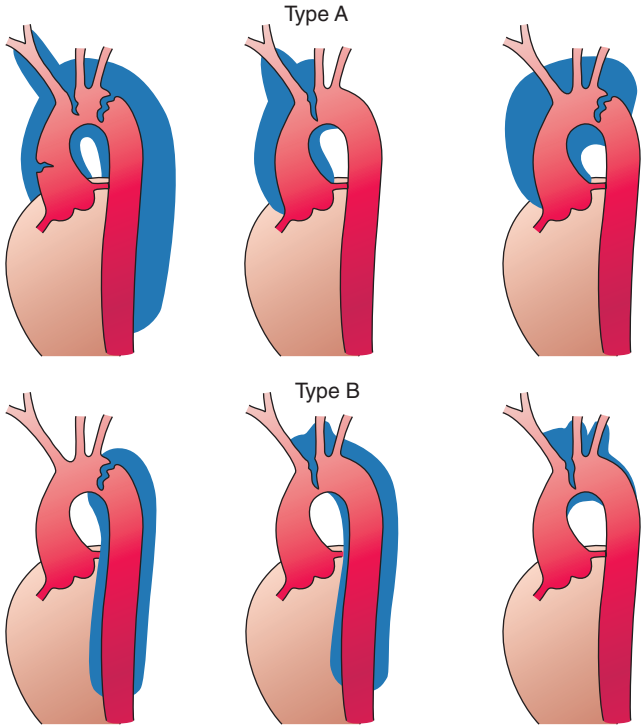


FIGURE 125-1 Classification of aortic dissections. Stanford classification: Top panels illustrate type A dissections that involve the ascending aorta independent of site of tear and distal extension; type B dissections (bottom panels) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (top left); type II dissection is limited to ascending or transverse aorta, without descending aorta (top center + top right); type III dissection involves descending aorta only (bottom left). *(From DC Miller, in RM Doroghazi, EE Slater [eds].* Aortic Dissection. *New York, McGraw-Hill, 1983, with permission.)*

TREATMENT AORTIC DISSECTION

Reduce cardiac contractility and treat hypertension to maintain systolic bp between 100 and 120 mmHg using IV agents (Table 125-1), e.g., sodium nitroprusside accompanied by a beta blocker (e.g., IV metoprolol, labetolol, or esmolol, aiming for heart rate of 60 beats per min), followed by oral therapy. If beta blocker contraindicated, consider IV verapamil or diltiazem (see Table 123-2). Avoid direct vasodilators (e.g., hydralazine) because they may increase shear stress. Ascending aortic dissection (type A) requires surgical repair emergently or, if pt can be stabilized with medications, semielectively. Descending aortic dissections are stabilized medically (maintain systolic bp between 110 and 120 mmHg) with oral antihypertensive agents (esp. beta blockers); surgical repair is not usually indicated unless continued pain or extension of dissection is observed (by serial MRI or CT performed every 6–12 months).

TABLE 125-1 TREATMENT OF AORTIC DISSECTION

Preferred Regimen	Dose
Sodium nitroprusside	20–400 μg/min IV
plus a beta blocker:	
Propranolol *or*	0.5 mg IV; then 1 mg q5min, to total of 0.15 mg/kg
Esmolol *or*	500 μg/kg IV over 1 min; then 50–200 (μg/kg)/min
Labetalol	20 mg IV over 2 min, then 40–80 mg q10–15min to max of 300 mg

OTHER ABNORMALITIES OF THE AORTA

Atherosclerotic Occlusive Disease of Abdominal Aorta

Particularly common in presence of diabetes mellitus or cigarette smoking. Symptoms include intermittent claudication of the buttocks and thighs and impotence (Leriche syndrome); femoral and other distal pulses are absent. Diagnosis is established by noninvasive leg pressure measurements and Doppler velocity analysis, and confirmed by MRI, CT, or aortography. Catheter-based endovascular treatment or aortic-femoral bypass surgery is required for symptomatic treatment.

Takayasu's ("Pulseless") Disease

Arteritis of aorta and major branches predominantly in young women. Anorexia, weight loss, fever, and night sweats occur. Localized symptoms relate to occlusion of aortic branches (cerebral ischemia, claudication, and loss of pulses in arms). ESR and C-reactive protein are increased; diagnosis confirmed by CT, MRI, or aortography. Glucocorticoid and immunosuppressive therapy may be beneficial.

For a more detailed discussion, see Creager MA, Loscalzo J: Diseases of the Aorta, Chap. 301, p. 1637, in HPIM-19.

126 Peripheral Vascular Disease

Occlusive or inflammatory disease that develops within the peripheral arteries, veins, or lymphatics. Pathologic contributors include atherosclerosis, thromboembolism, vasculitis, and fibromuscular dysplasia.

ARTERIOSCLEROSIS OF PERIPHERAL ARTERIES

History

Intermittent claudication is muscular cramping with exercise, quickly relieved by rest. Pain in buttocks and thighs suggests aortoiliac disease; calf muscle pain implies femoral or popliteal artery disease. More advanced arteriosclerotic obstruction

results in pain at rest; painful ulcers of the feet (sometimes painless in diabetics) may result.

Physical Examination

Decreased peripheral pulses (ankle:brachial index <1.0, <0.5 with severe ischemia), blanching of affected limb with elevation, dependent rubor (redness). Ischemic ulcers or gangrene of toes may be present.

Laboratory

Segmental pressure measurements and Doppler ultrasound of peripheral pulses before and immediately after exercise localizes stenoses; magnetic resonance angiography, computed tomographic angiography (CTA), or conventional arteriography is performed if mechanical revascularization (surgical or percutaneous) is planned.

TREATMENT ARTERIOSCLEROSIS

Most pts can be managed medically with daily exercise program, careful foot care (especially in diabetics), treatment of hypercholesterolemia, and local debridement of ulcerations. Abstinence from cigarettes is mandatory. Antiplatelet and statin therapies are indicated to reduce future cardiovascular events. Some, but not all, pts note symptomatic improvement with drug therapy (cilostazol or pentoxifylline). Pts with severe claudication, rest pain, or gangrene are candidates for revascularization (arterial reconstructive surgery or percutaneous transluminal angioplasty/stent placement).

OTHER CONDITIONS THAT IMPAIR PERIPHERAL ARTERIAL FLOW

Arterial Embolism

Results from thrombus or vegetation within the heart or aorta, or paradoxically from a venous thrombus through a right-to-left intracardiac shunt.

History

Sudden pain or numbness in an extremity in the absence of previous history of claudication.

Physical Examination

Absent pulse, pallor, and decreased temperature of limb distal to the occlusion. Lesion is identified by angiography.

TREATMENT ARTERIAL EMBOLISM

IV heparin is administered to prevent propagation of clot. For acute severe ischemia, immediate endovascular or surgical embolectomy is indicated. Thrombolytic therapy (e.g., tissue plasminogen activator, reteplase, or tenecteplase) may be effective for recent thrombus within atherosclerotic vessel or arterial bypass graft.

Atheroembolism

A subset of acute arterial occlusion due to embolization of fibrin, platelets, and cholesterol debris from more proximal atheromas or aneurysm; typically occurs after intraarterial instrumentation. Depending on location, may lead to stroke, renal insufficiency, or pain and tenderness in embolized tissue. Atheroembolism to lower extremities results in blue toe syndrome, which can progress to necrosis and

TABLE 126-1 CLASSIFICATION OF RAYNAUD'S PHENOMENON

Primary or idiopathic Raynaud's phenomenon: Raynaud's disease
Secondary Raynaud's phenomenon
Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis
Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome
Pulmonary hypertension
Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome
Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, Waldenström's macroglobulinemia
Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing
Drugs: ergot derivatives, methysergide, β-adrenergic receptor blockers, bleomycin, vinblastine, cisplatin

gangrene. Treatment is supportive; for recurrent episodes, surgical intervention in the proximal atherosclerotic vessel or aneurysm may be required.

Vasospastic Disorders

Manifest by Raynaud's phenomenon in which cold exposure results in triphasic color response: blanching of the fingers, followed by cyanosis, then rubor. Usually a benign disorder. However, suspect an underlying disease (Table 126-1) if tissue necrosis occurs, if disease is unilateral, or if it develops after age 50.

TREATMENT VASOSPASTIC DISORDERS

Keep extremities warm. Tobacco use is contraindicated. Dihydropyridine calcium channel blockers (e.g., nifedipine XL 30–90 mg PO qd) or α_1-adrenergic antagonists (e.g., prazosin 1–5 mg tid) may be effective. Phosphodiesterase-5 inhibitors (e.g., sildenafil) may improve symptoms in secondary Raynaud's phenomenon.

Thromboangiitis Obliterans (Buerger's Disease)

Occurs in young men who are heavy smokers and involves both upper and lower extremities; nonatheromatous inflammatory reaction develops in veins and small arteries, leading to superficial thrombophlebitis and arterial obstruction with ulceration or gangrene of digits. Imaging with CT, MR, or conventional angiography shows smooth tapering lesions in distal vessels, often without proximal atherosclerotic disease. Abstinence from tobacco is essential.

VENOUS DISEASE

Superficial Thrombophlebitis

A benign disorder characterized by erythema, tenderness, and edema along involved vein. Conservative therapy includes local heat, elevation, and anti-inflammatory drugs such as aspirin. More serious conditions such as cellulitis or lymphangitis may present similarly, but these are associated with fever, chills, lymphadenopathy, and red superficial streaks along inflamed lymphatic channels.

Deep-Vein Thrombosis (DVT)

More serious condition that may lead to pulmonary embolism as described in Chap. 133.

Chronic Venous Insufficiency

Results from prior DVT or venous valvular incompetence and manifests as chronic dull ache in leg that worsens with prolonged standing, edema, and superficial varicosities. May lead to erythema, hyperpigmentation, and recurrent cellulitis; ulcers may appear at medial and lateral malleoli. Treatment includes graduated compression stockings and leg elevation.

LYMPHEDEMA

Chronic, painless edema, usually of the lower extremities; may be primary (inherited) or secondary to lymphatic damage or obstruction (e.g., recurrent lymphangitis, tumor, filariasis).

Physical Examination

Marked pitting edema in early stages; limb becomes indurated with *non*pitting edema chronically. Differentiate from chronic *venous* insufficiency, which displays hyperpigmentation, stasis dermatitis, and superficial venous varicosities.

Laboratory

Abdominal and pelvic ultrasound or CT or MRI to identify obstructing lesions. Lymphangiography or lymphoscintigraphy (rarely done) to confirm diagnosis. If *unilateral* edema, differentiate from DVT by noninvasive venous studies (above).

TREATMENT **LYMPHEDEMA**

(1) Meticulous foot hygiene to prevent infection, (2) leg elevation, (3) compression stockings and/or pneumatic compression boots. Diuretics should be *avoided* to prevent intravascular volume depletion.



For a more detailed discussion, see Creager MA, Loscalzo J: Arterial Diseases of the Extremities, Chap. 302, p. 1643; Creager MA, Loscalzo J: Chronic Venous Disease and Lymphedema, Chap. 303, p. 1650, in HPIM-19.

127 Pulmonary Hypertension

Definition

Elevation of pulmonary artery (PA) pressure due to pulmonary vascular or parenchymal disease, increased left heart filling pressures, or a combination. Table 127-1 lists etiologies by categories.

TABLE 127-1 CLASSIFICATION OF PULMONARY HYPERTENSION

1. **Pulmonary Arterial Hypertension**
   - Idiopathic
   - Heritable (mutations/familial cases)
   - Collagen vascular diseases (e.g., scleroderma, SLE, RA)
   - Congenital systemic to pulmonary shunts (e.g., ventricular septal defect, patent ductus arteriosus, atrial septal defect)
   - Portal hypertension
   - HIV infection
   - Drugs or toxins (e.g., fenfluramine)
2. **Pulmonary Hypertension Due to Left Heart Disease**
   - LV systolic or diastolic dysfunction
   - Left-sided valvular disease
3. **Pulmonary Hypertension Due to Lung Disease or Hypoxia**
   - Chronic obstructive lung disease
   - Interstitial lung disease
   - Sleep-disordered breathing
   - Chronic hypoventilation
4. **Chronic Pulmonary Thromboembolic Disease**
   - Chronic pulmonary embolism
5. **Miscellaneous**
   - Systemic conditions (e.g., sarcoidosis, pulmonary histiocytosis)
   - Hematologic conditions (e.g., myeloproliferative diseases)

Abbreviations: RA, rheumatoid arthritis.

Symptoms

Exertional dyspnea, fatigue, angina (due to RV ischemia), syncope, peripheral edema.

Physical Examination

Jugular venous distention, RV lift, increased P_2, right-sided S_4, tricuspid regurgitation. Peripheral cyanosis and edema are late manifestations.

Laboratory Findings

CXR shows enlarged central PA. *ECG* may demonstrate RV hypertrophy and RA enlargement. *Echocardiogram* shows RV and RA enlargement, RV hypertrophy; RV systolic pressure can be estimated from Doppler recording of tricuspid regurgitation. *Pulmonary function tests* (*PFTs*) identify underlying obstructive or restrictive lung disease; impaired CO diffusion capacity is common. *Chest CT* identifies contributing interstitial lung disease or pulmonary thromboembolic disease. *ANA titer*, rheumatoid factor, anti-Scl-70 antibodies are elevated in specific collagen vascular conditions that can result in pulmonary hypertension. *HIV testing* should be performed in individuals at risk. *Cardiac catheterization* accurately assesses PA pressures, cardiac output, and pulmonary vascular resistance, and quantifies underlying congenital vascular shunts; during procedure, response to short-acting vasodilators can be assessed.

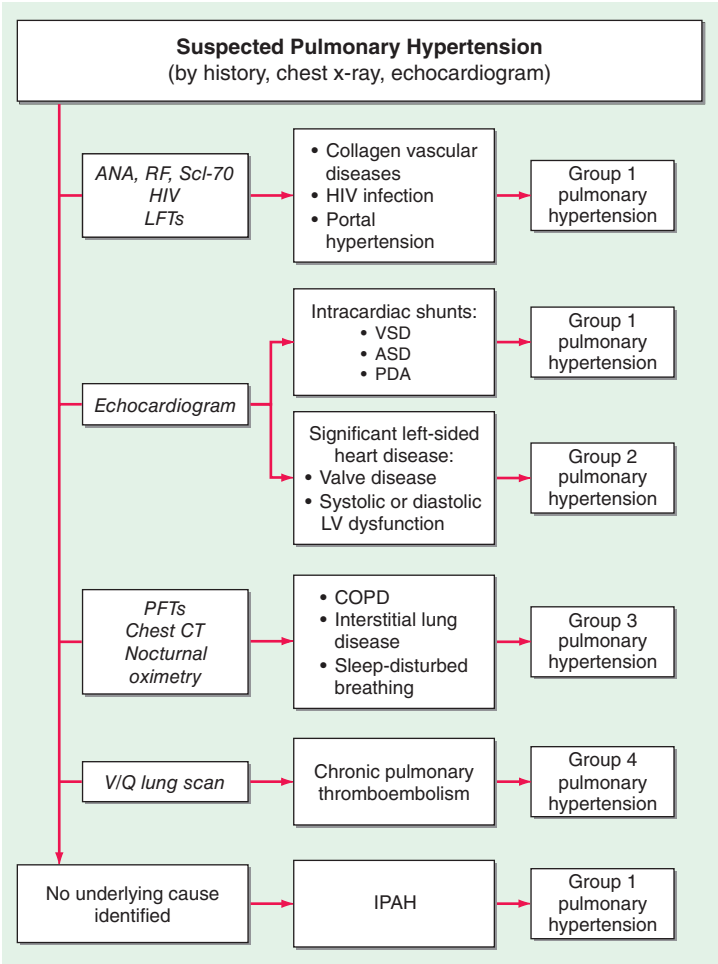


FIGURE 127-1 An algorithm to assess for causes of pulmonary hypertension. In the absence of an identifiable etiology, idiopathic pulmonary arterial hypertension would be suspected. ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; PDA, patent ductus arteriosus; PFTs, pulmonary function tests; RF, rheumatoid factor; Scl-70, anti-topoisomerase 1 antibodies; V/Q, ventilation/perfusion; VSD, ventricular septal defect.

Figure 127-1 summarizes a testing approach for pts with unexplained pulmonary hypertension.

PULMONARY ARTERIAL HYPERTENSION (PAH)

Uncommon (two cases per million), very serious form of pulmonary hypertension. Most pts present in fourth and fifth decades, female >> male predominance; up to 20% of cases are familial. Major symptom is dyspnea, often with insidious onset. Mean survival <3 years in absence of therapy.

Physical Examination

Prominent *a* wave in jugular venous pulse, right ventricular heave, narrowly split S_2 with accentuated P_2. Terminal course is characterized by signs of right-sided heart failure.

Laboratory

CXR: RV and central pulmonary arterial prominence. Pulmonary arteries taper sharply. *PFTs:* usually normal or mild restrictive defect. *ECG:* RV enlargement, right axis deviation, and RV hypertrophy. *Echocardiogram:* RA and RV enlargement and tricuspid regurgitation. Cardiac catheterization demonstrates a mean pulmonary artery pressure ≥25 mmHg, pulmonary vascular resistance >240 dyne-s/cm^5, with a mean pulmonary capillary wedge pressure ≤15 mmHg.

Differential Diagnosis (Fig. 127-1)

Other disorders of heart, lungs, and pulmonary vasculature must be considered. Lung function studies will identify chronic pulmonary disease causing pulmonary hypertension and cor pulmonale. Interstitial diseases (PFTs, CT scan) and hypoxic pulmonary hypertension (ABGs, SaO_2) should be excluded. Perfusion lung scan should be considered to exclude chronic pulmonary embolism (PE). Cardiovascular disorders that may present similarly and need to be excluded include PA and pulmonic valve stenosis, ventricular and atrial shunts with secondary pulmonary vascular disease (Eisenmenger syndrome), and clinically silent mitral stenosis.

TREATMENT PULMONARY ARTERIAL HYPERTENSION

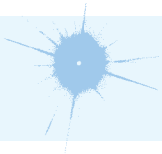
Limit physical activities, use diuretics for peripheral edema, O_2 supplementation if PO_2 reduced, and chronic warfarin anticoagulation (target INR = 2.0–3.0).

If short-acting vasodilators are beneficial during acute testing in catheterization laboratory, pt may benefit from high-dose *calcium channel blocker* (e.g., nifedipine, up to 240 mg/d, or amlodipine up to 20 mg/d); must monitor for hypotension or worsening of right heart failure during such therapy.

Additional approved therapies for PAH include:

1. Endothelin receptor antagonists: *bosentan* (62.5 mg PO bid × 1 month, then 125 mg PO bid) and *ambrisentan* (5–10 mg daily) significantly improve exercise tolerance. Hepatic transaminases should be monitored. Bosentan is contraindicated in pts taking cyclosporine (which greatly increases bosentan plasma levels) or glyburide (combination is associated with increased hepatic transaminases).
2. Phosphodiesterase-5 inhibitors: *sildenafil* (20–80 mg PO tid) and *tadalafil* (40 mg daily) also improve exercise tolerance in PAH. Do not prescribe concurrently with nitrates; the combination could result in marked hypotension.
3. Prostaglandins (*iloprost* by inhalation, *epoprostenol* by continuous IV infusion, and *treprostinil* by IV, SC, or inhalation routes) improve symptoms, exercise tolerance, and, in the case of epoprostenol, survival. The most common side effect is flushing.
4. The oral soluble guanylyl cyclase stimulator riociguat has been shown to improve exertional capacity in pts with PAH.

For selected pts with persistent right heart failure, lung transplantation may be considered.



For a more detailed discussion, see Waxman AB, Loscalzo J: Pulmonary Hypertension, Chap. 304, p. 1655, in HPIM-19.

This page intentionally left blank

128 Respiratory Function and Pulmonary Diagnostic Procedures

RESPIRATORY FUNCTION

The major classes of lung diseases include obstructive lung diseases (e.g., asthma, chronic obstructive pulmonary disease, and bronchiectasis), restrictive lung diseases (e.g., interstitial lung diseases, chest wall abnormalities, and neuromuscular diseases), and vascular abnormalities (e.g., pulmonary thromboembolism, pulmonary arterial hypertension, and pulmonary veno-occlusive disease). The respiratory system includes not only the lungs but also the chest wall, pulmonary circulation, and central nervous system. There are three key types of respiratory system physiologic disturbances that occur in varying combinations in different lung diseases: ventilatory function, pulmonary circulation, and gas exchange.

Disturbances in Ventilatory Function

Ventilation involves the delivery of gas to the alveoli. Pulmonary function tests are used to assess ventilatory function. The classification of lung volumes, which are measured with pulmonary function testing, is shown in Fig. 128-1. Spirometry involves forced exhalation from total lung capacity (TLC) to residual volume (RV); key measurements from a spirogram are the forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC). Expiratory flow rates may be plotted against lung volumes to yield a flow-volume curve. Plateau of the inspiratory curve on the flow-volume loop suggests extrathoracic large airway obstruction, while plateau of the expiratory curve suggests intrathoracic large airway obstruction. Other lung volumes, including TLC and RV, are measured under static conditions using either inert gas dilution or body plethysmography. Lung volumes and flow rates are typically compared with population-based normal values that adjust for the age, height, sex, and race of the pt.

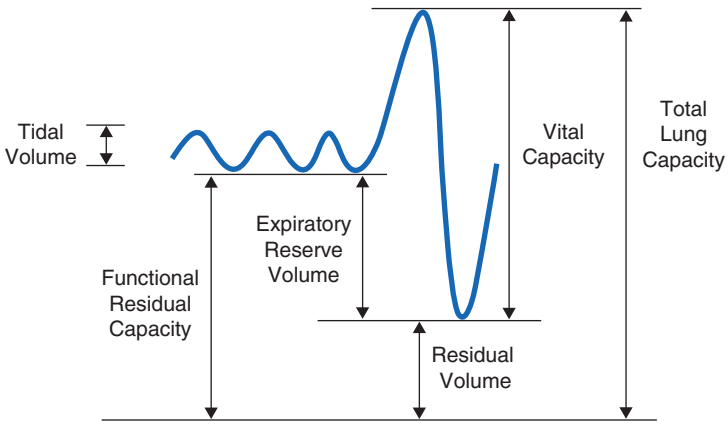


FIGURE 128-1 Spirogram of a slow vital capacity maneuver demonstrating various lung volumes.

TABLE 128-1 COMMON RESPIRATORY DISEASES BY DIAGNOSTIC CATEGORIES

Obstructive	
Asthma	Bronchiectasis
Chronic obstructive pulmonary disease	Cystic fibrosis
	Bronchiolitis
Restrictive—Parenchymal	
Sarcoidosis	Pneumoconiosis
Idiopathic pulmonary fibrosis	Drug- or radiation-induced interstitial lung disease
Desquamative interstitial pneumonitis	Asbestosis
Restrictive—Extraparenchymal	
Neuromuscular	Chest wall/Pleural disease
Diaphragmatic weakness/paralysis	Kyphoscoliosis
Myasthenia gravis	Obesity
Guillain-Barré syndrome	Ankylosing spondylitis
Muscular dystrophies	Chronic pleural effusions
Cervical spine injury	
Amyotrophic lateral sclerosis	
Pulmonary Vascular Disease	
Pulmonary embolism	Pulmonary arterial hypertension
Malignancy	
Bronchogenic carcinoma (small cell or non-small-cell)	Cancer metastatic to lung
Infectious Diseases	
Pneumonia	Tracheitis
	Bronchitis

There are two major patterns of abnormal ventilatory function detected by pulmonary function testing: restrictive and obstructive (Tables 128-1 and 128-2). The presence of obstruction is determined by a reduced ratio of FEV_1/FVC (with abnormal often defined as <0.7), and the severity of airflow obstruction is determined by the level of reduction of FEV_1. With airflow obstruction, TLC may be normal or increased, and RV is typically elevated. With severe airflow obstruction, the FVC is often also reduced.

The presence of a restrictive pattern is determined by a reduction in TLC to <80% of the pt's predicted value. When pulmonary parenchymal processes cause restriction, RV is also decreased, but the FEV_1/FVC is normal. With extraparenchymal etiologies of restrictive ventilatory defects, such as neuromuscular weakness or chest

TABLE 128-2 ALTERATIONS IN PULMONARY FUNCTION IN DIFFERENT RESPIRATORY DISEASE CATEGORIES

	TLC	RV	VC	FEV_1/FVC
Obstructive	N to ↑	↑	↓	↓
Restrictive				
Pulmonary parenchymal	↓	↓	↓	N to ↑
Extraparenchymal—neuromuscular weakness	↓	Variable	↓	Variable
Extraparenchymal—chest wall deformity	↓	Variable	↓	N

Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; N, normal; RV, residual volume.

wall abnormalities, the impact on RV and FEV_1/FVC is more variable. Weakness of the respiratory muscles can be assessed by measuring maximal inspiratory and expiratory pressures.

Disturbances in Pulmonary Circulation

The pulmonary vasculature normally handles the right ventricular output (~5 L/min) at a low pressure. Normal mean pulmonary artery pressure (PAP) is 15 mmHg. When cardiac output increases, pulmonary vascular resistance (PVR) normally falls, leading to only small increases in mean PAP.

Assessment of the pulmonary vasculature requires measuring pulmonary vascular pressures and cardiac output to derive PVR. PVR rises with hypoxemia (due to vasoconstriction), intraluminal thrombi (due to diminished cross-sectional area from obstruction), or destruction of small pulmonary vessels (due to scarring or loss of the alveolar walls).

All diseases of the respiratory system causing hypoxemia are capable of causing pulmonary hypertension. However, pts with prolonged hypoxemia related to chronic obstructive pulmonary disease, interstitial lung disease, chest wall disease, and obesity-hypoventilation/obstructive sleep apnea are particularly likely to develop pulmonary hypertension. When pulmonary vessels are directly affected, as with recurrent pulmonary emboli, the decrease in cross-sectional area of the pulmonary vasculature is the primary mechanism for increased PVR, rather than hypoxemia.

Disturbances in Gas Exchange

The primary functions of the respiratory system are to remove CO_2 from blood entering the pulmonary circulation and to provide O_2 to blood leaving the pulmonary circulation. Normal tidal volume is approximately 500 mL and normal respiratory rate is approximately 15 breaths/min, leading to a total minute ventilation of approximately 7.5 L/min. Because of anatomic dead space, alveolar ventilation is approximately 5 L/min. Gas exchange depends on alveolar ventilation rather than total minute ventilation.

Partial pressure of CO_2 in arterial blood ($Paco_2$) is directly proportional to the amount of CO_2 produced each minute ($\dot{V}co_2$) and inversely proportional to alveolar ventilation ($\dot{V}A$).

$$Paco_2 = 0.863 \times \dot{V}co_2/\dot{V}A$$

Adequate movement of gas between alveoli and pulmonary capillaries by diffusion is required for normal gas exchange. Diffusion can be tested by measuring the diffusing capacity of the lung for a low (and safe) concentration of carbon monoxide (DLCO) during a 10-s breath hold. DLCO measurement is typically corrected for the pt's hemoglobin level. Diffusion abnormalities rarely result in arterial hypoxemia at rest but can cause hypoxemia with exercise. A restrictive ventilatory defect with reduced DLCO suggests parenchymal lung disease. The pattern of normal spirometry, normal lung volumes, and reduced DLCO is consistent with pulmonary vascular disease. Gas exchange is critically dependent on proper matching of ventilation and perfusion.

Assessment of gas exchange is commonly performed with arterial blood gases, which provide measurements of the partial pressures of O_2 and CO_2. The actual content of O_2 in blood is determined by both Po_2 and hemoglobin concentration. The alveolar-arterial O_2 difference ([A-a] gradient) is reduced in diseases causing ventilation-perfusion mismatch or shunt physiology. The normal (A-a) gradient is <15 mmHg under age 30 but increases with aging. In order to calculate the (A-a) gradient, the alveolar Po_2 ($Paco_2$) must be calculated:

$$Pao_2 = [FIO_2 \times (PB - PH_2O)] - (Paco_2/R)$$

where FIO_2 = fractional concentration of inspired O_2 (0.21 while breathing room air), PB = barometric pressure (760 mmHg at sea level), PH_2O = water vapor pressure (47 mmHg when air is saturated at 37°C [98.6°F]), and R = respiratory quotient (the ratio

of CO_2 production to O_2 consumption, usually assumed to be 0.8). Severe arterial hypoxemia rarely occurs purely due to alveolar hypoventilation while breathing air at sea level. The (A-a) gradient is calculated by subtracting the measured Pa_{O_2} from the calculated P_{AO_2}.

Adequacy of CO_2 removal is reflected in the partial pressure of CO_2 measured in an arterial blood gas. Pulse oximetry is a valuable, widely used, and noninvasive tool to assess O_2 saturation, but it provides no information about Pa_{CO_2}. Other limitations of pulse oximetry include relative insensitivity to oxygenation changes when Pa_{O_2} is >60 mmHg, problems with obtaining an adequate signal when cutaneous perfusion is decreased, and inability to distinguish oxyhemoglobin from other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin.

Mechanisms of Abnormal Respiratory Function

The four basic mechanisms of hypoxemia are: (1) decrease in inspired P_{O_2}, (2) alveolar hypoventilation, (3) shunt, and (4) ventilation/perfusion mismatch. Decrease in inspired P_{O_2} (e.g., at high altitude) and hypoventilation (characterized by an increased Pa_{CO_2}) both lower arterial oxygenation by reducing alveolar oxygenation; thus, the (A-a) gradient is normal. Shunting (e.g., intracardiac shunt) causes hypoxemia by bypassing the alveolar capillaries. Shunting is characterized by an elevated (A-a) gradient and is relatively refractory to oxygenation improvement with supplemental O_2. Ventilation/perfusion mismatch is the most common cause of hypoxemia; it is associated with an elevated (A-a) gradient, but supplemental O_2 corrects the hypoxemia by raising the O_2 content of blood from regions with low ventilation/perfusion ratios. An algorithm for approaching the hypoxemic pt is shown in Fig. 128-2.

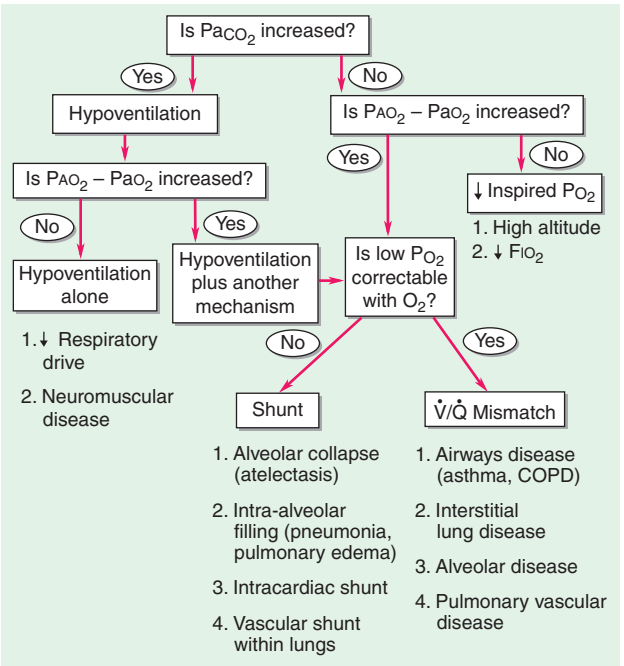


FIGURE 128-2 Flow diagram outlining the diagnostic approach to the pt with hypoxemia. COPD, chronic obstructive pulmonary disease. *(From SE Weinberger: Principles of Pulmonary Medicine, 4th ed. Philadelphia, Saunders, 2004; with permission.)*

Hypercapnia is caused by inadequate alveolar ventilation. Potential contributing factors include (1) increased CO_2 production, (2) decreased ventilatory drive, (3) malfunction of the respiratory pump or increased airway resistance, and (4) inefficiency of gas exchange (increased dead space or ventilation/perfusion mismatch).

Although diffusion abnormalities rarely cause hypoxemia at rest, assessment of DLCO can be used to determine the functional integrity of the alveolar-capillary membrane. Diseases that solely affect the airways typically do not reduce the DLCO. DLCO is reduced in interstitial lung disease, emphysema, and pulmonary vascular disease. DLCO can be elevated in alveolar hemorrhage, asthma, and congestive heart failure.

DIAGNOSTIC PROCEDURES

NONINVASIVE PROCEDURES

Radiographic Studies

The chest x-ray (CXR), generally including both posteroanterior and lateral views, is often the first diagnostic study in pts presenting with respiratory symptoms. With some exceptions (e.g., pneumothorax), the CXR pattern is usually not sufficiently specific to *establish* a diagnosis; instead, the CXR serves to *detect* disease, assess magnitude, and guide further diagnostic investigation. With diffuse lung disease, CXR can detect an alveolar, interstitial, or nodular pattern. CXR can also detect pleural effusion and pneumothorax, as well as abnormalities in the hila and mediastinum. Lateral decubitus views can be used to estimate the size of freely flowing pleural effusions.

Chest CT, typically performed with helical scanning and multiple detectors, is widely used to clarify radiographic abnormalities detected by CXR. Advantages of chest CT compared with CXR include (1) ability to distinguish superimposed structures due to cross-sectional imaging; (2) superior assessment of tissue density, permitting accurate assessment of the size and density of pulmonary nodules and improved identification of abnormalities adjacent to the chest wall, such as pleural disease; (3) with the use of IV contrast, ability to distinguish vascular from nonvascular structures, which is especially useful in assessing hilar and mediastinal abnormalities; (4) with CT angiography, ability to detect pulmonary emboli; and (5) due to superior visible detail, improved recognition of parenchymal and airway diseases, including emphysema, bronchiectasis, lymphangitic carcinoma, and interstitial lung disease.

A variety of other imaging techniques are used less commonly to assess respiratory disease. Magnetic resonance imaging (MRI) is generally less useful than CT for evaluation of the respiratory system but can be helpful to assist in the evaluation of intrathoracic cardiovascular pathology without radiation exposure and to distinguish vascular and nonvascular structures without IV contrast. Ultrasound is not useful for assessing the pulmonary parenchyma, but it can detect pleural abnormalities and guide thoracentesis of a pleural effusion. Pulmonary angiography can assess the pulmonary arterial system for venous thromboembolism but has largely been replaced by CT angiography.

Nuclear Medicine Imaging

Ventilation-perfusion lung scans can be used to assess for pulmonary thromboembolism but have also largely been replaced by CT angiography. Positron emission tomographic (PET) scanning assesses the uptake and metabolism of a radiolabeled glucose analogue. Because malignant lesions usually have increased metabolic activity, PET scanning, especially when combined with CT images in PET/CT, is useful to assess pulmonary nodules for potential malignancy and to stage lung cancer. PET studies are limited in assessing lesions <1 cm in diameter; false-negative screening for malignancy can result from lesions with low metabolic activity, such as carcinoid

tumors or bronchioloalveolar cell carcinoma. False-positive PET signals can be observed in inflammatory conditions such as pneumonia.

Sputum Examination

Sputum can be obtained by spontaneous expectoration or induced by inhalation of an irritating aerosol like hypertonic saline. Sputum is distinguished from saliva by the presence of bronchial epithelial cells and alveolar macrophages as opposed to squamous epithelial cells. Sputum examination should include gross inspection for blood, color, and odor, as well as Gram's stain and routine bacterial culture. Bacterial culture of expectorated sputum may be misleading due to contamination with oropharyngeal flora. Sputum samples can also be assessed for a variety of other pathogens, including mycobacteria, fungi, and viruses. Sputum samples induced by hypertonic saline can be stained for the presence of *Pneumocystis jirovecii*. Cytologic examination of sputum samples can be used as an initial screen for malignancy.

INVASIVE PROCEDURES

Bronchoscopy

Bronchoscopy is a procedure that provides direct visualization of the tracheobronchial tree, typically to the subsegmental level. The fiberoptic bronchoscope is used in most cases, but rigid bronchoscopy is valuable in specific circumstances, including massive hemorrhage and foreign body removal. Flexible fiberoptic bronchoscopy allows visualization of the airways; identification of endobronchial abnormalities, including tumors and sites of bleeding; and collection of diagnostic specimens by washing, brushing, biopsy, or lavage. Washing involves instilling sterile saline through the bronchoscope channel onto the surface of a lesion; part of the saline is suctioned back through the bronchoscope and processed for cytology and microorganisms. Bronchial brushings can be obtained from the surface of an endobronchial lesion or from a more distal mass or infiltrate (potentially with fluoroscopic guidance) for cytologic and microbiologic studies. Biopsy forceps can be used to obtain biopsies of endobronchial lesions or passed into peribronchial alveolar tissue (often with fluoroscopic guidance) to obtain transbronchial biopsies of more distal lung tissue. Transbronchial biopsy is particularly useful in diagnosing diffuse infectious processes, lymphangitic spread of cancer, and granulomatous diseases. Complications of transbronchial biopsy include hemorrhage and pneumothorax.

Bronchoalveolar lavage (BAL) is an adjunct to fiberoptic bronchoscopy, permitting collection of cells and fluid from distal air spaces. After wedging the bronchoscope in a subsegmental airway, saline is instilled and then suctioned back through the bronchoscope for analyses, which can include cytology, microbiology, and cell counts. BAL is especially useful in the diagnosis of *P. jirovecii* pneumonia and some other infections.

Additional bronchoscopic approaches to obtain tissue samples from locations adjacent to the trachea or large bronchi for cytologic assessment of malignancy include transbronchial needle aspiration (TBNA). TBNA can be supplemented with endobronchial ultrasound (EBUS), which can allow guided aspiration of hilar and mediastinal lymph nodes based on real-time ultrasound images.

Percutaneous Needle Aspiration of the Lung

A needle can be inserted through the chest wall and into a pulmonary lesion to aspirate material for cytologic and microbiologic studies. Percutaneous needle aspiration is usually performed under CT guidance. Owing to the small size of the sample obtained, sampling error is a limitation of the procedure.

Thoracentesis

Thoracentesis should be performed as an early step in the evaluation of a pleural effusion of uncertain etiology. Analysis of pleural fluid can determine the etiology

of the effusion (Chap. 135). Large-volume thoracentesis can be therapeutic by palliating dyspnea.

Mediastinoscopy

Tissue biopsy of mediastinal masses or lymph nodes is often required for cancer diagnosis and staging. Mediastinoscopy is performed from a suprasternal approach, and a rigid mediastinoscope is inserted—from which biopsies can be obtained. Lymph nodes in the aortopulmonary location typically require a parasternal mediastinotomy to provide access for biopsy.

Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS), also known as thoracoscopy, is widely used for the diagnosis of pleural lesions as well as peripheral parenchymal infiltrates and nodules. VATS, which requires that the pt tolerate single-lung ventilation during the procedure, involves passing a rigid scope with a camera through a trocar and into the pleural space; instruments can be inserted and manipulated through separate intercostal incisions. VATS has largely replaced "open biopsy," which requires a thoracotomy.

For a more detailed discussion, see Kritek P, Choi AMK: Approach to the Patient with Disease of the Respiratory System, Chap. 305, p. 1661; Naureckas ET, Solway J: Disturbances of Respiratory Function, Chap. 306e; Fuhlbrigge AL, Choi AMK: Diagnostic Procedures in Respiratory Disease, Chap. 307, p. 1663, in HPIM-19.

129 Asthma

Definition and Epidemiology

Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment. Chronic airway inflammation causes airway hyperresponsiveness to a variety of triggers, leading to airflow obstruction and respiratory symptoms including dyspnea and wheezing. Although asthmatics typically have periods of normal lung function with intermittent airflow obstruction, a subset of pts develop chronic airflow obstruction.

The prevalence of asthma has increased markedly over the past 30 years. In developed countries, approximately 10% of adults and 15% of children have asthma. The majority of asthmatics have childhood-onset disease. Most asthmatics have atopy, and they often have atopic dermatitis (eczema) and/or allergic rhinitis. A minority of asthmatic pts do not have atopy (negative skin prick tests to common allergens and normal serum total IgE levels). These individuals, occasionally referred to as *intrinsic asthmatics*, often have adult-onset disease. Occupational asthma can result from a variety of chemicals, including toluene diisocyanate and trimellitic anhydride, and often has onset in adulthood.

Asthmatics can develop increased airflow obstruction and respiratory symptoms in response to a variety of different triggers. Inhaled allergens can be potent asthma triggers for individuals with specific sensitivity to those agents. Viral upper respiratory infections (URIs) commonly trigger asthma exacerbations. β-Adrenergic blocking medications can markedly worsen asthma symptoms and should typically be avoided in asthmatics. Exercise often triggers increased asthma symptoms, which usually begin after exercise has ended. Other triggers of increased asthma symptoms include air pollution, cold air, occupational exposures, and stress.

Clinical Evaluation of the Patient History

Common respiratory symptoms in asthma include wheezing, dyspnea, and cough. These symptoms often vary widely within a particular individual, and they can change spontaneously or with age, season of the year, and treatment. Symptoms may be worse at night, and nocturnal awakenings are an indicator of inadequate asthma control. The severity of a pt's asthmatic symptoms, as well as the pt's need for systemic steroid treatment, hospitalization, and intensive care treatment, are important to ascertain. Types of asthmatic triggers for the particular pt, and their recent exposure to them, should be determined. Approximately 1–5% of asthmatics have sensitivity to aspirin and other cyclooxygenase inhibitors; they typically are nonatopic and have nasal polyps. Cigarette smoking leads to more hospital admissions and more rapid decline in lung function in asthmatics; smoking cessation is essential.

Physical Examination

It is important to assess for signs of respiratory distress, including tachypnea, use of accessory respiratory muscles, and cyanosis. On lung examination, there may be wheezing and rhonchi throughout the chest, typically more prominent in expiration than inspiration. Localized wheezing may indicate an endobronchial lesion. Evidence of allergic nasal, sinus, or skin disease should be assessed. When asthma is adequately controlled, the physical examination may be normal.

Pulmonary Function Tests

Spirometry often shows airflow obstruction, with a reduction in forced expiratory volume in 1 s (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. However, spirometry may be normal, especially if asthma symptoms are adequately treated. Bronchodilator reversibility is demonstrated by an increase in FEV_1 by ≥200 mL and ≥12% from baseline FEV_1 15 min after a short-acting β agonist (often albuterol metered-dose inhaler two puffs or 180 μg). Many but not all asthmatics will demonstrate significant bronchodilator reversibility; optimal pharmacologic treatment may reduce bronchodilator reversibility. Airway hyperresponsiveness is characteristic of asthma; it can be assessed by exposure to direct bronchoconstrictors such as methacholine or histamine. Greater airway responsiveness is associated with increased asthmatic symptoms. The peak expiratory flow rate (PEFR) can be used by the pt to track asthma control objectively at home. Measurement of lung volumes is not typically performed, but increases in total lung capacity and residual volume may be observed. The diffusing capacity for carbon monoxide is usually normal.

Other Laboratory Tests

Blood tests are usually not helpful. CBC may demonstrate eosinophilia. Specific IgE measurements for inhaled allergens (radioallergosorbent test [RAST]) or allergy skin testing may assist in determining allergic triggers. Total serum IgE is markedly elevated in bronchopulmonary aspergillosis (BPA). Exhaled nitric oxide levels can provide an assessment of eosinophilic airway inflammation.

Radiographic Findings

Chest x-ray is usually normal. In acute exacerbations, pneumothorax may be identified. In BPA, eosinophilic pulmonary infiltrates may be observed. Chest CT scan is not typically performed in routine asthma but may show central bronchiectasis in BPA.

Differential Diagnosis

The differential diagnosis of asthma includes other disorders that can cause wheezing and dyspnea. Upper airway obstruction by tumor or laryngeal edema can mimic asthma, but stridor in the large airways is typically noted on physical examination. Localized wheezing in the chest may indicate an endobronchial tumor or foreign body. Congestive heart failure can cause wheezing but is typically accompanied by bibasilar crackles. Eosinophilic pneumonias and Churg-Strauss syndrome may present with wheezing. Vocal cord dysfunction can mimic severe asthma and may require direct laryngoscopy to assess. When asthma involves chronic airflow obstruction, distinguishing it from chronic obstructive pulmonary disease (COPD) can be very difficult.

TREATMENT CHRONIC ASTHMA

If a specific inciting agent for asthmatic symptoms can be identified and eliminated, that is an optimal part of treatment. In most cases, pharmacologic therapy is required. The two major classes of drugs are bronchodilators, which provide rapid symptomatic relief by relaxing airway smooth muscle, and controllers, which limit airway inflammation.

Bronchodilators The most widely used class of bronchodilators is β_2-adrenergic agonists, which relax airway smooth muscle by activating β_2-adrenergic receptors. Two types of inhaled β_2 agonists are widely used in asthma treatment: short-acting β_2 agonists (SABAs) and long-acting β_2 agonists (LABAs). SABAs, which include albuterol, have rapid onset of action and last for up to 6 h. SABAs are effective rescue medications, but excessive use indicates inadequate asthma control. SABAs can prevent exercise-induced asthma if administered before exercise. LABAs, which include salmeterol and formoterol, have a slower onset of action but last for >12 h. LABAs have replaced regularly scheduled use of SABAs, but they do not control airway inflammation and should not be used without inhaled corticosteroid (ICS) therapy. Combinations of LABAs with ICS reduce asthma exacerbations and provide an excellent long-term treatment option for asthma severity of moderate persistent degree or greater.

Common side effects of β_2-adrenergic agonists include muscle tremors and palpitations. These side effects are more prominent with oral formulations, which should not generally be used. There have been ongoing concerns about mortality risks associated with β_2-adrenergic agonists, which have not been completely resolved. LABAs taken without concomitant inhaled steroid treatment may increase this risk.

Other available bronchodilator medications include anticholinergics and theophylline. Anticholinergics, which are available in short-acting and long-acting inhaled formulations, are commonly used in COPD. They appear to be less effective than β_2-adrenergic agonists in asthma, and they are typically considered as an additional treatment option only if other asthma medications do not provide adequate asthma control. Theophylline may have both bronchodilator and anti-inflammatory effects; it is not widely used due to the potential toxicities associated with high plasma levels. Low doses of theophylline may have additive effects with ICS at levels below the standard therapeutic range, and this can be a useful treatment option for severe asthma.

Controller Therapies ICSs are the most effective controller treatments for asthma. ICSs are usually given twice daily; a variety of ICS medications are available. Although

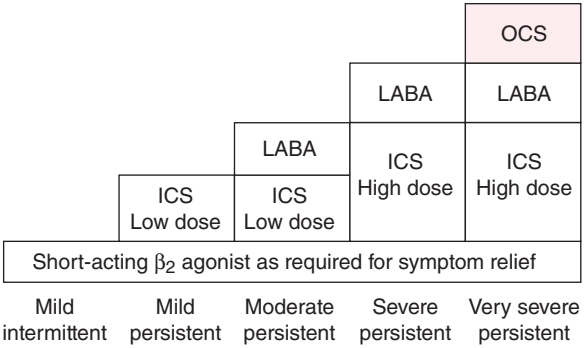


FIGURE 129-1 Stepwise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroid; LABA, long-acting β_2 agonists; OCS, oral corticosteroid.

they do not provide immediate symptom relief, respiratory symptoms and lung function often begin to improve within several days of initiating treatment. ICS reduces exercise-induced symptoms, nocturnal symptoms, and acute exacerbations. ICS treatment typically leads to reductions in airway hyperresponsiveness.

ICS side effects include hoarseness and oral candidiasis; these effects may be minimized by use of a spacer device and by rinsing out the mouth after taking ICS.

Other available controller therapies for asthma include systemic corticosteroids. Although quite helpful in the management of acute asthma exacerbations, oral or IV steroid use should be avoided if at all possible in the chronic management of asthma due to multiple potential side effects. Antileukotrienes, such as montelukast, may be quite beneficial in some pts. Cromolyn sodium and nedocromil sodium are not widely used due to their brief durations of action and typically modest effects. Omalizumab is a blocking antibody that neutralizes IgE; with SC injection every 2–4 wk, it appears to reduce acute asthma exacerbation frequency in severe asthmatics. However, it is expensive and considered only for highly selected pts with elevated total serum IgE levels and refractory asthma symptoms despite maximal inhaled bronchodilator and ICS therapy.

Overall Treatment Approach In addition to limiting exposure to their environmental triggers for asthma, pts should receive stepwise therapy appropriate for their disease severity (Fig. 129-1). Asthmatics with mild intermittent symptoms are typically managed adequately with SABAs taken on an as-needed basis. Use of SABAs more than three times a week suggests that controller therapy, typically with an ICS twice per day, is required. If symptoms are not adequately controlled with ICS, LABAs can be added. If symptoms are still not adequately controlled, higher doses of ICS and/or alternative controller therapies should be considered.

ASTHMA EXACERBATIONS

Clinical Features

Asthma exacerbations are periods of acute worsening of asthma symptoms that may be life threatening. Exacerbations are commonly triggered by viral URIs, but other triggers also can be involved. Symptoms often include increased dyspnea, wheezing, and chest tightness. Physical examination can reveal tachypnea, tachycardia, and

lung hyperinflation. Pulmonary function testing reveals a reduction in FEV_1 and PEF. Hypoxemia can result; Pco_2 is usually reduced due to hyperventilation. Normal or rising Pco_2 can signal impending respiratory failure.

TREATMENT ASTHMA EXACERBATIONS

The mainstays of asthma exacerbation treatment are high doses of SABAs and systemic corticosteroids. SABAs may be administered by nebulizer or metered-dose inhaler with a spacer; very frequent dosing (q1h or more often) may be required initially. Inhaled anticholinergic bronchodilator medication can be added to the SABAs. IV corticosteroids, such as methylprednisolone (e.g., 80 mg IV q8h), may be used, although oral corticosteroids (e.g., prednisone 30–45 mg once daily for 5–10 days) also may be used. Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%). If respiratory failure occurs, mechanical ventilation should be instituted, with care to minimize airway pressures and auto-PEEP. Because bacterial infections rarely trigger asthma exacerbations, antibiotics are not routinely administered unless there are signs of pneumonia.

In an effort to treat asthma exacerbations before they become severe, asthma pts should receive written action plans with instructions for self-initiation of treatment based on respiratory symptoms and reductions in PEF.

For a more detailed discussion, see Barnes PJ: Asthma, Chap. 309, p. 1669, in HPIM-19.

130 Environmental Lung Diseases

The susceptibility to develop many pulmonary diseases is influenced by environmental factors. This chapter will focus on occupational and toxic chemical exposures. However, a variety of nonoccupational indoor exposures such as environmental tobacco smoke exposure (lung cancer), radon gas (lung cancer), and biomass fuel cooking (chronic obstructive pulmonary disease [COPD]) also should be considered. Particle size is an important determinant of the impact of inhaled environmental exposures on the respiratory system. Particles >10 μm in diameter typically are captured by the upper airway. Particles 2.5–10 μm in diameter will likely deposit in the upper tracheobronchial tree, while smaller particles (including nanoparticles) will reach the alveoli. Water-soluble gases like ammonia are absorbed in the upper airways and produce irritative and bronchoconstrictive responses, while less water-soluble gases (e.g., phosgene) may reach the alveoli and cause a life-threatening acute chemical pneumonitis.

APPROACH TO THE PATIENT: Environmental Lung Diseases

Because there are many types of occupational lung disease (pneumoconiosis) that can mimic diseases not known to relate to environmental factors, obtaining a careful occupational history is essential. In addition to the types of occupation

performed by the pt, the specific environmental exposures, use of protective respiratory devices, and ventilation of the work environment can provide key information. Assessing the temporal development of symptoms relative to the pt's work schedule also can be very useful.

The physical examination may indicate the type and severity of lung disease, but usually does not assist in identifying a specific environmental etiology. Pulmonary function tests should be used to assess the severity of impairment, but they typically do not suggest a specific diagnosis. Changes in spirometry before and after a work shift can provide strong evidence for bronchoconstriction in suspected occupational asthma. Chest x-ray is helpful in the assessment of environmental lung disease, but it may over- or underestimate the functional impact of pneumoconioses. Some chest x-ray patterns are distinctive for certain occupational lung diseases; chest CT scans can provide a more detailed evaluation. Specific laboratory tests can be invaluable for diagnosing certain environmental lung diseases, such as evaluation of urinary heavy metal concentrations to assess cadmium in battery plant workers.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

INORGANIC DUSTS

Asbestos-Related Diseases

In addition to exposures to asbestos that may occur during the production of asbestos products (from mining to manufacturing), common occupational asbestos exposures occur in shipbuilding and other construction trades (e.g., pipefitting, boilermaking) and in the manufacture of safety garments and friction materials (e.g., brake and clutch linings). Along with worker exposure in these areas, bystander exposure (e.g., spouses) can be responsible for some asbestos-related lung diseases.

A range of respiratory diseases has been associated with asbestos exposure. Pleural plaques indicate that asbestos exposure has occurred, but they are typically not symptomatic. Interstitial lung disease, often referred to as asbestosis, is pathologically and radiologically similar to idiopathic pulmonary fibrosis; it is typically accompanied by a restrictive ventilatory defect with reduced diffusing capacity of the lung for carbon monoxide (DLCO) on pulmonary function testing. Asbestosis usually develops at least 10 years after exposure, and no specific therapy is available.

Benign pleural effusions can also occur from asbestos exposure. Lung cancer is clearly associated with asbestos exposure, but does not typically present for at least 15 years after initial exposure. The lung cancer risk increases multiplicatively with cigarette smoking. In addition, mesotheliomas (both pleural and peritoneal) are strongly associated with asbestos exposure, but they are not related to smoking. Relatively brief asbestos exposures may lead to mesotheliomas, which typically do not develop for decades after the initial exposure. Biopsy of pleural tissue, typically by thoracoscopic surgery, is required for diagnosing mesothelioma.

Silicosis

Silicosis results from exposure to free silica (crystalline quartz), which occurs in mining, stone cutting, abrasive industries (e.g., stone, clay, glass, and cement manufacturing), foundry work, and quarrying. Heavy exposures over relatively brief time periods (as little as 10 months) can cause acute silicosis—which is pathologically similar to pulmonary alveolar proteinosis and associated with a characteristic chest CT pattern known as "crazy paving." Acute silicosis can be severe and progressive; whole lung lavage may be of some therapeutic benefit.

Longer-term exposures can result in simple silicosis, with small rounded opacities in the upper lobes of the lungs. Calcification of hilar lymph nodes can give a

characteristic "eggshell" appearance on radiographic studies. Progressive nodular fibrosis can result in masses >1 cm in diameter in complicated silicosis. When such masses become very large, the term *progressive massive fibrosis* is used to describe the condition. Due to impaired cell-mediated immunity, silicosis pts are at increased risk of tuberculosis, atypical mycobacterial infections, and fungal infections. Silica may also be a lung carcinogen.

Coal Worker's Pneumoconiosis

Occupational exposure to coal dust predisposes to coal worker's pneumoconiosis (CWP), which is less common among coal workers in the western United States due to a lower risk from the bituminous coal found in that region. Simple CWP is defined radiologically by small nodular opacities and is not typically symptomatic; however, an increased risk of COPD may occur. The development of larger nodules (>1 cm in diameter), usually in the upper lobes, characterizes complicated CWP. Complicated CWP is often symptomatic and is associated with reduced pulmonary function and increased mortality.

Berylliosis

Beryllium exposure may occur in the manufacturing of alloys, ceramics, and electronic devices. Although acute beryllium exposure can rarely produce acute pneumonitis, a chronic granulomatous disease very similar to sarcoidosis is much more common. Radiologically, chronic beryllium disease, like sarcoidosis, is characterized by pulmonary nodules along septal lines. As in sarcoidosis, either a restrictive or obstructive ventilatory pattern with reduced DLCO on pulmonary function testing can be seen. Bronchoscopy with transbronchial biopsy is typically required to diagnose chronic beryllium disease. The most effective way to distinguish chronic beryllium disease from sarcoidosis is to assess for delayed hypersensitivity to beryllium by performing a lymphocyte proliferation test using blood or bronchoalveolar lavage lymphocytes. Removal from further beryllium exposure is required, and corticosteroids may be beneficial.

ORGANIC DUSTS

Cotton Dust (Byssinosis)

Cotton dust exposures occur in the production of yarns for textiles and rope making. At the early stages of byssinosis, chest tightness occurs near the end of the first day of the workweek. In progressive cases, symptoms are present throughout the workweek. After at least 10 years of exposure, chronic airflow obstruction can develop. In symptomatic individuals, limiting further exposure is essential.

Grain Dust

Farmers and grain elevator operators are at risk for grain dust–related lung disease, which is similar to COPD. Symptoms include productive cough, wheezing, and dyspnea. Pulmonary function tests typically show airflow obstruction.

Farmer's Lung

Exposure to moldy hay containing spores of thermophilic actinomycetes can lead to the development of hypersensitivity pneumonitis. Within 8 h after exposure, the acute presentation of farmer's lung includes fever, cough, and dyspnea. With repeated exposures, chronic and patchy interstitial lung disease can develop.

Toxic Chemicals

Many toxic chemicals can affect the lung in the form of vapors and gases. For example, smoke inhalation can be lethal to firefighters and fire victims through a variety of mechanisms; carbon monoxide poisoning can cause life-threatening hypoxemia, while combustion of plastics and polyurethanes can release toxic agents including

cyanide. Occupational asthma can result from exposure to diisocyanates in polyurethanes and acid anhydrides in epoxies. Radon gas, released from earth materials and concentrated within buildings, is a risk factor for lung cancer.

PRINCIPLES OF MANAGEMENT

Treatment of environmental lung diseases typically involves limiting or avoiding exposures to the toxic substance. Chronic interstitial lung diseases (e.g., asbestosis, CWP) are not responsive to glucocorticoids, but acute organic dust exposures may respond to corticosteroids. Therapy of occupational asthma (e.g., diisocyanates) follows usual asthma guidelines (Chap. 129), and therapy of occupational COPD (e.g., byssinosis) follows usual COPD guidelines (Chap. 131).

For a more detailed discussion, see Balmes JR, Speizer FE: Occupational and Environmental Lung Disease, Chap. 311, p. 1687, in HPIM-19.

131 Chronic Obstructive Pulmonary Disease

DEFINITION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by chronic airflow obstruction; thus, pulmonary function testing is central to its diagnosis. The presence of airflow obstruction is determined by a reduced ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC). Among individuals with a reduced FEV_1/FVC ratio, the severity of airflow obstruction is determined by the level of reduction in FEV_1 (Table 131-1): ≥80% is stage I, 50–80% is stage II, 30–50% is stage III, and <30% is stage IV. Cigarette smoking is the major environmental risk factor for COPD. The risk of COPD increases with cigarette smoking intensity, which is typically quantified as pack-years. (One pack of cigarettes smoked per day for 1 year equals 1 pack-year.) Individuals with airway hyperresponsiveness and

TABLE 131-1 GOLD SPIROMETRIC GRADING CRITERIA FOR COPD SEVERITY

GOLD Stage	Severity	Spirometry
I	Mild	FEV_1/FVC <0.7 and FEV_1 ≥80% predicted
II	Moderate	FEV_1/FVC <0.7 and FEV_1 ≥50% but <80% predicted
III	Severe	FEV_1/FVC <0.7 and FEV_1 ≥30% but <50% predicted
IV	Very severe	FEV_1/FVC <0.7 and FEV_1 <30% predicted

Abbreviation: GOLD, Global Initiative for Lung Disease.
Source: From the Global Strategy for Diagnosis, Management and Prevention of COPD 2014. Available from http://www.goldcopd.org; with permission.

certain occupational exposures (e.g., coal mining, gold mining, and cotton textiles) are likely also at increased risk for COPD. In countries in which biomass combustion with poor ventilation is used for cooking, an increased risk of COPD among women has been reported. COPD is a progressive disorder; however, the rate of loss of lung function often slows markedly if smoking cessation occurs. In normal individuals, FEV_1 reaches a lifetime peak at around age 25 years, enters a plateau phase, and subsequently declines gradually and progressively. Subjects can develop COPD by having reduced maximally attained lung function, shortened plateau phase, or accelerated decline in lung function.

Symptoms often occur only when COPD is advanced; thus, early detection requires spirometric testing. The PaO_2 typically remains near normal until the FEV_1 falls to <50% of the predicted value. Hypercarbia and pulmonary hypertension are most common after FEV_1 has fallen to <25% of predicted. COPD pts with similar FEV_1 values can vary markedly in their respiratory symptoms and functional impairment. COPD often includes periods of increased respiratory symptoms, such as dyspnea, cough, and phlegm production, which are known as exacerbations. Exacerbations are often triggered by bacterial and/or viral respiratory infections. These exacerbations become more common as COPD severity increases, but some individuals are much more susceptible to developing exacerbations than others with similar degrees of airflow obstruction.

CLINICAL MANIFESTATIONS

History

Subjects with COPD usually have smoked ≥20 pack-years of cigarettes. Common symptoms include cough and phlegm production; individuals with chronic productive cough for 3 months per year for two consecutive years have chronic bronchitis. However, chronic bronchitis without airflow obstruction is not included within COPD. Exertional dyspnea is a common and potentially disabling symptom in COPD pts. Exercise involving upper-body activity is especially difficult for severe COPD pts. Weight loss and cachexia are common in advanced disease.

Exacerbations are more frequent as disease progresses and are most often triggered by respiratory infections, often with a bacterial component. The history of prior exacerbations is a strong predictor of future exacerbations.

Physical Findings

The physical examination may be normal until COPD is fairly advanced. As disease progresses, signs of hyperinflation may become more prominent, including barrel chest and poor diaphragmatic excursion. Expiratory wheezing may be observed, but it does not predict the severity of obstruction or response to therapy. Persistently localized wheezing and digital clubbing raise the possibility of lung cancer.

During COPD exacerbations, signs of respiratory distress may be prominent, including tachycardia, tachypnea, use of accessory muscles of respiration, and cyanosis.

Radiographic Findings

Plain chest x-ray may show hyperinflation, emphysema, and pulmonary hypertension. It is typically performed to exclude other disease processes during routine evaluation and to exclude pneumonia during exacerbations. Chest CT scanning has much greater sensitivity for detecting emphysema, but is typically reserved for the evaluation of advanced disease when surgical options such as lung volume reduction and lung transplantation are being considered, or as part of lung cancer screening in smokers.

Pulmonary Function Tests

Objective documentation of airflow obstruction is essential for diagnosing COPD. Standardized staging of COPD is based on post-bronchodilator spirometry. In

COPD, the FEV_1/FVC ratio is reduced below 0.7. Despite prolonged expiratory efforts, subjects may not be able to achieve a plateau in their FVC. Increases in total lung capacity and residual volume, as well as reduced diffusing capacity for carbon monoxide, are typically seen in emphysema.

Laboratory Tests

α_1 Antitrypsin (α_1AT) testing, typically by measurement of the protein level in the bloodstream, is recommended to exclude severe α_1AT deficiency. Augmentation therapy (a weekly IV infusion) is available for individuals with severe α_1AT deficiency (e.g., PI Z). Pulse oximetry can determine the O_2 saturation. However, arterial blood gases remain useful to assess the severity of CO_2 retention as well as acid-base disorders. During acute exacerbations, arterial blood gases should be considered in pts with mental status changes, significant respiratory distress, very severe COPD, or a history of hypercarbia. Complete blood counts are useful in advanced disease to assess for erythrocytosis, which can occur secondary to hypoxemia, and anemia, which can worsen dyspnea.

TREATMENT COPD

OUTPATIENT MANAGEMENT

Smoking Cessation Elimination of tobacco smoking has been convincingly shown to reduce decline in pulmonary function and to prolong survival in pts with COPD. Although lung function does not typically improve substantially after smoking cessation, the rate of decline in FEV_1 often reverts to that of nonsmokers. Pharmacologic treatment to assist with smoking cessation is often beneficial. Use of nicotine replacement therapy (available as a transdermal patch, gum, lozenge, nasal spray, and oral inhaler) can increase rates of smoking cessation; oral bupropion (150 mg twice per day after starting at 150 mg per day for 3 days) also produces significant benefit and can be combined successfully with nicotine replacement. Varenicline, a partial agonist for nicotinic acetylcholine receptors, also can promote smoking cessation. All adult, nonpregnant smokers without specific contraindications should be offered pharmacologic treatment to assist with smoking cessation.

Nonpharmacologic Treatment Pulmonary rehabilitation improves dyspnea and functional status and reduces hospitalizations. Annual influenza vaccinations are strongly recommended; in addition, pneumococcal vaccination is recommended.

Bronchodilators Although inhaled bronchodilator medications have not been proven to increase longevity in COPD, they may significantly reduce respiratory symptoms. Short- and long-acting β-adrenergic agonists, short- and long-acting anticholinergics, and theophylline derivatives all may be used. Although oral medications are associated with greater rates of adherence, inhaled medications generally have fewer side effects.

Pts with mild disease can usually be managed with an inhaled short-acting anticholinergic such as ipratropium or a short-acting β agonist such as albuterol. Combination therapy and long-acting β agonists and/or long-acting anticholinergics should be added in pts with severe disease. The narrow toxic-therapeutic ratio of theophylline compounds limits their use, and either low doses or regular monitoring of serum levels are required.

Corticosteroids Chronic systemic corticosteroid treatment is not recommended in COPD pts due to the risk of multiple complications, including osteoporosis, weight gain, cataracts, and diabetes mellitus. Although inhaled steroids have not been proven to reduce the rate of decline of FEV_1 in COPD, inhaled steroid medications reduce the frequency of exacerbations in individuals with severe COPD. Combinations of inhaled steroids and long-acting β agonists reduce COPD

exacerbations and may reduce mortality—although that has not been conclusively shown.

Oxygen Long-term supplemental oxygen therapy has been shown to reduce symptoms and improve survival in COPD pts who are chronically hypoxemic. Documentation of the need for O_2 requires a measurement of PaO_2 or oxygen saturation (SaO_2) after a period of stability. Pts with a PaO_2 ≤55 mmHg or SaO_2 ≤88% should receive O_2 to raise the SaO_2 to ≥90%. O_2 is also indicated for pts with PaO_2 of 56–59 mmHg or SaO_2 <90% if associated with signs and symptoms of pulmonary hypertension or cor pulmonale. For individuals who meet these guidelines, continuous O_2 therapy is recommended because the number of hours per day of oxygen use is directly related to the mortality benefit. Supplemental oxygen may also be prescribed for selected COPD pts who desaturate only with exercise or during sleep, although the evidence for benefit is less compelling.

Surgical Options for Severe COPD Two main types of surgical options are available for end-stage COPD. Lung volume reduction surgery can reduce mortality and improve lung function in selected pts with upper lobe–predominant emphysema and low exercise capacity (after pulmonary rehabilitation). Individuals who meet the criteria for the high-risk group (FEV_1 <20% predicted and either a diffuse distribution of emphysema or lung carbon monoxide diffusing capacity <20% predicted) should not be considered for lung volume reduction surgery. Lung transplantation should be considered for COPD pts who have very severe chronic airflow obstruction and disability at a relatively young age despite maximal medical therapy.

MANAGEMENT OF COPD EXACERBATIONS

COPD exacerbations are a major cause of morbidity and mortality. Critical decisions in management include whether hospitalization is required. Although there are no definitive guidelines to determine which COPD pts require hospitalization for an exacerbation, the development of respiratory acidosis, worsening hypoxemia, severe underlying COPD, pneumonia, or social situations without adequate home support for the treatment required should prompt consideration of hospitalization. Chronic treatment with azithromycin or roflumilast has been shown to reduce the frequency of COPD exacerbations.

Key components of exacerbation treatment include bronchodilators, antibiotics, and short courses of systemic glucocorticoids.

Antibiotics Because bacterial infections often trigger COPD exacerbations, antibiotic therapy should be strongly considered, especially with increased sputum volume or change in sputum color. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antibiotic choice should depend on the local antibiotic sensitivity patterns and the severity of disease. Trimethoprim-sulfamethoxazole, doxycycline, and amoxicillin are reasonable choices for subjects with mild to moderate COPD; broader-spectrum antibiotics should be considered for subjects with more severe underlying COPD and/or more severe exacerbations.

Bronchodilators Bronchodilator therapy is essential during COPD exacerbations. Short-acting β-adrenergic agonists by inhalation (e.g., albuterol q1–2h) are used; addition of anticholinergics is likely of benefit (e.g., ipratropium q4–6h). Administration of bronchodilators by nebulizer is often used initially because it is easier to administer to pts in respiratory distress. Conversion to metered-dose inhaler administration can be successfully achieved with appropriate training of the pt and staff.

Glucocorticoids Systemic steroids hasten resolution of symptoms and reduce relapses and subsequent exacerbations for up to 6 months. Dosing is not well

worked out, but 30–40 mg of prednisone daily (or IV equivalent) is standard, with a total course of 10–14 days. Hyperglycemia is the most commonly reported complication and should be monitored.

Oxygen Hypoxemia often worsens during COPD exacerbations. Supplemental O_2 should be administered to maintain SaO_2 ≥90%. Very high O_2 delivery can worsen hypercarbia, primarily due to increasing ventilation-perfusion mismatch. However, providing adequate O_2 to obtain saturation of ~90% is the key goal. Therefore, supplemental O_2 delivery should be focused on providing adequate oxygenation without providing unnecessarily high O_2 saturations. Pts may require use of supplemental O_2 after hospital discharge until the exacerbation completely resolves.

Ventilatory Support Numerous studies suggest that noninvasive mask ventilation (noninvasive ventilation [NIV]) can improve outcomes in acute COPD exacerbations with respiratory failure ($PaCO_2$ >45 mmHg). Contraindications to NIV include cardiovascular instability, impaired mental status, inability to cooperate, copious secretions, craniofacial abnormalities or facial trauma, extreme obesity, or significant burns. Progressive hypercarbia, refractory hypoxemia, or alterations in mental status that compromise ability to comply with NIV therapy, hemodynamic instability, and respiratory arrest may necessitate endotracheal intubation for mechanical ventilation. Sufficient expiratory time is required to avoid the development of auto-PEEP.

For a more detailed discussion, see Reilly JJ Jr., Silverman EK, Shapiro SD: Chronic Obstructive Pulmonary Disease, Chap. 314, p. 1700, in HPIM-19.

132 Pneumonia, Bronchiectasis, and Lung Abscess

PNEUMONIA

Pneumonia, an infection of the lung parenchyma, is classified as community-acquired (CAP) or health care–associated (HCAP). The HCAP category is subdivided into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). HCAP is associated with current hospitalization for ≥48 h, hospitalization for ≥2 days in the prior 3 months, residence in a nursing home or extended-care facility, antibiotic therapy in the preceding 3 months, chronic dialysis, home infusion therapy, home wound care, and contact with a family member who has a multidrug-resistant (MDR) infection.

PATHOPHYSIOLOGY

- Microorganisms gain access to the lower respiratory tract via microaspiration from the oropharynx (the most common route), inhalation of contaminated droplets, hematogenous spread, or contiguous extension from an infected pleural or mediastinal space.

- Before disease manifests, the size of the organism burden must overcome the ability of macrophages and other components of innate immunity (e.g., surfactant proteins A and D) to clear bacteria.
- Classic pneumonia (typified by that due to *Streptococcus pneumoniae*) presents as a lobar pattern and evolves through four phases characterized by changes in the alveoli:
  - *Edema:* Proteinaceous exudates are present in the alveoli.
  - *Red hepatization:* Erythrocytes and neutrophils are present in the intraalveolar exudate.
  - *Gray hepatization:* Neutrophils and fibrin deposition are abundant.
  - *Resolution:* Macrophages are the dominant cell type.
- In VAP, respiratory bronchiolitis can precede a radiologically apparent infiltrate.

COMMUNITY-ACQUIRED PNEUMONIA

Microbiology

Although many bacteria, viruses, fungi, and protozoa can cause CAP, most cases are caused by relatively few pathogens. In >50% of cases, a specific etiology is never determined.

- Typical bacterial pathogens include *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
- Atypical organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp., and respiratory viruses (e.g., influenza viruses, adenoviruses, human metapneumovirus, respiratory syncytial viruses).
  - A virus may be responsible for a large proportion of CAP cases that require hospital admission, even in adults.
  - 10–15% of CAP cases are polymicrobial and involve a combination of typical and atypical organisms.
- Involvement of anaerobes, which play a significant role in CAP only when aspiration precedes presentation by days or weeks, often results in significant empyemas.

Epidemiology

CAP affects >5 million adults each year in the United States, 80% of whom are treated on an outpatient basis. CAP causes >55,000 deaths annually and is associated with an overall yearly cost of ~$12 billion.

- Incidence rates of CAP are highest at the extremes of age (i.e., <4 and >60 years).
- Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥70 years (vs. 60–69 years).
- Many factors—e.g., tobacco smoking, chronic obstructive pulmonary disease, colonization with methicillin-resistant *S. aureus* (MRSA), recent hospitalization or antibiotic therapy—influence the types of pathogens that should be considered in the etiologic diagnosis.

Clinical Manifestations

Pts frequently have fever, chills, sweats, cough (either nonproductive or productive of mucoid, purulent, or blood-tinged sputum), pleuritic chest pain, and dyspnea.

- Other common symptoms include nausea, vomiting, diarrhea, fatigue, headache, myalgias, and arthralgias.
- Elderly pts may present atypically, with confusion but few other manifestations.
- Physical examination often reveals tachypnea; increased or decreased tactile fremitus; dull or flat percussion reflecting consolidation and pleural fluid, respectively; crackles; bronchial breath sounds; or a pleural friction rub.

Diagnosis

Both confirmation of the diagnosis and assessment of the likely etiology are required. Although no data have demonstrated that treatment directed at a specific pathogen is superior to empirical treatment, an etiologic diagnosis allows narrowing of the empirical regimen, identification of organisms with public safety implications (e.g., *Mycobacterium tuberculosis*, influenza virus), and monitoring of antibiotic susceptibility trends.

- *Chest radiography* is often required to differentiate CAP from other conditions, particularly since the sensitivity and specificity of physical exam findings for CAP are only 58% and 67%, respectively.
  - CT of the chest may be helpful for pts with suspected postobstructive pneumonia or suspected cavitary disease.
  - Some radiographic patterns suggest an etiology; e.g., pneumatoceles suggest *S. aureus*.
- *Sputum samples* must have >25 WBCs and <10 squamous epithelial cells per high-power field to be appropriate for culture. The sensitivity of sputum cultures is highly variable; in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%.
- *Blood cultures* are positive in 5–14% of cases, most commonly yielding *S. pneumoniae*. Blood cultures are optional for most CAP pts but should be performed for high-risk pts (e.g., pts with chronic liver disease or asplenia).
- *Urine antigen tests* for *S. pneumoniae* and *Legionella pneumophila* type 1 can be helpful.
- *PCR* of nasopharyngeal swabs has become the standard for diagnosis of respiratory viral infection and is also useful for detection of many atypical bacteria.
- *Serology:* A fourfold rise in titer of specific IgM antibody can assist in the diagnosis of pneumonia due to some pathogens; however, the time required to obtain a final result makes serology of limited clinical utility.

TREATMENT COMMUNITY-ACQUIRED PNEUMONIA

DECIDING WHETHER TO HOSPITALIZE PTS

- Two sets of criteria identify pts who will benefit from hospital care. It is not clear which set is superior, and application of each tool should be tempered by a consideration of factors relevant to the individual pt.
  - Pneumonia Severity Index (PSI): Points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On this basis, pts are assigned to one of five classes of mortality risk.
  - CURB-65: Five variables are included: confusion (C); urea >7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure, systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years (65). Pts with a score of 0 can be treated at home, pts with a score of 2 should be hospitalized, and pts with a score of ≥3 may require management in the ICU.

ANTIBIOTIC THERAPY

- For recommendations on empirical antibiotic treatment of CAP, see **Table 132-1**. U.S. guidelines always target *S. pneumoniae* and atypical pathogens. Retrospective data suggest that this approach lowers the mortality rate.
- Pts initially treated with IV antibiotics can be switched to oral agents when they can ingest and absorb drugs, are hemodynamically stable, and are improving clinically.
- CAP has historically been treated for 10–14 days, but a 5-day course of a fluoroquinolone is sufficient for cases of uncomplicated CAP. A longer course may be required for pts with bacteremia, metastatic infection, or infection with a particularly virulent pathogen.

TABLE 132-1 EMPIRICAL ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Outpatients

1. Previously healthy and no antibiotics in past 3 months
   - A macrolide (clarithromycin [500 mg PO bid] or azithromycin [500 mg PO once, then 250 mg qd]) ***or***
   - Doxycycline (100 mg PO bid)
2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class
   - A respiratory fluoroquinolone (moxifloxacin [400 mg PO qd], gemifloxacin [320 mg PO qd], levofloxacin [750 mg PO qd]) ***or***
   - A β-lactam (preferred: high-dose amoxicillin [1 g tid] or amoxicillin/clavulanate [2 g bid]; alternatives: ceftriaxone [1–2 g IV qd], cefpodoxime [200 mg PO bid], cefuroxime [500 mg PO bid]) *plus* a macrolide[a]
3. In regions with a high rate of "high-level" pneumococcal macrolide resistance,[b] consider alternatives listed above for pts with comorbidities.

Inpatients, Non-ICU

- A respiratory fluoroquinolone (e.g., moxifloxacin [400 mg PO or IV qd] or levofloxacin [750 mg PO or IV qd])
- A β-lactam[c] (e.g., ceftriaxone [1–2 g IV qd], ampicillin [1–2 g IV q4–6h], cefotaxime [1–2 g IV q8h], ertapenem [1 g IV qd]) *plus* a macrolide[d] (e.g., oral clarithromycin or azithromycin [as listed above] or IV azithromycin [1 g once, then 500 mg qd])

Inpatients, ICU

- A β-lactam[e] (e.g., ceftriaxone [2 g IV qd], ampicillin-sulbactam [2 g IV q8h], or cefotaxime [1–2 g IV q8h]) *plus* either azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)

Special Concerns

If Pseudomonas is a consideration:

- An antipseudomonal β-lactam (e.g., piperacillin/tazobactam [4. 5 g IV q6h], cefepime [1–2 g IV q12h], imipenem [500 mg IV q6h], meropenem [1 g IV q8h]) *plus* either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd)
- The above β-lactams *plus* an aminoglycoside (amikacin [15 mg/kg qd] or tobramycin [1. 7 mg/kg qd]) *plus* azithromycin
- The above β-lactams[f] *plus* an aminoglycoside *plus* an antipneumococcal fluoroquinolone

If CA-MRSA is a consideration:

- Add linezolid (600 mg IV q12h) or vancomycin (15 mg/kg q12h initially, with adjusted doses)

[a]Doxycycline (100 mg PO bid) is an alternative to the macrolide.
[b]MICs of >16 μg/mL in 25% of isolates.
[c]A respiratory fluoroquinolone should be used for penicillin-allergic pts.
[d]Doxycycline (100 mg IV q12h) is an alternative to the macrolide.
[e]For penicillin-allergic pts, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h).
[f]For penicillin-allergic pts, substitute aztreonam.
Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.

- Fever and leukocytosis usually resolve within 2–4 days. Pts who have not responded to therapy by day 3 should be reevaluated, with consideration of alternative diagnoses, antibiotic resistance in the pathogen, and the possibility that the wrong drug is being given.

Complications

Common complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, and exacerbation of comorbid disease. Metastatic infection (e.g., brain abscess, endocarditis) occurs rarely and requires immediate attention.

- Lung abscess may occur in association with aspiration or infection caused by single CAP pathogens (e.g., community-acquired MRSA [CA-MRSA] or *P. aeruginosa*). Drainage should be established and proper antibiotics administered.
- Any significant pleural effusion should be tapped for diagnostic and therapeutic purposes. If the fluid has a pH <7, a glucose level <2.2 mmol/L, and an LDH content >1000 U or if bacteria are seen or cultured, fluid should be drained; a chest tube is usually required.

Follow-Up

CXR abnormalities may require 4–12 weeks to clear. Pts should receive influenza and pneumococcal vaccines, as appropriate.

HEALTH CARE–ASSOCIATED PNEUMONIA (SEE ALSO CHAP. 78)

VENTILATOR-ASSOCIATED PNEUMONIA

Microbiology

Potential etiologic agents include MDR and non-MDR pathogens; the prominence of the various pathogens depends on the length of hospital stay at the time of infection.

Epidemiology, Pathogenesis, and Clinical Manifestations

Prevalence estimates of VAP are 6–52 cases per 100 pts, with the highest hazard ratio in the first 5 days of mechanical ventilation.

- Three factors important in the pathogenesis of VAP are colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms to the lower respiratory tract, and compromise of normal host defense mechanisms.
- Clinical manifestations are similar to those in other forms of pneumonia.

Diagnosis

Application of clinical criteria consistently results in overdiagnosis of VAP. Use of quantitative cultures to discriminate between colonization and true infection by determining bacterial burden may be helpful; the more distal in the respiratory tree the diagnostic sampling, the more specific the results.

TREATMENT VENTILATOR-ASSOCIATED PNEUMONIA

- See Table 132-2 for recommended options for empirical therapy for HCAP.
  - Higher mortality rates are associated with inappropriate initial empirical treatment.
  - Broad-spectrum treatment should be modified when a pathogen is identified.
  - Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment.
- Treatment failure in VAP is not uncommon, especially when MDR pathogens are involved; MRSA and *P. aeruginosa* are associated with high failure rates.

TABLE 132-2 EMPIRICAL ANTIBIOTIC TREATMENT OF HEALTH CARE–ASSOCIATED PNEUMONIA

Patients without Risk Factors for MDR Pathogens
Ceftriaxone (2 g IV q24h) or cefotaxime (2 g IV q6–8 h) ***or***
Moxifloxacin (400 mg IV q24h), ciprofloxacin (400 mg IV q8h), or levofloxacin (750 mg IV q24h) ***or***
Ampicillin/sulbactam (3 g IV q6h) ***or***
Ertapenem (1 g IV q24h)
Patients with Risk Factors for MDR Pathogens
1. A β-lactam:
Ceftazidime (2 g IV q8h) or cefepime (2 g IV q8–12h) ***or***
Piperacillin/tazobactam (4. 5 g IV q6h) ***or***
Imipenem (500 mg IV q6h or 1 g IV q8h) or meropenem (1 g IV q8h)
plus
2. A second agent active against gram-negative bacterial pathogens:
Gentamicin or tobramycin (7 mg/kg IV q24h) or amikacin (20 mg/kg IV q24h) ***or***
Ciprofloxacin (400 mg IV q8h) or levofloxacin (750 mg IV q24h)
plus
3. An agent active against gram-positive bacterial pathogens:
Linezolid (600 mg IV q12h) ***or***
Vancomycin (15 mg/kg q12h initially with adjusted doses)

Abbreviation: MDR, multidrug-resistant.

- VAP complications include prolongation of mechanical ventilation, increased length of ICU stay, and necrotizing pneumonia with pulmonary hemorrhage or bronchiectasis. VAP is associated with significant mortality risk.
- Strategies effective for the prevention of VAP are listed in Table 132-3.

HOSPITAL-ACQUIRED PNEUMONIA

Less well studied than VAP, HAP more commonly involves non-MDR pathogens. Anaerobes may also be more commonly involved in non-VAP pts because of the increased risk of macroaspiration in pts who are not intubated.

BRONCHIECTASIS

Etiology and Epidemiology

Bronchiectasis is an irreversible airway dilation that involves the lung in either a focal (due to obstruction) or a diffuse (due to a systemic or infectious process) manner. Bronchiectasis can arise from infectious or noninfectious causes.

- The epidemiology varies greatly with the underlying etiology; in general, the incidence of bronchiectasis increases with age and is higher among women than among men.
- 25–50% of pts with bronchiectasis have idiopathic disease.

Pathogenesis

The most widely cited mechanism of infectious bronchiectasis is the "vicious cycle hypothesis," in which susceptibility to infection and poor mucociliary clearance

TABLE 132-3 PATHOGENIC MECHANISMS AND CORRESPONDING PREVENTION STRATEGIES FOR VENTILATOR-ASSOCIATED PNEUMONIA

Pathogenic Mechanism	Prevention Strategy
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose pts[a]
Gastroesophageal reflux	Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b]
Cross-infection from other colonized pts	Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation[a]
Prolonged duration of ventilation	Daily awakening from sedation,[a] weaning protocols[a]
Abnormal swallowing function	Early percutaneous tracheostomy[a]
Secretions pooled above endotracheal tube	Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and pt transport
Altered lower respiratory host defenses	Tight glycemic control[b]; lowering of hemoglobin transfusion threshold

[a]Strategies demonstrated to be effective in at least one randomized controlled trial.
[b]Strategies with negative randomized trials or conflicting results.

result in microbial colonization of the bronchial tree. Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that damage the bronchial wall and parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

Clinical Manifestations

Presenting pts typically have a persistent productive cough with ongoing production of thick, tenacious sputum.

- Physical examination usually reveals crackles and wheezing on lung auscultation and occasionally reveals digital clubbing.
- Acute exacerbations are associated with increased purulent-sputum production.

Diagnosis

The diagnosis of bronchiectasis is based on clinical presentation with consistent radiographic findings, such as parallel "tram tracks," a "signet-ring sign" (a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering, bronchial wall thickening, or cysts emanating from the bronchial wall.

TREATMENT BRONCHIECTASIS

Treatment of infectious bronchiectasis is directed at the control of active infection and at improvements in secretion clearance and bronchial hygiene.

- Acute exacerbations should be treated with a 7- to 10-day course of antibiotics targeting the causative or presumptive pathogen; *H. influenzae* and *P. aeruginosa* are isolated commonly.
- Hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy can be used to enhance secretion clearance.
- For pts with ≥3 recurrences per year, suppressive antibiotic treatment to minimize the microbial load and reduce the frequency of exacerbations has been proposed.
- In select cases, surgery (including lung transplantation) should be considered.

LUNG ABSCESS

Microbiology

Lung abscess—necrosis and cavitation of the lung following microbial infection—can be categorized as primary (~80% of cases) or secondary; alternatively, it can be categorized as acute (<4–6 weeks in duration) or chronic (~40% of cases).

- Primary lung abscesses usually arise from aspiration in the absence of an underlying pulmonary or systemic condition, are often polymicrobial (primarily including anaerobic organisms and microaerophilic streptococci), and occur preferentially in dependent segments (posterior upper and superior lower lobes) of the right lung.
- Secondary lung abscesses arise in the setting of an underlying condition (e.g., a postobstructive process, an immunocompromising condition) and can be due to a number of different organisms, among which *P. aeruginosa* and other gram-negative rods are most common.

Clinical Manifestations

Initial presentation of lung abscess may be similar to that of pneumonia. Anaerobic lung abscesses may have a more chronic and indolent presentation, with night sweats, fatigue, and anemia; in addition, pts may have discolored phlegm and foul-tasting or foul-smelling sputum. Pts with lung abscesses due to non-anaerobic organisms (e.g., *S. aureus*) may present with a more fulminant course characterized by high fevers and rapid progression.

Diagnosis

Chest CT is the preferred radiographic study for precise delineation of the lesion.

- It is not clear whether invasive diagnostics (e.g., transtracheal aspiration) to identify an etiologic agent in primary lung abscesses is helpful.
- Sputum and blood cultures, serologic studies for opportunistic pathogens, and—if needed—more invasive methods of sample collection (e.g., bronchoalveolar lavage, CT-guided percutaneous aspiration) are recommended for secondary lung abscesses or when empirical therapy fails.

TREATMENT LUNG ABSCESS

Treatment depends on the presumed or established etiology.

- For primary lung abscesses, the recommended regimens are clindamycin (600 mg IV tid) or an IV-administered β-lactam/β-lactamase combination. After clinical improvement, the pt can be transitioned to an oral regimen (clindamycin, 300 mg qid; or amoxicillin/clavulanate).
- In secondary lung abscesses, antibiotic coverage should be directed at the identified pathogen.
- Continuation of oral treatment is recommended until imaging shows that the lung abscess has cleared or regressed to a small scar.
- Pts who continue to have fever ≥7 days after antibiotic initiation and whose additional diagnostic studies fail to identify an another treatable pathogen may require surgical resection or percutaneous drainage of the abscess.

For a more detailed discussion, see Mandell LA, Wunderink RG: Pneumonia, Chap. 153, p. 803; Baron RM, Baron Barshak M: Lung Abscess, Chap. 154, p. 813; and Baron RM, Baron Barshak M: Bronchiectasis, Chap. 312, p. 1694, in HPIM-19.

133 Pulmonary Thromboembolism and Deep-Vein Thrombosis

DEFINITION AND NATURAL HISTORY

Venous thromboembolism includes both deep-vein thrombosis (DVT) and pulmonary thromboembolism (PE). DVT results from blood clot formation within large veins, usually in the legs. PE results from DVTs that have broken off and traveled to the pulmonary arterial circulation. Isolated calf vein thrombi have much lower risk of PE. Although DVTs are typically related to thrombus formation in the legs and/or pelvis, indwelling venous catheters, pacemakers, and internal cardiac defibrillators have increased the occurrence of upper extremity DVT. In the absence of PE, the major complication of DVT is postthrombotic syndrome, which causes chronic leg swelling and discomfort due to damage to the venous valves of the affected leg. In its most severe form, postthrombotic syndrome causes skin ulceration. PE is often fatal, usually due to progressive right ventricular failure. Chronic thromboembolic pulmonary hypertension is another long-term complication of PE.

Some genetic risk factors, including factor V Leiden and the prothrombin G20210A mutation, have been identified, but they account for only a minority of venous thromboembolic disease. Medical conditions that increase the risk of venous thromboembolism include cancer and antiphospholipid antibody syndrome. A variety of other risk factors have been identified, including immobilization during prolonged travel, obesity, smoking, surgery, trauma, pregnancy, oral contraceptives, and postmenopausal hormone replacement.

Massive PE, with thrombosis affecting at least half of the pulmonary vasculature, often includes dyspnea, syncope, hypotension, and cyanosis. Submassive PE includes RV dysfunction in the setting of normal systemic arterial pressure. Low-risk PE, which includes normal RV function and systemic arterial pressure, has an excellent prognosis.

CLINICAL EVALUATION

History

DVTs often present with progressive lower calf discomfort. For PE, dyspnea is the most common presenting symptom. Chest pain, cough, or hemoptysis can indicate pulmonary infarction with pleural irritation. Syncope can occur with massive PE.

Physical Examination

Tachypnea and tachycardia are common in PE. Low-grade fever, neck vein distention, and a loud P_2 on cardiac examination can be seen. Hypotension and cyanosis suggest massive PE. Physical examination with DVT may be notable only for mild calf tenderness. However, with massive DVT, marked thigh swelling and inguinal tenderness can be observed.

Laboratory Tests

Normal D-dimer level (<500 μg/mL by enzyme-linked immunosorbent assay) essentially rules out PE in pts with low-to-moderate likelihood of PE, although hospitalized pts often have elevated D-dimer levels due to other disease processes. Although hypoxemia and an increased alveolar-arterial O_2 gradient may be observed in PE, arterial blood gases are rarely useful in diagnosing PE. Elevated serum troponin, plasma heart-type fatty acid-binding protein, and brain natriuretic peptide levels can be seen in PE. The electrocardiogram can show an S1Q3T3 sign in PE, but that finding is not frequently observed.

Imaging Studies

Venous ultrasonography can detect DVT by demonstrating loss of normal venous compressibility. For pts with nondiagnostic venous ultrasound studies, CT or MRI can be used to assess for DVT. About one-half of pts with PE have no imaging evidence for DVT.

In PE, a normal chest x-ray (CXR) is common. Although not commonly observed, focal oligemia and peripheral wedge-shaped densities on CXR are well-established findings in PE. Chest CT with IV contrast has become the primary diagnostic imaging test for PE. Ventilation-perfusion lung scanning is primarily used for subjects unable to tolerate IV contrast. Transthoracic echocardiography can identify right ventricular hypokinesis with moderate to large PE, but it is not typically useful for diagnosing the presence of a PE. Transesophageal echocardiography can be used to identify large central PE when IV contrast chest CT scans are not appropriate (e.g., renal failure or severe contrast allergy). With the advent of contrast chest CT scans for PE diagnosis, pulmonary angiography studies are rarely performed.

Integrated Diagnostic Approach

An integrated diagnostic approach that considers the clinical suspicion for DVT and PE is required. For individuals with a low clinical likelihood of DVT or with a low-to-moderate clinical likelihood of PE, the D-dimer level can be used to determine if further imaging studies are required. An algorithm for imaging studies in both DVT and PE is shown in Fig. 133-1. The differential diagnosis of DVT includes a ruptured Baker's cyst and cellulitis. The differential diagnosis of PE is broad and includes pneumonia, acute myocardial infarction, and aortic dissection.

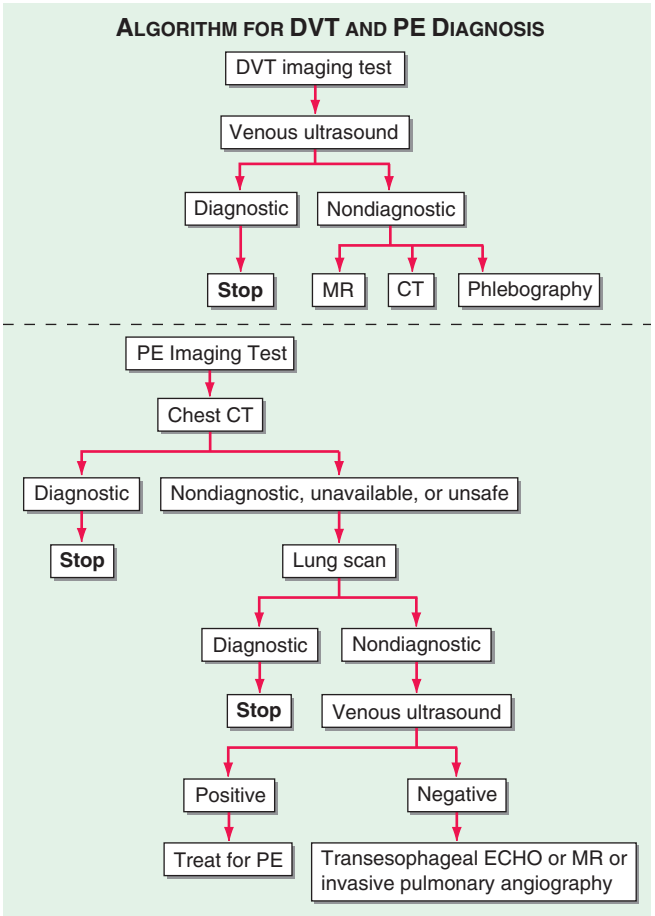


FIGURE 133-1 Imaging tests useful to diagnose DVT and PE. ECHO, echocardiogram.

TREATMENT DEEP-VEIN THROMBOSIS AND PULMONARY THROMBOEMBOLISM

ANTICOAGULATION Although anticoagulants do not dissolve existing clots in DVT or PE directly, they limit further thrombus formation and allow fibrinolysis to occur. Three general approaches can be used for anticoagulation in DVT and PE: (1) Parenteral therapy with transition to warfarin; (2) parenteral therapy with transition to an oral anticoagulant such as dabigatran or edoxaban; or (3) oral anticoagulation with rivaroxaban or apixaban without parenteral anticoagulation.

Traditionally, intravenous unfractionated heparin (UFH) has been used, with a target activated partial thromboplastin time (aPTT) of 60–80 s. UFH is typically administered with a bolus of 80 U/kg followed by a continuous infusion of approximately 18 U/kg per hour. Frequent dosage adjustments are often required to achieve and maintain a therapeutic aPTT with UFH. Heparin-induced

thrombocytopenia can occur with UFH. However, the short half-life of UFH remains a significant advantage.

Alternatives to UFH for acute anticoagulation include low-molecular-weight heparins (LMWHs) such as enoxaparin and dalteparin. Laboratory monitoring is not required, but doses are adjusted for renal impairment or obesity. Fondaparinux, a synthetic parenteral alternative to UFH, does not require laboratory monitoring but does require dose adjustment for body weight and renal insufficiency. In pts with heparin-induced thrombocytopenia, direct thrombin inhibitors (e.g., argatroban or bivalirudin) should be used.

After initiating treatment with a parenteral agent, warfarin is typically used for long-term oral anticoagulation. Warfarin can be initiated soon after a parenteral agent is given; however, at least 5 days are required for warfarin to achieve therapeutic anticoagulation. Warfarin is given to achieve a therapeutic international normalized ratio (INR) of the prothrombin time, which is typically an INR of 2.0–3.0. Pts vary widely in their required warfarin doses due to effects of genetics, diet, and other drugs; dosing often begins at 5 mg/d, with adjustment based on the INR.

Novel oral anticoagulants, including rivaroxaban, apixaban, and dabigatran, have the advantages of fixed dose regimens, rapid onset of effective anticoagulation, no laboratory monitoring, and fewer drug and dietary interactions. However, anticoagulation with these Factor Xa or thrombin inhibitors is not readily reversed (with the exception of dabigatran, which has been shown in one study to be reversed by idarucizumab [Pollack C et al., N Engl J Med 2015;373:511-520]).

The most troublesome adverse event from anticoagulation treatment is hemorrhage. For severe hemorrhage while undergoing treatment with UFH or LMWH, protamine can be given to reverse anticoagulation. Severe bleeding while anticoagulated with warfarin can be treated with prothrombin complex concentrate; milder hemorrhage or markedly elevated INR values can be treated with vitamin K. Warfarin should be avoided in pregnant pts.

The duration of anticoagulation for an initial DVT or PE is at least 3–6 months. Pts with DVT or PE in the setting of trauma, surgery, indwelling central venous catheters, or high estrogen states have a low recurrence rate after 3–6 months of anticoagulation. However, recurrence rate is high in pts with cancer or with idiopathic, unprovoked DVT or PE, and prolonged anticoagulation should be considered. Recurrent DVT or PE typically requires lifelong anticoagulation.

OTHER TREATMENT MODALITIES

Although anticoagulation is the mainstay of therapy for venous thromboembolism, additional therapeutic modalities also can be employed, based on risk stratification (**Fig. 133-2**). Inferior vena cava filters can be used if thrombosis recurs despite adequate anticoagulation or if active bleeding precludes anticoagulation. Fibrinolytic therapy (often with tissue plasminogen activator) should be considered for PE causing right heart failure, although the risk of hemorrhage is significant. Surgical or catheter embolectomy also can be considered for massive PE. Low-dose, catheter-directed thrombolysis can be used for pts with extensive femoral, iliofemoral, or upper extremity DVT.

If PE pts develop chronic thromboembolic pulmonary hypertension, surgical intervention (pulmonary thromboendarterectomy) can be performed.

To reduce the severity of postthrombotic syndrome, below-knee graduated compression stockings can be used for 2 years after a DVT.

Prevention of DVT and PE in hospitalized pts is often performed with low-dose UFH or LMWH. After cancer surgery or hip or knee replacement operations, pharmacological prophylaxis is usually performed for at least 4 weeks.

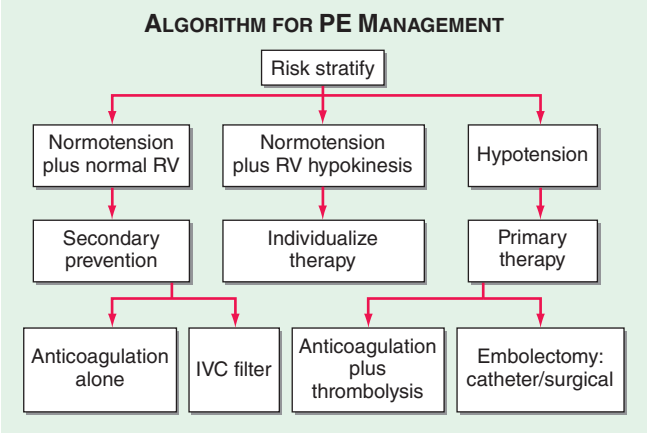


FIGURE 133-2 Acute management of pulmonary thromboembolism.

For a more detailed discussion, see Goldhaber SZ: Deep Venous Thrombosis and Pulmonary Thromboembolism, Chap. 300, p. 1631, in HPIM-19.

134 Interstitial Lung Disease

Interstitial lung diseases (ILDs) are a group of >200 disease entities characterized by diffuse lung parenchymal abnormalities. ILDs can be classified into two major groups: (1) diseases associated with predominant inflammation and fibrosis, and (2) diseases with predominantly granulomatous reaction in interstitial or vascular areas (Table 134-1). ILDs are nonmalignant and noninfectious, and they are typically chronic. The differential diagnosis of ILDs often includes infections (e.g., atypical mycobacteria, fungi) and malignancy (e.g., lymphangitic carcinomatosis). One of the most common ILDs associated with a granulomatous reaction, sarcoidosis, is discussed in Chap. 166. Many ILDs are of unknown etiology; however, some ILDs are known to be associated with specific environmental exposures including asbestos, radiation therapy, and organic dusts.

APPROACH TO THE PATIENT: Interstitial Lung Disease

History: Common presenting symptoms for pts with ILDs include dyspnea and nonproductive cough. Symptom onset and duration can assist in the differential

TABLE 134-1 MAJOR CATEGORIES OF ALVEOLAR AND INTERSTITIAL INFLAMMATORY LUNG DISEASE

Lung Response: Alveolitis, Interstitial Inflammation, and Fibrosis	
Known cause	
Asbestos	Radiation
Fumes, gases	Aspiration pneumonia
Drugs (antibiotics, amiodarone, gold) and chemotherapy drugs	Residual of adult respiratory distress syndrome
Smoking-related	
Desquamative interstitial pneumonia	
Respiratory bronchiolitis-associated interstitial lung disease	
Langerhans cell granulomatosis (eosinophilic granulomatosis of the lung)	
Unknown cause	
Idiopathic interstitial pneumonias	Pulmonary alveolar proteinosis
Idiopathic pulmonary fibrosis (usual interstitial pneumonia)	Lymphocytic infiltrative disorders (lymphocytic interstitial pneumonitis associated with connective tissue disease)
	Eosinophilic pneumonias
Acute interstitial pneumonia (diffuse alveolar damage)	Lymphangioleiomyomatosis
	Amyloidosis
Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia)	Inherited diseases
	Tuberous sclerosis, neurofibromatosis, Niemann-Pick disease, Gaucher's disease, Hermansky-Pudlak syndrome
Nonspecific interstitial pneumonia	
Connective tissue diseases	Gastrointestinal or liver diseases (Crohn's disease, primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis)
Systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, Sjögren's syndrome, polymyositis-dermatomyositis	Graft-versus-host disease (bone marrow transplantation; solid organ transplantation)
Pulmonary hemorrhage syndromes	
Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, isolated pulmonary capillaritis	

(*Continued*)

TABLE 134-1 MAJOR CATEGORIES OF ALVEOLAR AND INTERSTITIAL INFLAMMATORY LUNG DISEASE (*CONTINUED*)

Lung Response: Granulomatous	
Known cause	
Hypersensitivity pneumonitis (organic dusts)	Inorganic dusts: beryllium, silica
Unknown cause	
Sarcoidosis	Bronchocentric granulomatosis
Granulomatous vasculitides	Lymphomatoid granulomatosis
Granulomatosis with polyangiitis (Wegener's), allergic granulomatosis of Churg-Strauss	

diagnosis. Chronic symptoms (over months to years) are typically seen in most ILDs, including idiopathic pulmonary fibrosis (IPF), pneumoconioses, connective tissue diseases, and pulmonary Langerhans cell histiocytosis (PLCH or eosinophilic granuloma). Subacute symptoms (over weeks to months) can also be observed in many ILDs, especially in sarcoidosis, drug-induced ILDs, cryptogenic organizing pneumonitis (COP, also known as bronchiolitis obliterans with organizing pneumonia [BOOP]), and alveolar hemorrhage syndromes. Acute presentations are uncommon for ILDs but are typically observed with acute interstitial pneumonia (AIP), and they can also occur with eosinophilic pneumonia and hypersensitivity (HS) pneumonitis. Sudden onset of dyspnea can indicate a pneumothorax, which occurs in PLCH and tuberous sclerosis/lymphangioleiomyomatosis. Fatigue and weight loss are common in all ILDs. Episodic presentations also are unusual, but they are more typical for eosinophilic pneumonia, hypersensitivity pneumonitis, pulmonary hemorrhage, Churg-Strauss syndrome, and COP.

Age at presentation also can guide the differential diagnosis. IPF pts typically present at age >60, while sarcoidosis, PLCH, lymphangioleiomyomatosis (LAM), and connective tissue disease–related ILD often present between the ages of 20 and 40. LAM occurs exclusively in women, while IPF and ILD in rheumatoid arthritis (RA) occur more often in men. Cigarette smoking is a risk factor for several ILDs including IPF, PLCH, Goodpasture syndrome, pulmonary alveolar proteinosis (PAP), and respiratory bronchiolitis/desquamative interstitial pneumonia. Occupational exposures and hobbies can be important risk factors for many types of hypersensitivity pneumonitis as well as pneumoconioses. Previous medical treatment with radiation and drugs also should be assessed.

Physical examination: Tachypnea and bibasilar end-inspiratory crackles are commonly observed in inflammatory ILDs, but they are less frequent in granulomatous ILDs. Clubbing of the digits is observed in some pts with advanced ILD.

Laboratory studies: Antinuclear antibodies and rheumatoid factor at low titers are observed in some IPF pts without a connective tissue disorder. Specific serum antibodies can confirm exposure to relevant antigens in hypersensitivity pneumonitis, but they do not prove causation. Anti-GM-CSF antibodies are diagnostic of acquired PAP.

Chest imaging: Chest x-ray (CXR) does not typically provide a specific diagnosis but often raises the possibility of ILD by demonstrating a bibasilar reticular pattern. Upper-lung-zone predominance of nodular opacities is noted in several

ILDs, including PLCH, sarcoidosis, chronic hypersensitivity pneumonitis, and silicosis. High-resolution chest CT scans provide improved sensitivity for the early detection of ILDs and may be sufficiently specific to allow a diagnosis to be made in ILDs such as IPF, PLCH, and asbestosis. Honeycombing is indicative of advanced fibrosis.

Pulmonary function testing: Lung function measurements can assess the extent of pulmonary involvement in pts with ILD. Most ILDs produce a restrictive ventilatory defect with reduced total lung capacity. The forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) are typically reduced, but the ratio of FEV_1/FVC is usually normal to increased. Reduction in the diffusing capacity of the lung for carbon monoxide (DL_{CO}) is commonly observed. Cardiopulmonary exercise testing and 6-minute walk testing can be useful to detect exercise-induced hypoxemia and to monitor disease activity and response to treatment.

Tissue and cellular examination: In order to provide a specific diagnosis and assess disease activity, lung biopsy is often required. Bronchoscopy with transbronchial biopsies can be diagnostic in some ILDs, including sarcoidosis and eosinophilic pneumonia. In addition, bronchoscopy can assist by excluding chronic infections or lymphangitic carcinomatosis. However, the more extensive tissue samples provided by open lung biopsies, typically obtained by video-assisted thoracic surgery, are often required to establish a specific diagnosis. Evidence for diffuse end-stage disease, such as widespread honeycombing, or other major operative risks are relative contraindications to lung biopsy procedures.

PRINCIPLES OF MANAGEMENT

If a causative agent can be identified (e.g., thermophilic actinomyces in hypersensitivity pneumonitis), cessation of exposure to that agent is imperative. Because the response to treatment among different ILDs is so variable, identification of treatable causes is essential. Glucocorticoids can be highly effective for eosinophilic pneumonias, COP, hypersensitivity pneumonitis (HP), acute radiation pneumonitis, and drug-induced ILD. Prednisone at 0.5–1.0 mg/kg per day is commonly given for 4–12 weeks, followed by a gradual tapering dose. On the other hand, glucocorticoids are usually not beneficial in IPF. Smoking cessation is essential, especially for smoking-related ILDs such as PLCH and respiratory bronchiolitis.

Supportive therapeutic measures include providing supplemental O_2 for pts with significant hypoxemia (Pa_{O2} <55 mmHg at rest and/or with exercise). Pulmonary rehabilitation is often beneficial. For younger pts with end-stage ILD, lung transplantation should be considered.

SELECTED INDIVIDUAL ILDS

Idiopathic Pulmonary Fibrosis

IPF, which is also known as usual interstitial pneumonia (UIP), is the most common idiopathic interstitial pneumonia. Cigarette smoking is a risk factor for IPF. Common respiratory symptoms include exertional dyspnea and a nonproductive cough. Physical examination is notable for inspiratory crackles at the lung bases. Clubbing may occur. High-resolution chest CT scans show subpleural reticular opacities predominantly in the lower lung fields, which are associated with honeycombing in advanced disease. Surgical lung biopsy is usually required to confirm the diagnosis, although pts with classic UIP patterns on CT scan may not require a biopsy. IPF can include acute exacerbations characterized by accelerated clinical deterioration over days to weeks. IPF is poorly responsive to available

pharmacologic treatment, although recent studies have suggested benefit from pirfenidone and nintedanib.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is a histologic pattern that can be observed in connective tissue disease, drug-induced ILD, and chronic HP. NSIP is a subacute restrictive process with similar presentation to IPF. High-resolution CT (HRCT) shows bilateral ground-glass opacities, and honeycombing is rare. Unlike IPF, NSIP pts have a good prognosis and typically respond well to systemic glucocorticoid treatment.

ILD Associated with Connective Tissue Disorders

Pulmonary manifestations may precede systemic manifestations of a connective tissue disorder. In addition to direct pulmonary involvement, it is necessary to consider complications of therapy (e.g., opportunistic infections), respiratory muscle weakness, esophageal dysfunction, and associated malignancies as contributors to pulmonary parenchymal abnormalities in pts with connective tissue disorders.

Progressive systemic sclerosis (scleroderma) commonly includes ILD as well as pulmonary vascular disease. Lung involvement tends to be highly resistant to available treatment.

In addition to pulmonary fibrosis (ILD), RA can involve a range of pulmonary complications, including pleural effusions, pulmonary nodules, and pulmonary vasculitis. ILD in RA pts is more common in men.

Systemic lupus erythematosus (SLE) also can involve a range of pulmonary complications, including pleural effusions, pulmonary vascular disease, pulmonary hemorrhage, and BOOP. Chronic, progressive ILD is not commonly observed.

Except for progressive systemic sclerosis, connective tissue-related ILD is typically treated with systemic glucocorticoids, often along with an immunosuppressive agent.

Cryptogenic Organizing Pneumonia

When the BOOP pathologic pattern occurs without another primary pulmonary disorder, the term *cryptogenic organizing pneumonia* (*COP*) is used. COP may present with a flu-like illness. Recurrent and migratory pulmonary opacities are common. Glucocorticoid therapy is often effective.

Desquamative Interstitial Pneumonia and Respiratory Bronchiolitis-Associated ILD

Desquamative interstitial pneumonia (DIP) includes extensive macrophage accumulation in intraalveolar spaces with minimal fibrosis. It is seen almost exclusively in cigarette smokers and improves with smoking cessation. Respiratory bronchiolitis-associated ILD is a subset of DIP that includes bronchial wall thickening, ground-glass opacities, and air trapping on HRCT; it also resolves in most pts after smoking cessation.

Pulmonary Alveolar Proteinosis

PAP is a rare diffuse lung disease, with a male predominance, that involves the accumulation of lipoproteinaceous material in the distal airspaces, rather than a classic ILD. More common in males, PAP usually presents insidiously, with dyspnea, fatigue, weight loss, cough, and low-grade fever. Whole-lung lavage is often of therapeutic benefit.

Pulmonary Infiltrates with Eosinophilia

Several disorders are characterized by pulmonary infiltrates and peripheral blood eosinophilia. Acute eosinophilic pneumonia involves fevers and diffuse

pulmonary eosinophilic infiltrates with severe hypoxemia. Chronic eosinophilic pneumonia is often in the differential diagnosis with other ILDs; it includes low-grade fever, cough, dyspnea, and weight loss, with a CXR notable for peripheral lung infiltrates. Eosinophilic pneumonias tend to be rapidly responsive to glucocorticoid therapy. Churg-Strauss syndrome, also known as eosinophilic granulomatosis with polyangiitis, occurs in asthmatics and includes eosinophilic vasculitis with multiorgan system involvement. Parasitic infections can cause Löffler syndrome, which includes migratory pulmonary infiltrates and self-limited clinical symptoms, and tropical eosinophilia. Multiple medications can also cause pulmonary eosinophilia.

Alveolar Hemorrhage Syndromes

A variety of diseases can cause diffuse alveolar hemorrhage, including systemic vasculitic syndromes (e.g., granulomatosis with polyangiitis [Wegener's]), connective tissue diseases (e.g., SLE), and Goodpasture syndrome. Although typically an acute process, recurrent episodes can lead to pulmonary fibrosis. Hemoptysis may not occur initially in one-third of cases. CXR typically shows patchy or diffuse alveolar opacities. The DLCO may be increased. High doses of IV methylprednisolone are typically required, followed by gradual tapering of systemic steroid doses. Plasmapheresis may be effective for Goodpasture syndrome.

Pulmonary Langerhans Cell Histiocytosis

PLCH is a smoking-related diffuse lung disease that typically affects men 20–40 years of age. Presenting symptoms often include cough, dyspnea, chest pain, weight loss, and fever. Pneumothorax occurs in 25% of pts. High-resolution chest CT scan reveals upper-zone-predominant nodular opacities and thin-walled cysts, which are virtually diagnostic of this disorder. Smoking cessation is the key therapeutic intervention.

Hypersensitivity Pneumonitis

HP is an inflammatory lung disorder caused by repeated inhalation of an organic antigen in a susceptible individual. Many different antigens have been implicated. Clinical presentations can be acute, with cough, fever, malaise, and dyspnea developing within 4–8 h after exposure; subacute, with cough and dyspnea that can become progressively worse over weeks; and chronic, which can appear similar to IPF. Serum precipitins can be measured as an indicator of an environmental exposure. Although helpful in implicating specific agents, the presence of a specific serum precipitin is not diagnostic since many exposed individuals without HP will have such precipitins; false-negative results can also occur. Diagnosis is made based on symptoms, physical findings, pulmonary function tests (restrictive or obstructive pattern), and radiographic studies (chest CT scans typically show ground-glass opacification in acute and subacute forms) that are consistent with HP; history of exposure to a recognized antigen; and presence of an antibody to that antigen. In some cases, lung biopsy (transbronchial or open lung) may be required to confirm the diagnosis. Treatment involves avoiding exposure to the causative antigen; systemic corticosteroids may be required in subacute or chronic HP.



For a more detailed discussion, see King TE Jr: Interstitial Lung Diseases, Chap. 315, p. 1708; Akuthota P, Wechsler ME: Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia, Chap. 310, p. 1681, in HPIM-19.

135 Diseases of the Pleura and Mediastinum

PLEURAL EFFUSION

Pleural effusion is defined as excess fluid accumulation in the pleural space. The two major classes of pleural effusions are transudates, which are caused by systemic influences on pleural fluid formation or resorption, and exudates, which are caused by local influences on pleural fluid formation and resorption. Common causes of transudative effusions are left ventricular heart failure, cirrhosis, and nephrotic syndrome. Common causes of exudative effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism. A more comprehensive list of the etiologies of transudative and exudative pleural effusions is provided in Table 135-1. Additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

Exudates fulfill at least one of the following three criteria: high pleural fluid/serum protein ratio (>0.5), pleural fluid lactate dehydrogenase (LDH) greater than two-thirds of the laboratory normal upper limit for serum LDH, or pleural/serum LDH ratio >0.6. Transudative effusions typically do not meet any of these criteria. However, these criteria misidentify about 25% of transudates as exudates. For exudative effusions, pleural fluid should also be tested for pH, glucose, white blood cell count with differential, microbiologic studies, cytology, and amylase. An algorithm for determining the etiology of a pleural effusion is presented in Fig. 135-1.

TABLE 135-1 DIFFERENTIAL DIAGNOSES OF PLEURAL EFFUSIONS

Transudative Pleural Effusions

1. Congestive heart failure
2. Cirrhosis
3. Pulmonary embolism (Note: Effusion usually is exudative)
4. Nephrotic syndrome
5. Peritoneal dialysis
6. Superior vena cava obstruction
7. Myxedema
8. Urinothorax

Exudative Pleural Effusions

1. Neoplastic diseases
   a. Metastatic disease
   b. Mesothelioma
2. Infectious diseases
   a. Bacterial infections
   b. Tuberculosis
   c. Fungal infections
   d. Viral infections
   e. Parasitic infections

(*Continued*)

TABLE 135-1 DIFFERENTIAL DIAGNOSES OF PLEURAL EFFUSIONS (*CONTINUED*)

3. Pulmonary embolism
4. Gastrointestinal disease
   a. Esophageal perforation
   b. Pancreatic disease
   c. Intraabdominal abscess
   d. Diaphragmatic hernia
   e. After abdominal surgery
   f. Endoscopic variceal sclerotherapy
   g. After liver transplant
5. Collagen-vascular diseases
   a. Rheumatoid pleuritis
   b. Systemic lupus erythematosus
   c. Drug-induced lupus
   d. Immunoblastic lymphadenopathy
   e. Sjögren's syndrome
   f. Granulomatosis with polyangiitis (Wegener's)
   g. Churg-Strauss syndrome
6. Post-coronary artery bypass surgery
7. Asbestos exposure
8. Sarcoidosis
9. Uremia
10. Meigs' syndrome
11. Yellow nail syndrome
12. Drug-induced pleural disease
    a. Nitrofurantoin
    b. Dantrolene
    c. Methysergide
    d. Bromocriptine
    e. Procarbazine
    f. Amiodarone
    g. Dasatinib
13. Trapped lung
14. Radiation therapy
15. Post-cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

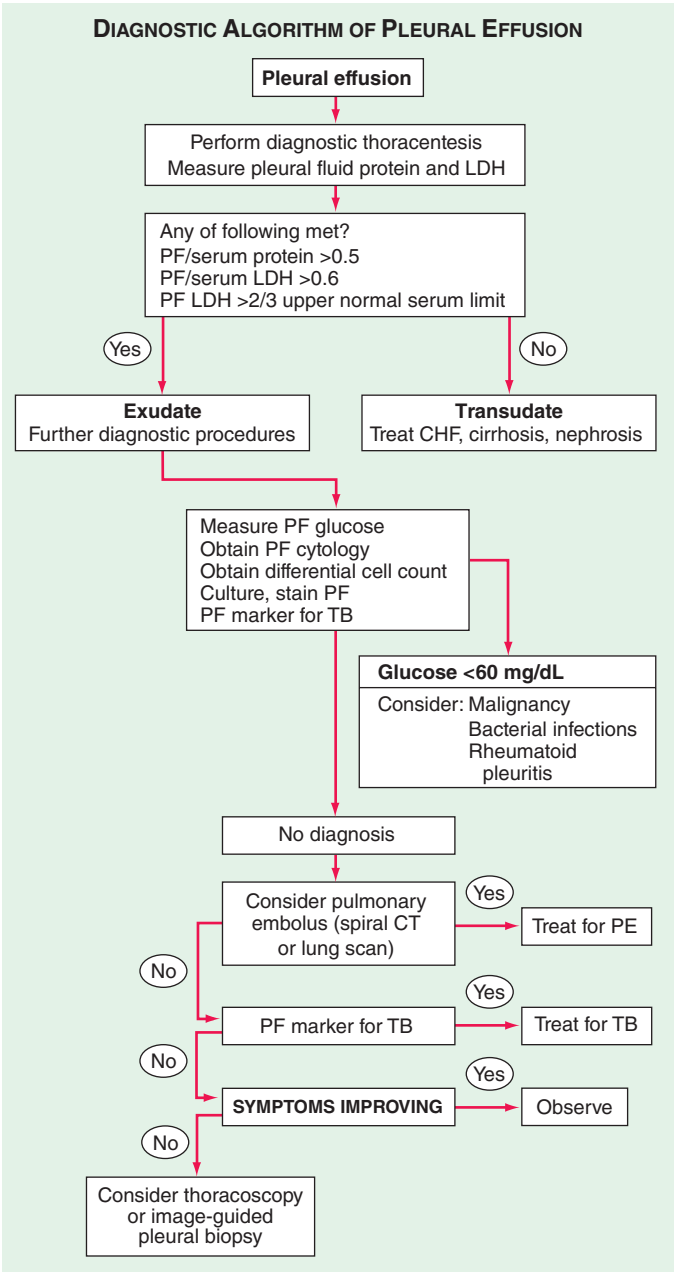


FIGURE 135-1 Approach to the diagnosis of pleural effusions. PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

PNEUMOTHORAX

Pneumothorax (Ptx) is defined as gas in the pleural space. Spontaneous Ptx occurs without trauma to the thorax. Primary spontaneous Ptx occurs in the absence of underlying lung disease and typically results from apical pleural blebs. Simple aspiration may be adequate treatment for an initial primary spontaneous Ptx, but recurrence typically requires thoracoscopic intervention. Secondary spontaneous Ptx occurs in the setting of underlying lung disease, most commonly chronic obstructive pulmonary disease. Chest tube placement is typically required for secondary spontaneous Ptx; thoracoscopy and/or pleurodesis (with pleural abrasion or a sclerosing agent) should also be considered.

Traumatic Ptx, resulting from either penetrating or nonpenetrating chest trauma, usually requires chest tube placement. Iatrogenic Ptx can occur from transthoracic needle biopsy, thoracentesis, placement of a central venous catheter, or transbronchial biopsy. Treatment with O_2 or aspiration is often adequate for iatrogenic Ptx, but chest tube placement may be required. Tension Ptx can result from trauma or mechanical ventilation. Positive pleural pressure in mechanical ventilation can rapidly lead to a tension Ptx with reduced cardiac output. Urgent treatment is required, either with a chest tube or, if not immediately available, with a large-bore needle inserted into the pleural space through the second anterior intercostal space.

MEDIASTINAL DISEASE

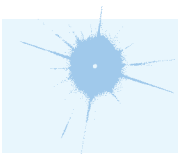
Mediastinitis

Mediastinitis can be an acute or chronic process. Acute mediastinitis can result from esophageal perforation or after cardiac surgery with median sternotomy. Esophageal perforation can occur spontaneously or iatrogenically; surgical exploration of the mediastinum, repair of the esophageal perforation, and drainage of the pleural space and mediastinum are required. Mediastinitis after median sternotomy typically presents with wound drainage and is diagnosed by mediastinal needle aspiration. Treatment requires immediate drainage, debridement, and IV antibiotics.

Mediastinal Masses

Different types of mediastinal masses are found in the anterior, middle, and posterior mediastinal compartments. The most common mass lesions in the anterior mediastinum are thymomas, lymphomas, teratomas, and thyroid lesions. In the middle mediastinum, vascular masses, enlarged lymph nodes (e.g., metastatic cancer or granulomatous disease), and bronchogenic or pleuropericardial cysts are found. Posterior mediastinal masses include neurogenic tumors, gastroenteric cysts, and esophageal diverticula.

Chest CT scans are invaluable for evaluating mediastinal masses. Biopsy procedures are typically required to diagnose mediastinal masses; needle biopsy procedures (e.g., percutaneous or bronchoscopy), mediastinoscopy, and thoracoscopy are potential options.



For a more detailed discussion, see Light RW: Disorders of the Pleura, Chap. 316, p. 1716; Light RW: Disorders of the Mediastinum, Chap. 317, p. 1719, in HPIM-19.

136 Disorders of Ventilation

DEFINITION

Ventilatory disorders, reflected by abnormalities in $PaCO_2$, include alterations in CO_2 production, minute ventilation, or respiratory system dead space. Many diseases can cause acute elevations in CO_2 production; chronic ventilatory disorders typically relate to inappropriate minute ventilation or dead space fraction.

HYPOVENTILATION

ETIOLOGY

Chronic hypoventilation can result from parenchymal lung diseases, chest wall abnormalities (e.g., severe kyphoscoliosis), sleep-disordered breathing, neuromuscular diseases, and abnormal respiratory drive. Obesity-hypoventilation syndrome (OHS) is diagnosed by body mass index ≥30 kg/m^2 and $PaCO_2$ >45 mmHg in the absence of other causes of hypercapnia. Sleep-disordered breathing, typically obstructive sleep apnea, is seen in most OHS pts. Central hypoventilation syndrome is a rare disorder that includes a failure of the normal respiratory response to hypoxemia and/or hypercapnia.

CLINICAL ASSESSMENT

Key symptoms of hypoventilation can include exertional dyspnea, orthopnea, daytime somnolence, morning headache, and anxiety. Parenchymal lung diseases, such as chronic obstructive pulmonary disease and interstitial lung disease, often include dyspnea and cough. Sleep-disordered breathing includes daytime somnolence, snoring, and fragmented sleep. Orthopnea is common in neuromuscular disorders, although weakness of the extremities or other muscle groups often precedes respiratory system muscular weakness. Hypoventilation related to neuromuscular and chest wall disorders typically begins with nocturnal hypoventilation and progresses to daytime hypercapnia. Chronic narcotic use and hypothyroidism can lead to reduced respiratory drive.

Physical examination, chest radiographic studies (CXR and possibly chest CT), and pulmonary function tests reveal most lung parenchymal and chest wall causes of hypoventilation. Measurements of maximal inspiratory and expiratory pressures or forced vital capacity can assess and monitor respiratory muscle strength. Polysomnography to assess for sleep-disordered breathing should also be considered. When pts have hypercapnia with normal pulmonary function, normal respiratory muscle strength, and normal alveolar-arterial PO_2 difference, respiratory drive abnormalities may be present, which can be revealed by polysomnography. Laboratory findings include increased $PaCO_2$ and often reduced PaO_2 as well. Compensatory increases in plasma bicarbonate levels and normal pH are seen in chronic hypoventilation. Eventually, pulmonary hypertension and cor pulmonale can develop. In central hypoventilation syndrome, hypercapnia worsens substantially during sleep.

TREATMENT HYPOVENTILATION

In all forms of hypoventilation, supplemental oxygen should be given to correct hypoxemia. OHS is treated with weight reduction and nocturnal noninvasive positive pressure ventilation (NIPPV). Continuous positive airway pressure (CPAP)

during sleep is adequate treatment for many OHS pts, but others require bilevel positive airway pressure (BiPAP).

Noninvasive positive pressure ventilation during sleep can provide ventilatory support and treat sleep apnea associated with neuromuscular disorders, chest wall disorders, and central hypoventilation. With progressive neuromuscular disorders, full-time mechanical ventilatory support is often required. Pts with respiratory drive disorders may benefit from phrenic nerve or diaphragm pacing.

HYPERVENTILATION

ETIOLOGY

Hyperventilation is caused by ventilation in excess of requirements based on CO_2 production, leading to a reduced $PaCO_2$. Although anxiety can contribute to the initiation and progression of hyperventilation, hyperventilation is not always related to anxiety. Hyperventilation can precede systemic illnesses such as diabetic ketoacidosis.

CLINICAL ASSESSMENT

Symptoms of chronic hyperventilation can include dyspnea, paresthesias, headache, tetany, visual disturbances, and atypical chest pain. Laboratory findings of chronic hyperventilation include a reduced $PaCO_2$, but low serum bicarbonate level and near normal pH on arterial blood gas analysis.

TREATMENT HYPERVENTILATION

Treatment of chronic hyperventilation is problematic. Identification of initiating factors and excluding alternative diagnoses can be helpful.

For a more detailed discussion, see McConville JF, Mokhlesi B, Solway J: Disorders of Ventilation, Chap. 318, p. 1720, in HPIM-19.

137 Sleep Apnea

DEFINITION AND ETIOLOGY

Sleep apnea is defined by the presence of at least five episodes per hour of apnea (no airflow for ≥10 seconds) and/or hypopnea (reduction in airflow by at least 30% from baseline for ≥10 seconds accompanied by oxygen desaturation or arousal from sleep). Obstructive sleep apnea/hypopnea syndrome (OSAHS) is caused by upper airway closure during inspiration, punctuated by brief arousals that terminate apneic episodes. Risk factors for OSAHS include obesity, craniofacial factors such as micrognathia, family history of OSAHS, and male sex. Hypothyroidism and acromegaly are systemic diseases associated with OSAHS. OSAHS increases the risk of multiple

cardiovascular conditions, including coronary artery disease, heart failure, stroke, and arrhythmias.

Central sleep apnea (CSA) is characterized by respiratory pauses during sleep related to absence of respiratory effort. CSA is less common than OSAHS but may occur in conjunction with it. CSA is commonly found in heart failure and stroke pts, but may also occur from opioid medications and hypoxia (e.g., breathing at high altitudes).

CLINICAL ASSESSMENT

Key symptoms of OSAHS include daytime somnolence and nocturnal breathing disturbances (loud snoring, snorting, gasping, or breathing pauses). Other symptoms may include dry mouth, nocturia, morning headaches, and difficulty concentrating. Sleeping partners can provide essential historical information. Depression and hypertension are associated with OSAHS. Differential diagnosis of OSAHS includes insufficient amount of sleep, somnolence related to shift work, depression, drug effects (both stimulants and sedatives), narcolepsy, and idiopathic hypersomnolence.

Severity of OSAHS is based on the frequency of breathing disturbances (apnea-hypopnea index), duration of apneas and hypopneas, amount of oxygen desaturation during respiratory disturbances, degree of sleep fragmentation, and intensity of daytime somnolence.

Physical examination should include assessment of body mass index, jaw and upper airway structure, and blood pressure. Potentially related systemic illnesses, including acromegaly and hypothyroidism, should be considered.

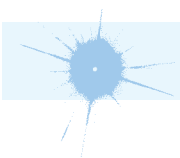
Diagnostic testing often includes a polysomnogram in a sleep laboratory. However, home sleep studies without neurophysiologic monitoring may be used for screening. Significant daytime somnolence with a negative home screening study should be followed by a full polysomnogram.

TREATMENT SLEEP APNEA

In pts with OSAHS, efforts to reduce weight in obese pts, limit alcohol use, optimize sleep duration, regulate sleep schedules, treat nasal allergies, and carefully withdraw sedative medications should be pursued.

The primary therapy for OSAHS is continuous positive airway pressure (CPAP), delivered through a nasal or nasal-oral mask. Selecting a comfortable mask delivery system and titrating the appropriate amount of CPAP are essential. Airway drying related to CPAP can be reduced by including a heated humidification component in the CPAP system. Alternative OSAHS therapies include mandibular repositioning splints (oral devices), which hold the jaw and tongue forward to widen the pharyngeal airway. These devices are typically used for mild OSAHS pts or pts who do not tolerate CPAP. Several types of surgical procedures have been used in OSAHS, including bariatric surgery in obese pts, tonsillectomy, jaw advancement surgery, and pharyngeal surgery. Tracheostomy is curative since it bypasses the upper airway obstruction site, but it is rarely used. No drugs have been proven to reduce apneic events.

Treatment of CSA involves managing any predisposing conditions, such as congestive heart failure. Adaptive servoventilation, which provides variable inspiratory ventilatory support in response to apneas and hypopneas, may be helpful in CSA.



For a more detailed discussion, see Wellman A, Redline S: Sleep Apnea, Chap. 319, p. 1723, in HPIM-19.

138 Acute Renal Failure

DEFINITION

Acute renal failure (ARF) or acute kidney injury (AKI), defined as a measurable increase in the serum creatinine (Cr) concentration (usually relative increase of 50% or absolute increase by 44–88 μmol/L [0.5–1.0 mg/dL]), occurs in ~5–7% of hospitalized pts. It is associated with a substantial increase in in-hospital mortality and morbidity. AKI can be anticipated in some clinical circumstances (e.g., after radiocontrast exposure or major surgery), and there are no specific pharmacologic therapies proven helpful at preventing or reversing the condition. Maintaining optimal renal perfusion and intravascular volume appears to be important in most clinical circumstances; important cofactors in AKI include hypovolemia and drugs that interfere with renal perfusion and/or glomerular filtration (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers).

DIFFERENTIAL DIAGNOSIS

The separation into three broad categories (prerenal, intrinsic renal, and postrenal failure) is of considerable clinical utility (Table 138-1). *Prerenal failure* is most common among hospitalized pts. It may result from true volume depletion (e.g., diarrhea, vomiting, GI or other hemorrhage) or "arterial underfilling," i.e., reduced renal perfusion in the setting of adequate or excess blood volume. Reduced renal perfusion may be seen in congestive heart failure (CHF) (due to reduced cardiac output and/

TABLE 138-1 COMMON CAUSES OF ACUTE KIDNEY INJURY

Prerenal
Volume depletion
Blood loss
GI fluid loss (e.g., vomiting, diarrhea)
Overzealous diuretic use
Volume overload with reduced renal perfusion
Congestive heart failure
Low-output with systolic dysfunction
"High-output" (e.g., anemia, thyrotoxicosis)
Hepatic cirrhosis
Severe hypoproteinemia
Renovascular disease
Drugs
NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, ARBs, cisplatin, aminoglycosides
Other
Hypercalcemia, "third spacing" (e.g., pancreatitis, systemic inflammatory response), hepatorenal syndrome

(*Continued*)

TABLE 138-1 COMMON CAUSES OF ACUTE KIDNEY INJURY (*CONTINUED*)

Intrinsic
ATN
Hypotension or shock, prolonged prerenal azotemia, postoperative sepsis syndrome, rhabdomyolysis, hemolysis, drugs
Radiocontrast, aminoglycosides, cisplatin
Other tubulointerstitial disease
Allergic interstitial nephritis
Pyelonephritis (bilateral, or unilateral in single functional kidney)
Heavy metal poisoning
Atheroembolic disease—after vascular procedures, thrombolysis, or anticoagulation
Glomerulonephritis
1. ANCA-associated: granulomatosis with polyangiitis (GPA), idiopathic pauci-immune GN, PAN
2. Anti-GBM disease; isolated or with pulmonary involvement (Goodpasture's syndrome)
3. Immune complex–mediated
Subacute bacterial endocarditis, SLE, cryoglobulinemia (with or without hepatitis C infection), postinfectious GN (classically poststreptococcal)
IgA nephropathy and Henoch-Schönlein purpura
Glomerular endotheliopathies
Thrombotic microangiopathy, malignant hypertension, scleroderma, antiphospholipid syndrome, preeclampsia
Postrenal (urinary tract obstruction)
Bladder neck obstruction, bladder calculi
Prostatic hypertrophy
Ureteral obstruction due to compression
Pelvic or abdominal malignancy, retroperitoneal fibrosis
Nephrolithiasis
Papillary necrosis with obstruction

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ARBs, angiotensin receptor blockers; ATN, acute tubular necrosis; GBM, glomerular basement membrane; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; PAN, polyarteritis nodosa.

or potent vasodilator therapy), hepatic cirrhosis (due mostly to peripheral vasodilation and arteriovenous shunting), nephrotic syndrome and other states of severe hypoproteinemia (total serum protein <54 g/L [<5.4 g/dL]), and renovascular disease (because of fixed stenosis at the level of the main renal artery or large branch vessels). Several drugs can reduce renal perfusion, most notably NSAIDs. ACE inhibitors and angiotensin II receptor antagonists may reduce glomerular filtration rate but do not tend to reduce renal perfusion.

Causes of *intrinsic renal failure* depend on the clinical setting. Among hospitalized pts, especially on surgical services or in intensive care units, acute tubular necrosis (ATN) is the most common diagnosis. A well-defined ischemic event or toxic exposure (e.g., aminoglycoside therapy) may lead to in-hospital ATN. Alternatively, pts may be admitted to the hospital with ATN associated with rhabdomyolysis; common predisposing factors in rhabdomyolysis include alcoholism, hypokalemia, and various drugs (e.g., statins). Allergic interstitial nephritis, usually due to antibiotics

(e.g., penicillins, cephalosporins, sulfa drugs, quinolones, and rifampin), or NSAIDs, may also be responsible. Radiographic contrast dyes may cause AKI in pts with preexisting kidney disease; the risk is substantially higher in diabetics with chronic kidney disease. Coronary angiography, other vascular procedures, thrombolysis, or anticoagulation may lead to atheroemboli, which cause AKI due to both hemodynamic and inflammatory effects; livedo reticularis, embolic phenomena with preserved peripheral pulses, and eosinophilia are important clues to this diagnosis. Acute glomerulonephritis (Chap. 142) and thrombotic microangiopathies may also cause AKI. Thrombotic microangiopathies can be clinically subdivided into renal-limited forms (e.g., *Escherichia coli*–associated hemolytic uremic syndrome [HUS]) and systemic forms (e.g., thrombotic thrombocytopenic purpura [TTP]). "Atypical HUS," occurring in the absence of HUS-associated bacterial toxins, is associated with hereditary mutations in complement proteins or complement regulatory proteins, leading to exaggerated endothelial sensitivity to complement-mediated cytolysis. A variety of drugs can cause thrombotic microangiopathies, including calcineurin inhibitors (cyclosporine and tacrolimus), quinine, antiplatelet agents (e.g., ticlopidine), inhibitors of the action of vascular endothelial growth factor (VEGF), and chemotherapeutics (e.g., mitomycin C and gemcitabine). Important associated disorders in TTP include HIV infection, bone marrow transplantation, systemic lupus erythematosus (SLE), and antiphospholipid syndrome.

Postrenal failure is due to urinary tract obstruction, which is also more common among ambulatory rather than hospitalized pts. More common in men than women, it is most often caused by ureteral or urethral blockade. Occasionally, stones, sloughed renal papillae, or malignancy (primary or metastatic) may cause more proximal obstruction.

CHARACTERISTIC FINDINGS AND DIAGNOSTIC WORKUP

All pts with AKI manifest some degree of azotemia (increased blood urea nitrogen [BUN] and Cr). Other clinical features depend on the etiology of renal disease. Pts with *prerenal azotemia* due to volume depletion usually demonstrate orthostatic hypotension, tachycardia, low jugular venous pressure, and dry mucous membranes. Pts with prerenal azotemia and CHF ("cardiorenal syndrome") may show jugular venous distention, an S_3 gallop, and peripheral and pulmonary edema. Therefore, the physical examination is critical in the workup of pts with prerenal AKI. In general, the BUN/Cr ratio tends to be high (>20:1), more so with volume depletion and CHF than with cirrhosis. The uric acid may also be disproportionately elevated in noncirrhotic prerenal states (due to increased proximal tubular absorption). Urine chemistries tend to show low urine [Na^+] (<10–20 mmol/L, <10 with hepatorenal syndrome) and a fractional excretion of sodium (FE_{Na}) of <1% (Table 138-2). The urinalysis (UA) typically shows hyaline and a few granular casts, without cells or cellular casts. Renal ultrasonography is usually normal.

Pts with *intrinsic renal disease* present with varying complaints. Glomerulonephritis (GN) is often accompanied by hypertension and mild to moderate edema (associated with Na retention and proteinuria, and sometimes with gross hematuria). An antecedent prodromal illness and/or prominent extrarenal symptoms and signs may occur if GN occurs in the context of a systemic illness, e.g., vasculitis or SLE; these may include hemoptysis or pulmonary hemorrhage (vasculitis and Goodpasture's syndrome), arthralgias/arthritis (vasculitis or SLE), serositis (SLE), and unexplained sinusitis (vasculitis). The urine chemistries may be indistinguishable from those in pts with prerenal failure; in fact, some pts with GN have renal hypoperfusion (due to glomerular inflammation and ischemia) with resultant hyperreninemia leading to acute volume expansion and hypertension. The urine sediment can be very helpful in these cases. Red blood cell (RBC), white blood cell (WBC), and cellular casts are characteristic of GN; RBC casts are rarely seen in other conditions (i.e., they are highly specific). In the setting of inflammatory nephritis (GN or interstitial

TABLE 138-2 URINE DIAGNOSTIC INDICES IN DIFFERENTIATION OF PRERENAL VERSUS INTRINSIC RENAL AZOTEMIA

Diagnostic Index	Typical Findings	
	Prerenal Azotemia	Intrinsic Renal Azotemia
Fractional excretion of sodium (%)[a] $U_{Na} \times P_{Cr}/P_{Na} \times U_{Cr} \times 100$	<1	>1
Urine sodium concentration (mmol/L)	<10	>20
Urine creatinine to plasma creatinine ratio	>40	>20
Urine urea nitrogen to plasma urea nitrogen ratio	>8	<3
Urine specific gravity	>1.018	<1.015
Urine osmolality (mosmol/kg H_2O)	>500	<300
Plasma BUN/creatinine ratio	>20	<10–15
Renal failure index $U_{Na}/U_{Cr}/P_{Cr}$	<1	>1
Urinary sediment	Hyaline casts	Muddy brown granular casts

[a]Most sensitive indices.

Abbreviations: P_{Cr}, plasma creatinine concentration; P_{Na}, plasma sodium concentration; U_{Cr}, urine creatinine concentration; U_{Na}, urine sodium concentration.

nephritis, see below), there may be increased renal echogenicity on ultrasonography. Unlike pts with GN, pts with interstitial diseases are less likely to have hypertension or proteinuria; a notable exception is NSAID-associated acute interstitial nephritis, which can be accompanied by proteinuria due to an associated minimal-change glomerular lesion. Hematuria and pyuria may present on UA. The classic sediment finding in allergic interstitial nephritis is a predominance (>10%) of urinary eosinophils with Wright's or Hansel's stain; however, urinary eosinophils can be increased in several other causes of AKI, such that measurement of urine eosinophils has no diagnostic utility in renal disease. WBC casts may also be seen, particularly in cases of pyelonephritis.

The urinary sediment of pts with ischemic or toxic ATN will characteristically contain pigmented "muddy-brown" granular casts and casts containing tubular epithelial cells; free tubular epithelial cells can also be seen. The FE_{Na} is typically >1% in ATN, but may be <1% in pts with milder, nonoliguric ATN (e.g., from rhabdomyolysis) and in pts with underlying "prerenal" disorders, such as CHF or cirrhosis.

Pts with *postrenal* AKI due to urinary tract obstruction are usually less severely ill than pts with prerenal or intrinsic renal disease, and their presentation may be delayed until azotemia is markedly advanced (BUN >54 μmol/L [150 mg/dL], Cr >1060–1325 μmol/L [12–15 mg/dL]). An associated impairment of urinary concentrating ability often "protects" the pt from complications of volume overload. Urinary electrolytes typically show an FE_{Na} >1%, and microscopic examination of the urinary sediment is usually bland. Ultrasonography is the key initial diagnostic tool. More than 90% of pts with postrenal AKI show obstruction of the urinary collection system on ultrasound (e.g., dilated ureter, calyces); false negatives include hyperacute obstruction and encasement of the ureter and/or kidney by tumor or of the ureter by retroperitoneal fibrosis, functionally obstructing urinary outflow without structural dilation. Other imaging techniques, such as a furosemide renogram (MAG3 nuclear

medicine study), may be required to define better the presence or absence of obstructive uropathy.

TREATMENT ACUTE RENAL FAILURE

Treatment should focus on providing etiology-specific supportive care. For example, pts with prerenal failure due to GI fluid loss may experience relatively rapid correction of AKI after the administration of IV fluid to expand volume. The same treatment in prerenal pts with CHF would be counterproductive; in this case, treatment of the underlying disease with vasodilators and/or inotropic agents would more likely be of benefit.

There are relatively few intrinsic renal causes of AKI for which there is safe and effective therapy. GN associated with vasculitis or SLE may respond to high-dose glucocorticoids and cytotoxic agents (e.g., cyclophosphamide); plasmapheresis and plasma exchange may be useful in other selected circumstances (e.g., Goodpasture's syndrome and HUS/TTP, respectively). Antibiotic therapy may be sufficient for the treatment of AKI associated with pyelonephritis or endocarditis. There are conflicting data regarding the utility of glucocorticoids in allergic interstitial nephritis. Many practitioners advocate their use with clinical evidence of progressive renal insufficiency despite discontinuation of the offending drug, or with biopsy evidence of potentially reversible, severe disease.

The treatment of urinary tract obstruction often involves consultation with a urologist. Interventions as simple as Foley catheter placement or as complicated as multiple ureteral stents and/or nephrostomy tubes may be required.

DIALYSIS FOR AKI AND RECOVERY OF RENAL FUNCTION

Most cases of community- and hospital-acquired AKI resolve with conservative supportive measures, time, and patience. If nonprerenal AKI continues to progress, dialysis must be considered. The traditional indications for dialysis—volume overload refractory to diuretic agents; hyperkalemia; encephalopathy not otherwise explained; pericarditis, pleuritis, or other inflammatory serositis; and severe metabolic acidosis, compromising respiratory or circulatory function—can seriously compromise recovery from acute nonrenal illness. Therefore, dialysis should generally be provided in advance of these complications. The inability to provide requisite fluids for antibiotics, inotropes and other drugs, and/or nutrition should also be considered an indication for acute dialysis.

Dialytic options for AKI include (1) intermittent hemodialysis (IHD), (2) peritoneal dialysis (PD), and (3) continuous renal replacement therapy (CRRT, i.e., continuous arteriovenous or venovenous hemodiafiltration). Most pts are treated with IHD. It is unknown whether conventional thrice-weekly hemodialysis is sufficient or more frequent treatments are required. Few centers rely on PD for management of AKI (risks include infection associated with intraperitoneal catheter insertion and respiratory compromise due to abdominal distention). At some centers, CRRT is prescribed only in pts intolerant of IHD, usually because of hypotension; other centers use it as the modality of choice for pts in intensive care units. Hybrid hemodialysis techniques, such as slow low-efficiency dialysis (SLED), are equally effective and may be used in centers in which CRRT is not employed.



For a more detailed discussion, see Liu KD, Chertow GM: Dialysis in the Treatment of Acute Renal Failure, Chap. 336, p. 1822, in HPIM-19.

139 Chronic Kidney Disease and Uremia

EPIDEMIOLOGY

The prevalence of chronic kidney disease (CKD), generally defined as a long-standing, irreversible impairment of kidney function, is substantially greater than the number of pts with end-stage renal disease (ESRD), now ≥500,000 in the United States. There is a spectrum of disease related to decrements in renal function; clinical and therapeutic issues differ greatly depending on whether the glomerular filtration rate (GFR) reduction is moderate (stage 3 CKD, 30–59 mL/min per 1.73 m^2) (see Table 46-1), severe (stage 4 CKD, 15–29 mL/min per 1.73 m^2), or "end-stage renal disease" (stage 5 CKD, <15 mL/min per 1.73 m^2). Dialysis is usually required once GFR <10 mL/min per 1.73 m^2. Common causes of CKD are outlined in Table 139-1.

DIFFERENTIAL DIAGNOSIS

The first step in the differential diagnosis of CKD is establishing its chronicity, i.e., disproving a major acute component. The two most common means of determining disease chronicity are the history and prior laboratory data (if available) and the renal ultrasound, which is used to measure kidney size. In general, kidneys that have shrunk (<10–11.5 cm, depending on body size) are more likely affected by chronic disease. While reasonably specific (few false positives), reduced kidney size is only a moderately sensitive marker for CKD, i.e., there are several relatively common conditions in which kidney disease may be chronic without any reduction in renal size. Diabetic nephropathy, HIV-associated nephropathy, and infiltrative diseases such as multiple myeloma or amyloidosis may in fact be associated with relatively large kidneys despite chronicity. Renal biopsy, although rarely performed in pts with CKD, is a more reliable means of proving chronicity; a predominance of glomerulosclerosis or interstitial fibrosis argues strongly for chronic disease. Hyperphosphatemia, anemia, and other laboratory abnormalities are not reliable indicators in distinguishing acute from chronic disease.

Once chronicity has been established, clues from the physical examination, laboratory panel, and urine sediment evaluation can be used to determine etiology. A detailed history will identify important comorbid conditions, such as diabetes, HIV seropositivity, or peripheral vascular disease. The family history is paramount in the workup of autosomal dominant polycystic kidney disease or hereditary nephritis (Alport's syndrome). An occupational history may reveal exposure to environmental

TABLE 139-1 COMMON CAUSES OF CHRONIC RENAL FAILURE

Diabetic nephropathy
Hypertensive nephropathy[a]
Glomerulonephritis
Renovascular disease (ischemic nephropathy)
Polycystic kidney disease
Reflux nephropathy and other congenital renal diseases
Interstitial nephritis, including analgesic nephropathy
HIV-associated nephropathy
Transplant allograft failure ("chronic rejection")

[a]Often diagnosis of exclusion; very few pts undergo renal biopsy; may be occult renal disease with hypertension.

toxins or culprit drugs (including over-the-counter agents, such as analgesics or Chinese herbs).

Physical examination may demonstrate abdominal masses (i.e., polycystic kidneys), diminished pulses or femoral/carotid bruits (i.e., atherosclerotic peripheral vascular disease), or abdominal or femoral bruits (i.e., renovascular disease). The history and examination may also yield important data regarding severity of disease. Excoriations (uremic pruritus), pallor (anemia), muscle wasting, and a nitrogenous fetor are all signs of advanced CKD, as are pericarditis, pleuritis, and asterixis, complications of particular concern that usually prompt the initiation of dialysis.

Laboratory Findings

Serum and urine laboratory findings typically provide additional information useful in determining the etiology and severity of CKD; serial studies determine the pace of progression and/or whether the renal failure is in fact acute. Heavy proteinuria (>3.5 g/d), hypoalbuminemia, hypercholesterolemia, and edema suggest nephrotic syndrome (Chap. 142). Diabetic nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, amyloid, and HIV-associated nephropathy are principal causes. Proteinuria may decrease slightly with decreasing GFR, but rarely to normal levels. Hyperkalemia and metabolic acidosis may complicate all forms of CKD eventually, but can be more prominent in pts with interstitial renal diseases. Serum and urine protein electrophoresis, in addition to serum free light chains, should be obtained in all pts >35 years of age with CKD to exclude paraproteinemia-associated renal disease. If underlying glomerulonephritis is suspected, autoimmune disorders such as lupus and infectious etiologies such as hepatitis B and C should be assessed. Serum concentrations of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) should be measured to evaluate metabolic bone disease. Hemoglobin, vitamin B_{12}, folate, and iron studies should be measured to evaluate anemia.

THE UREMIC SYNDROME

The culprit toxin(s) responsible for the uremic syndrome remain elusive. The serum creatinine (Cr) is the most common laboratory surrogate of renal function. GFR can be estimated using serum Cr–based equations derived from the Modification of Diet in Renal Disease Study. This "eGFR" is now reported with serum Cr by most clinical laboratories in the United States and is the basis for the National Kidney Foundation classification of CKD (see Table 46-1).

Uremic symptoms tend to develop with serum Cr >530–710 μmol/L (>6–8 mg/dL) or Cr_{Cl} <10 mL/min, although these values vary widely. Uremia is thus a clinical diagnosis made in pts with CKD. Symptoms of advanced uremia include anorexia, weight loss, dyspnea, fatigue, pruritus, sleep and taste disturbance, and confusion and other forms of encephalopathy. Key findings on physical examination include hypertension, jugular venous distention, pericardial and/or pleural friction rub, muscle wasting, asterixis, excoriations, and ecchymoses. Pts may suffer from excessive bleeding due to uremic platelet dysfunction. Laboratory abnormalities may include hyperkalemia, hyperphosphatemia, metabolic acidosis, hypocalcemia, hyperuricemia, anemia, and hypoalbuminemia. Most of these abnormalities eventually resolve with initiation of dialysis or renal transplantation (Chaps. 140 and 141) or with appropriate drug therapies (see below).

TREATMENT CHRONIC KIDNEY DISEASE AND UREMIA

Hypertension complicates many forms of CKD and warrants aggressive treatment to reduce the risk of stroke and potentially to slow the progression of CKD (see below). Volume overload contributes to hypertension in many cases, and potent diuretic agents are frequently required. Anemia can be ameliorated

with recombinant human erythropoietin (rHuEPO); current practice is to target a hemoglobin concentration of 90–110 g/L. Iron deficiency and/or other causes of anemia can reduce the response to rHuEPO and should be investigated if present. Iron supplementation is often required; many pts require parenteral iron therapy, since intestinal iron absorption is reduced in CKD.

Hyperphosphatemia can be controlled with judicious restriction of dietary phosphorus and the use of postprandial phosphate binders, either calcium-based salts (calcium carbonate or acetate) or nonabsorbed agents (e.g., sevelamer). Hyperkalemia should be controlled with dietary potassium restriction. Dialysis should be considered if the potassium is >6 mmol/L on repeated occasions. If these conditions cannot be conservatively controlled, dialysis should be instituted (Chap. 140). It is also advisable to begin dialysis if severe anorexia, weight loss, and/or hypoalbuminemia develop, as it has been definitively shown that outcomes for dialysis pts with malnutrition are particularly poor.

SLOWING PROGRESSION OF RENAL DISEASE Prospective clinical trials have explored the roles of blood pressure control and dietary protein restriction on the rate of progression of renal failure. Control of hypertension is of benefit, although angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may exert unique beneficial effects, most likely due to their effects on intrarenal hemodynamics. The effects of ACE inhibitors and ARBs are most pronounced in pts with diabetic nephropathy and in those without diabetes but with significant proteinuria (>1 g/d). Diuretics and other antihypertensive agents are often required, in addition to ACE inhibitors and ARBs, to optimize hypertension control and attenuate disease progression; diuretics may also help control serum [K^+].

For a more detailed discussion, see Bargman JM, Skorecki K: Chronic Kidney Disease, Chap. 335, p. 1811, in HPIM-19.

140 Dialysis

OVERVIEW

The decision to initiate dialysis for the management of end stage renal disease (ESRD) usually depends on a combination of the pt's symptoms, comorbid conditions, and laboratory parameters. Unless a living donor is identified, transplantation is deferred by necessity, due to the scarcity of deceased donor organs (median waiting time, 3–6 years at most transplant centers). Dialytic options include hemodialysis and peritoneal dialysis (PD). Roughly 85% of U.S. pts are started on hemodialysis.

Absolute indications for dialysis include severe volume overload refractory to diuretic agents, severe hyperkalemia and/or acidosis, severe encephalopathy not otherwise explained, and pericarditis or other serositis. Additional indications for dialysis include symptomatic uremia (Chap. 139) (e.g., intractable fatigue, anorexia, dysgeusia,

TABLE 140-1 COMPLICATIONS OF HEMODIALYSIS

Hypotension	Dialysis-related amyloidosis
Accelerated vascular disease	Protein-energy malnutrition
Rapid loss of residual renal function	Hemorrhage
Access thrombosis	Anaphylactoid reaction[a]
Access or catheter sepsis	Thrombocytopenia[b]

[a]Primarily with first use of "bioincompatible" modified cellulosic dialyzer membranes.
[b]Associated with the use of dialyzers sterilized by e-beam treatment.

nausea, vomiting, pruritus, difficulty maintaining attention and concentration) and protein-energy malnutrition/failure to thrive without other overt cause. No absolute serum creatinine, blood urea nitrogen, creatinine or urea clearance, or glomerular filtration rate (GFR) is used as an absolute cutoff for requiring dialysis, although most individuals experience, or will soon develop, symptoms and complications when the GFR is below ~10 mL/min. However, the "pre-emptive" initiation of dialysis in such pts, prior to the onset of clinical indications, does not improve outcomes in ESRD.

HEMODIALYSIS

This requires direct access to the circulation, either via a native arteriovenous fistula (the preferred method of vascular access), usually at the wrist (a "Brescia-Cimino" fistula); an arteriovenous graft, usually made of polytetrafluoroethylene; a large-bore intravenous catheter; or a subcutaneous device attached to intravascular catheters. Blood is pumped though hollow fibers of an artificial kidney (the "dialyzer") and bathed with a solution of favorable chemical composition (isotonic, free of urea and other nitrogenous compounds, and generally low in potassium). Dialysate $[K^+]$ is varied from 1 to 4 mM, depending on predialysis $[K^+]$ and the clinical setting. Dialysate $[Ca^{2+}]$ is typically 2.5 mg/dL (1.25 mM), $[HCO_3^-]$ typically 35 meq/L, and dialysate $[Na^+]$ 140 mM; these can also be modified, depending on the clinical situation. Most pts undergo dialysis thrice weekly, usually for 3–4 h. The efficiency of dialysis is largely dependent on the duration of dialysis, blood flow rate, dialysate flow rate, and surface area of the dialyzer.

Complications of hemodialysis are outlined in Table 140-1. Many of these relate to the process of hemodialysis as an intense, intermittent therapy. In contrast to the native kidney or to PD, both major dialytic functions (i.e., clearance of solutes and fluid removal, or "ultrafiltration") are accomplished over relatively short time periods. The rapid flux of fluid can cause hypotension, even without a pt reaching "dry weight." Hemodialysis-related hypotension is common in diabetic pts whose neuropathy prevents the compensatory responses (vasoconstriction and tachycardia) to intravascular volume depletion. Occasionally, confusion or other central nervous system symptoms will occur. The dialysis "disequilibrium syndrome" refers to the development of headache, confusion, and rarely seizures, in association with rapid solute removal early in the pt's dialysis history, before adaptation to the procedure; this complication is largely avoided by an incremental induction of chronic dialytic therapy in uremic pts, starting with treatments of short duration, lower blood flows, and lower dialysate flow rates.

PERITONEAL DIALYSIS

PD does not require direct access to the circulation; rather, it obligates placement of a peritoneal catheter that allows infusion of a dialysate solution into the abdominal cavity; this allows transfer of solutes (i.e., urea, potassium, other uremic molecules) across the peritoneal membrane, which serves as the "artificial kidney." This solution is similar to that used for hemodialysis, except that it must be sterile, and it uses

TABLE 140-2 COMPLICATIONS OF PERITONEAL DIALYSIS

Peritonitis	Dialysis-related amyloidosis
Hyperglycemia	Insufficient clearance due to vascular disease or other factors
Hypertriglyceridemia	
Obesity	Uremia secondary to loss of residual renal function
Hypoproteinemia	Pleural effusion due to pleuro-peritoneal leak
Gastroesophageal reflux disease	Delayed gastric emptying

lactate, rather than bicarbonate, to provide base equivalents. PD is far less efficient at cleansing the bloodstream than hemodialysis and therefore requires a much longer duration of therapy. Pts generally have the choice of performing their own "exchanges" (2–3 L of dialysate, four to five times during daytime hours) or using an automated device at night. Compared with hemodialysis, PD offers the major advantages of (1) independence and flexibility, and (2) a more gentle hemodynamic profile, with better preservation of residual renal function.

Complications are outlined in Table 140-2. Peritonitis is the most important complication. The clinical presentation typically consists of abdominal pain and cloudy dialysate; peritoneal fluid leukocyte count is typically >100/μL, 50% neutrophils. In addition to the negative effects of the systemic inflammatory response, protein loss is magnified severalfold during the peritonitis episode. If severe or prolonged, an episode of peritonitis may prompt removal of the peritoneal catheter or even discontinuation of the modality (i.e., switch to hemodialysis). Gram-positive organisms (especially *Staphylococcus aureus* and other *Staphylococcus* spp.) predominate; *Pseudomonas* or fungal (usually *Candida*) infections tend to be more resistant to medical therapy and typically obligate catheter removal. Antibiotic administration may be intravenous or intraperitoneal when intensive therapy is required.

For a more detailed discussion, see Liu KD, Chertow GM: Dialysis in the Treatment of Renal Failure: Chap. 336, p. 1822, in HPIM-19.

141 Renal Transplantation

With the advent of more potent and well-tolerated immunosuppressive regimens and further improvements in short-term graft survival, renal transplantation remains the treatment of choice for most pts with end-stage renal disease. Results are best with living-related transplantation, in part because of optimized tissue matching and in part because waiting time and ischemic time can be minimized; ideally, these pts are transplanted prior to the onset of symptomatic uremia or indications for dialysis. Transplant centers now also perform living-unrelated donor (e.g., spousal) transplants, often in "chains" involving multiple donors to optimize tissue matching.

TABLE 141-1 SOME FACTORS THAT INFLUENCE GRAFT SURVIVAL IN RENAL TRANSPLANTATION

HLA mismatch	↓
Presensitization (preformed antibodies)	↓
Very young or older donor age	↓
Female donor sex	↓
African-American donor race (compared with white)	↓
At-risk APOL1 donor genotype (two risk alleles for ESRD)	↓
Older recipient age	↑
African-American recipient race (compared with white)	↓
Recipient diabetes as the cause of end-stage renal disease	↓
Prolonged cold ischemia time	↓
Hepatitis C infection	↓
Large recipient body size	↓

Graft survival in these cases is far superior to that observed with deceased donor transplants, although less favorable than with living-related transplants.

In 2011, there were 55,371 active adult candidates on the waiting list for deceased-donor kidneys, and less than 18,000 pts were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of deceased-donor kidneys and reduce discard rates of organs, criteria for the use of so-called expanded criteria donor (ECD) kidneys and kidneys from donors after cardiac death (DCD) have been developed. ECD kidneys are usually used for older pts who are expected to fare less well on dialysis.

Factors that influence graft survival are outlined in Table 141-1. Pretransplant blood transfusion should be avoided, so as to reduce the likelihood of sensitization to incompatible HLA antigens; if transfusion is necessary, leukocyte-reduced irradiated blood is preferred. Contraindications to renal transplantation are outlined in Table 141-2. Overall, the current standard of care is that the pt should have >5 years

TABLE 141-2 CONTRAINDICATIONS TO RENAL TRANSPLANTATION

Absolute contraindications
Active glomerulonephritis
Active bacterial or other infection
Active or very recent malignancy
Overt AIDS[a]
Active hepatitis
Severe degrees of comorbidity (e.g., advanced atherosclerotic vascular disease)
Relative contraindications
Severe psychiatric disease
Moderately severe degrees of comorbidity
Hepatitis C infection with chronic hepatitis or cirrhosis
Noncompliance with dialysis or other medical therapy
Primary renal diseases
Primary focal sclerosis with prior recurrence in transplant
Multiple myeloma
Amyloid
Oxalosis

[a]Most centers consider overt AIDS a contraindication to transplantation; however, transplantation of HIV-positive pts is increasing in frequency.

of life expectancy to be eligible for a renal transplant, since the benefits of transplantation are only realized after a perioperative period in which the mortality rate is higher than in comparable pts on dialysis.

REJECTION

Immunologic rejection is the major hazard to the short-term success of renal transplantation. Rejection may be (1) hyperacute (immediate graft dysfunction due to presensitization) or (2) acute (sudden change in renal function occurring within weeks to months). Rejection is usually detected by a rise in serum creatinine but may also lead to hypertension, fever, reduced urine output, and occasionally graft tenderness. A percutaneous renal transplant biopsy confirms the diagnosis. Treatment usually consists of a "pulse" of methylprednisolone (500–1000 mg/d for 3 days). In refractory or particularly severe cases, 7–10 days of a monoclonal antibody directed at human T lymphocytes may be given.

IMMUNOSUPPRESSION

Maintenance immunosuppressive therapy usually consists of a three-drug regimen, with each drug targeted at a different stage in the immune response. The calcineurin inhibitors cyclosporine and tacrolimus are the cornerstones of immunosuppressive therapy. The most potent of orally available agents, calcineurin inhibitors have vastly improved short-term graft survival. Side effects of cyclosporine include hypertension, hyperkalemia, resting tremor, hirsutism, gingival hypertrophy, hyperlipidemia, hyperuricemia and gout, and a slowly progressive loss of renal function with characteristic histopathologic patterns (also seen in exposed recipients of heart and liver transplants). Recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term calcineurin inhibitor toxicity. While the side effect profile of tacrolimus is generally similar to cyclosporine, there is a higher risk of hyperglycemia, a lower risk of hypertension, and occasional hair loss rather than hirsutism.

Prednisone is frequently used in conjunction with cyclosporine, at least for the first several months following successful graft function. Side effects of prednisone include hypertension, glucose intolerance, cushingoid features, osteoporosis, hyperlipidemia, acne, and depression and other mood disturbances. Some centers have adopted "steroid-free" immunosuppressive regimens to avoid prednisone-associated side-effects.

Mycophenolate mofetil has proved more effective than azathioprine in combination therapy with calcineurin inhibitors and prednisone. The major side effects of mycophenolate mofetil are gastrointestinal (diarrhea is most common); leukopenia (and thrombocytopenia to a lesser extent) develops in a fraction of pts.

Sirolimus is a newer immunosuppressive agent often used in combination with other drugs, particularly when calcineurin inhibitors are reduced or eliminated. Side effects include hyperlipidemia and oral ulcers.

OTHER COMPLICATIONS

Infection and neoplasia are important complications of renal transplantation. Infection is common in the heavily immunosuppressed host (e.g., cadaveric transplant recipient with multiple episodes of rejection requiring steroid pulses or monoclonal antibody treatment). The culprit organism depends in part on characteristics of the donor and recipient and timing following transplantation (Table 141-3). In the first month, bacterial organisms predominate. After 1 month, there is a significant risk of systemic infection with cytomegalovirus (CMV), particularly in recipients without prior exposure whose donor was CMV positive. Prophylactic use of ganciclovir or

TABLE 141-3 THE MOST COMMON OPPORTUNISTIC INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

Peritransplant (<1 month)	Late (>6 months)
Wound infections	*Aspergillus*
Herpesvirus	*Nocardia*
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
Pneumocystis carinii	Hepatitis C
Cytomegalovirus	
Legionella	
Listeria	
Hepatitis B	
Hepatitis C	

valacyclovir can reduce the risk of CMV disease. Later on, there is a substantial risk of fungal and related infections, especially in pts who are unable to taper prednisone to <20–30 mg/d. Daily low-dose trimethoprim-sulfamethoxazole is effective at reducing the risk of *Pneumocystis carinii* infection.

The polyoma group of DNA viruses (BK, JC, SV40) can be activated by immunosuppression. Reactivation of BK is associated with a typical pattern of renal inflammation, BK nephropathy, which can lead to loss of the allograft; therapy typically involves reduction of immunosuppression to aid in clearance of the reactivated virus.

Epstein-Barr virus–associated lymphoproliferative disease is the most important neoplastic complication of renal transplantation, especially in pts who receive polyclonal (antilymphocyte globulin, used at some centers for induction of immunosuppression) or monoclonal antibody therapy. Non-Hodgkin's lymphoma and squamous cell carcinoma of the skin are also more common in this population.



For a more detailed discussion, see Azzi J, Milford EL, Sayegh MH, Chandraker A: Transplantation in the Treatment of Renal Failure, Chap. 337, p. 1825, in HPIM-19.

142 Glomerular Diseases

ACUTE GLOMERULONEPHRITIS (GN)

Often called the "nephritic syndrome." Characterized by development, over days, of azotemia, hypertension, edema, hematuria, proteinuria, and sometimes oliguria. Salt and water retention are due to reduced glomerular filtration rate (GFR) and may result in circulatory congestion. Red blood cell (RBC) casts on urinalysis

TABLE 142-1 CAUSES OF ACUTE GLOMERULONEPHRITIS

I. Infectious diseases
   A. Poststreptococcal glomerulonephritis[a]
   B. Nonstreptococcal postinfectious glomerulonephritis
      1. Bacterial: infective endocarditis, "shunt nephritis," sepsis, pneumococcal pneumonia, typhoid fever, secondary syphilis, meningococcemia
      2. Viral: hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, and coxsackievirus
      3. Parasitic: malaria, toxoplasmosis
      4. IgA dominant postinfectious glomerulonephritis—usually poststaphylococcal
II. Multisystem diseases: SLE, vasculitis, Henoch-Schönlein purpura, Goodpasture's syndrome
III. Primary glomerular diseases: mesangiocapillary glomerulonephritis, Berger's disease (IgA nephropathy), "pure" mesangial proliferative glomerulonephritis
IV. Miscellaneous: Guillain-Barré syndrome, irradiation of Wilms' tumor, self-administered diphtheria-pertussis-tetanus vaccine, serum sickness

[a]Most common cause.
Source: RJ Glassock, BM Brenner: HPIM-13.

confirm diagnosis. Proteinuria is usually <3 g/d. Most forms of acute GN are mediated by humoral immune mechanisms. Clinical course depends on underlying lesion (Table 142-1).

Acute Poststreptococcal GN

This is the prototype of the nephritic syndrome and the most common cause in childhood. Nephritis develops 1–3 weeks after pharyngeal or cutaneous infection with "nephritogenic" strains of group A β-hemolytic streptococci. Diagnosis depends on a positive pharyngeal or skin culture (if available), positive titers for antistreptococcal antigens (ASO, anti-DNAse, or antihyaluronidase), and hypocomplementemia. Renal biopsy reveals diffuse proliferative GN. Treatment consists of correction of fluid and electrolyte imbalance. In most cases the disease is self-limited, although the prognosis is less favorable and urinary abnormalities are more likely to persist in adults.

Postinfectious GN

May follow other bacterial, viral, and parasitic infections. Examples are bacterial endocarditis, sepsis, hepatitis B, and pneumococcal pneumonia. Features are milder than with poststreptococcal GN. A specific IgA-dominant acute postinfectious glomerulonephritis, with a dominance of IgA deposits on immunofluorescence, can be seen after staphylococcal infections. Control of primary infection usually produces resolution of postinfectious GN, but steroids are often administered in severe cases to avoid dialysis.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Defined as a subacute reduction in GFR of >50%, with evidence of a proliferative GN; causes overlap with those of acute GN (Table 142-2). Broadly classified into three major subtypes on the basis of renal biopsy findings and pathophysiology: (1) immune complex–associated, e.g., in systemic lupus erythematosus (SLE); (2)

TABLE 142-2 CAUSES OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

I. Infectious diseases
  A. Poststreptococcal glomerulonephritis[a]
  B. Infective endocarditis
  C. Occult visceral sepsis
  D. Hepatitis B infection (with vasculitis and/or cryoglobulinemia)
  E. HIV infection
  F. Hepatitis C infection (with cryoglobulinemia, membranoproliferative glomerulonephritis)
II. Multisystem diseases
  A. Systemic lupus erythematosus
  B. Henoch-Schönlein purpura
  C. Systemic necrotizing vasculitis (including granulomatosis with polyangiitis [Wegener's])
  D. Goodpasture's syndrome
  E. Essential mixed (IgG/IgM) cryoglobulinemia
  F. Malignancy
  G. Relapsing polychondritis
  H. Rheumatoid arthritis (with vasculitis)
III. Drugs
  A. Penicillamine
  B. Hydralazine
  C. Allopurinol (with vasculitis)
  D. Rifampin
  E. Cocaine adulterated with levamisole (ANCA-associated)
IV. Idiopathic or primary glomerular disease
  A. Idiopathic crescentic glomerulonephritis
    1. Type I—with linear deposits of Ig (anti-GBM antibody–mediated)
    2. Type II—with granular deposits of Ig (immune complex–mediated)
    3. Type III—with few or no immune deposits of Ig ("pauci-immune")
    4. Antineutrophil cytoplasmic antibody–induced, forme fruste of vasculitis
    5. Immunotactoid glomerulonephritis
    6. Fibrillary glomerulonephritis
  B. Superimposed on another primary glomerular disease
    1. Mesangiocapillary (membranoproliferative) glomerulonephritis (especially type II)
    2. Membranous glomerulonephritis
    3. Berger's disease (IgA nephropathy)

[a]Most common cause.
Abbreviation: GBM, glomerular basement membrane.
Source: RJ Glassock, BM Brenner: HPIM-13.

"pauci-immune," associated with antineutrophil cytoplasmic antibodies (ANCA); and (3) associated with anti–glomerular basement (anti-GBM) antibodies, e.g., in Goodpasture's syndrome. All three forms will typically have a proliferative, crescentic GN by light microscopy but differ in the results of the immunofluorescence and electron microscopy components of the renal biopsy.

SLE (Lupus)

Renal involvement is due to deposition of circulating immune complexes. Clinical features of SLE with or without renal involvement include arthralgias, "butterfly" skin rash, serositis, alopecia (hair loss), and central nervous system disease. Nephrotic syndrome with renal insufficiency is common. Renal biopsy reveals mesangial, focal, or diffuse GN and/or membranous nephropathy. Diffuse GN, the most common finding in renal biopsy series, is typically characterized by an active sediment, severe proteinuria, and progressive renal insufficiency and may have an ominous prognosis. Pts have a positive antinuclear antibody test, anti-dsDNA antibodies, and hypocomplementemia. Treatment includes glucocorticoids and cytotoxic agents. Oral or IV monthly cyclophosphamide is most commonly employed, typically for a period of 6 months; pts of childbearing age should first bank sperm and eggs. Mycophenolate mofetil is an alternative.

Antineutrophil Cytoplasmic Antibody (ANCA)–Associated, Pauci-Immune GN

May be renal-limited (idiopathic pauci-immune GN) or associated with systemic vasculitis (granulomatosis with polyangiitis [GPA, formerly known as Wegener's] or microscopic polyarteritis nodosa). Defining characteristic is the presence of circulating ANCA. These are detected by immunofluorescence of alcohol-fixed neutrophils; a "perinuclear" pattern (pANCA) is usually due to antibodies against myeloperoxidase (MPO), whereas a "cytoplasmic" pattern (cANCA) is almost always due to reactivity against proteinase-3 (PR3). Confirmatory enzyme-linked immunosorbent assay testing against the MPO and PR3 antigens is mandatory, since the pANCA pattern can be caused by antibodies against other neutrophil components, e.g., lactoferrin; these do not have the same consistent relationship to vasculitis and pauci-immune GN. The anti-MPO or anti-PR3 titer does not always correlate with disease activity.

Pts typically have a prodromal, "flulike" syndrome, which may encompass myalgias, fever, arthralgias, anorexia, and weight loss. There may be associated cutaneous, pulmonary, upper respiratory (sinusitis), or neurologic (mononeuritis monoplex) complications of associated systemic vasculitis. In particular, pulmonary necrotizing capillaritis can lead to hemoptysis and pulmonary hemorrhage.

Standard initial therapy for ANCA-associated rapidly progressive GN includes methylprednisolone and cyclophosphamide; more specific depletion of B cells by anti-CD20 antibody therapy with rituximab is an alternative. Most centers will also utilize plasmapheresis in the initial management of pts with a severe pulmonary-renal syndrome or to stave off dialysis in pts with severe renal impairment. Steroids are quickly tapered soon after the acute inflammation subsides; cyclophosphamide is continued until a stable remission is achieved, typically within 3–6 months. Pts must receive prophylaxis for *Pneumocystis carinii* (*jiroveci*) pneumonia (PCP) with trimethoprim-sulfamethoxazole, atovaquone, or dapsone. Some form of maintenance immunosuppression is standard, typically for 12–18 months after achievement of a stable remission; drugs include methotrexate, mycophenolate mofetil, and azathioprine. Notably, however, pts treated with rituximab do not require maintenance oral immunosuppression, but may require maintenance with regular rituximab infusions or repeated rituximab therapy after a recurrence.

Anti–Glomerular Basement Membrane Disease

Caused by antibodies against the α3 NCI (noncollagenous) domain of type IV collagen; circulating anti-GBM antibody and linear immunofluorescence on renal biopsy

establish the diagnosis. Pts may have isolated GN; Goodpasture's syndrome encompasses GN and lung hemorrhage. Plasma exchange may produce remission; renal prognosis is worse in those who require dialytic support, with >50% crescents on renal biopsy, or creatinine >5–6 mg/dL. Severe lung hemorrhage is treated with IV glucocorticoids (e.g., 1 g/d × 3 days). Approximately 10–15% will also have ANCA against MPO, some with evidence of vasculitis, e.g., leukocytoclastic vasculitis in the skin.

Henoch-Schönlein Purpura

A generalized vasculitis causing IgA nephropathy, purpura, arthralgias, and abdominal pain; occurs mainly in children. Renal involvement is manifested by hematuria and proteinuria. Serum IgA is increased in half of pts. Renal biopsy is useful for prognosis. Treatment is symptomatic.

NEPHROTIC SYNDROME (NS)

Characterized by albuminuria (>3.5 g/d) and hypoalbuminemia (<30 g/L) and accompanied by edema, hyperlipidemia, and lipiduria. Protein excretion should be quantified by 24-h urine collection, but can be monitored by measurement of the urine protein:creatinine ratio or albumin:creatinine ratio on a random spot urine. The measurement of creatinine excretion helps define the adequacy of 24-h urine collections: daily creatinine excretion should be 20–25 mg/kg lean body weight in men and 15–20 mg/kg lean body weight in women. For random urine samples, the ratio of protein or albumin to creatinine in mg/dL approximates the 24-h urine protein excretion, since creatinine excretion is only slightly greater than 1000 mg/d per 1.73 m^2. A urine protein:creatinine ratio of 5 is thus consistent with 5 g/d per 1.73 m^2. Quantification of urine protein excretion on spot urines has largely supplanted formal 24-h urine collections for monitoring or screening, due to the greater ease and the need to verify a complete 24-h collection. The total protein:creatinine ratio does not detect microalbuminuria, a level of albumin excretion that is below the level of detection by tests for total protein; urine albumin:creatinine measurement is therefore preferred as a screening tool for lesser proteinuria.

In addition to edema, the complications of NS can include renal vein thrombosis and other thromboembolic events, infection, vitamin D deficiency, protein malnutrition, and drug toxicities due to decreased protein binding.

In adults, the most common cause of NS is diabetes. A minority of cases are secondary to SLE, amyloidosis, drugs, neoplasia, or other disorders (Table 142-3). By

TABLE 142-3 CAUSES OF NEPHROTIC SYNDROME (NS)

Systemic Causes	Glomerular Disease
Diabetes mellitus, SLE, amyloidosis, HIV-associated nephropathy	Membranous Minimal change disease
Drugs: gold, penicillamine, probenecid, street heroin, NSAIDs, pamidronate, interferons	Focal glomerulosclerosis
Infections: bacterial endocarditis, hepatitis B, shunt infections, syphilis, malaria, hepatic schistosomiasis	Membranoproliferative GN
Malignancy: multiple myeloma, light chain deposition disease, Hodgkin's and other lymphomas, leukemia, carcinoma of breast and GI tract	Mesangioproliferative GN Immunotactoid and fibrillary GN

Abbreviations: GN, glomerulonephritis.
Source: Modified from RJ Glassock, BM Brenner: HPIM-13.

exclusion, the remainder are idiopathic. With the exception of diabetic nephropathy, suggested by a compatible natural history of proteinuria in a diabetic pt, a renal biopsy is required to make the diagnosis and determine therapy in NS.

Minimal Change Disease

Causes about 10–15% of idiopathic NS in adults, but 70–90% of NS in children. Blood pressure is normal; GFR is normal or slightly reduced; urinary sediment is benign or may show few RBCs. Protein selectivity is variable in adults. Recent upper respiratory infection, allergies, or immunizations are present in some cases; nonsteroidal anti-inflammatory drugs can cause minimal change disease with interstitial nephritis. Acute renal failure due to associated acute tubular necrosis may rarely occur, particularly among elderly persons. Renal biopsy shows only foot process fusion on electron microscopy. Remission of proteinuria with glucocorticoids carries a good prognosis; cytotoxic therapy or calcineurin inhibitor therapy may be required for relapse. Progression to renal failure is uncommon. Focal sclerosis should be suspected in cases that are refractory to steroid therapy; these pts are more likely to progress to end-stage renal disease (ESRD). Children with steroid-resistant MCD/FSGS are more likely to have an underlying genetic cause.

Membranous GN

Characterized by subepithelial IgG deposits; accounts for ~30% of idiopathic adult NS. Pts present with edema and nephrotic proteinuria. Blood pressure, GFR, and urine sediment are usually normal at initial presentation. Hypertension, mild renal insufficiency, and abnormal urine sediment develop later. Renal vein thrombosis can occur, with low but greater frequency than with other forms of NS. Underlying diseases such as SLE, hepatitis B, and solid tumors and exposure to such drugs as high-dose captopril or penicillamine should be sought. The majority of pts with idiopathic membranous GN have detectable circulating autoantibodies to the M-type phospholipase A_2 (PLA_2R), which is expressed in glomerular podocytes; the PLA2R titre can be monitored during therapy or utilized as a screening tool for idiopathic membranous GN in nephrotic syndrome. Some pts progress to ESRD; however, 20–33% may experience a spontaneous remission. Male gender, older age, hypertension, and persistence of significant proteinuria (>6 g/d) are associated with a higher risk of progressive disease. Optimal immunosuppressive therapy is controversial. Glucocorticoids alone are ineffective. Cytotoxic agents may promote complete or partial remission in some pts, as may cyclosporine. Anti-CD20 antibody therapy with rituximab has recently shown considerable promise, consistent with a role for B cells and anti-PLA_2R antibodies in the pathophysiology. Reduction of proteinuria with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) is also an important mainstay of therapy. Venous thromboembolic events (DVTs, renal vein thrombosis, etc.) occur in about 7% of pts with membranous nephropathy; hypoalbuminemia is the most significant independent predictor of venous thrombotic risk. Prophylactic anticoagulation is not recommended for all pts, but should be considered in pts at very high risk for venous thrombosis (albumin <2.0 g/dL) with low or intermediate bleeding risk.

Focal Glomerulosclerosis (FGS)

Can be primary or secondary. Primary tends to be more acute, similar to minimal change disease in abruptness of NS, but with added features of hypertension, renal insufficiency, and hematuria. Involves fibrosis of portions of some (primarily juxtamedullary) glomeruli and is found in ~35% of pts with NS. There are several different pathologic subtypes of idiopathic FGS, with prognostic implications. In particular, the "collapsing glomerulopathy" variant has pathologic similarity to HIV-associated nephropathy (HIVAN); both nephropathies cause rapidly progressive disease.

African Americans are disproportionately affected by FGS, HIVAN, and other nondiabetic renal disease, with higher incidence, greater susceptibility (HIVAN),

and a much higher risk of developing ESRD. "African-specific" variants in the *APOL1* gene, which encodes apolipoprotein L1 expressed in glomerular podocytes, have recently been implicated in this enhanced genetic risk.

Treatment of primary FGS typically begins with an extended course of steroids; fewer than half of pts undergo remission. Cyclosporine is an alternative therapy for maintenance of remission and for steroid-resistant pts. As in other glomerulopathies, reduction of proteinuria with ACE inhibitors and/or ARBs is also an important component of therapy. Finally, primary FGS may recur after renal transplant, when it may lead to loss of the allograft.

Secondary FGS can occur in the late stages of any form of kidney disease associated with nephron loss (e.g., remote GN, prior severe pyelonephritis, sickle cell disease, vesicoureteral reflux). Treatment includes anti-proteinuric therapy with ACE inhibition and blood pressure control. There is no benefit of glucocorticoids or other immunsuppressive agents in secondary FGS. Clinical history, kidney size, biopsy findings, and associated conditions usually allow differentiation of primary versus secondary causes.

Membranoproliferative Glomerulonephritis (MPGN)

Mesangial expansion and proliferation extend into the capillary loop. Two ultrastructural variants exist. In MPGN I, subendothelial electron-dense deposits are present, C3 is deposited in a granular pattern indicative of immune-complex pathogenesis, and IgG and the early components of complement may or may not be present. In MPGN II, the lamina densa of the GBM is transformed into an electron-dense character, as is the basement membrane in Bowman's capsule and tubules. C3 is found irregularly in the GBM. Small amounts of Ig (usually IgM) are present, but early components of complement are absent.

Pts with MPGN may have associated genetic mutations in complement components or complement regulatory factors. MPGN has been proposed to be reclassified into immunoglobulin-mediated disease (driven by the classical complement pathway) and non-immunoglobulin-mediated disease (driven by the alternative complement pathway).

Serum complement levels are usually decreased. MPGN affects young adults. Blood pressure and GFR are abnormal, and the urine sediment is active. Some have acute nephritis or hematuria. Similar lesions occur in SLE and hemolytic-uremic syndrome. Infection with hepatitis C virus (HCV) has been linked to MPGN, often with associated cryoglobulinemia. Glucocorticoids, cytotoxic agents, antiplatelet agents, and plasmapheresis have been used with limited success in HCV-associated MPGN; rituximab is a newer therapy with greater evident efficacy. Therapy with a direct-acting, interferon-free antiviral regimen should be considered in pts with MPGN and/or cryoglobulinemic vasculitis associated with HCV infection, either as primary therapy or once the vasculitis and/or MPGN has been controlled with rituximab.

Diabetic Nephropathy

The most common cause of NS. Although prior duration of diabetes mellitus (DM) is variable, in type 1 DM proteinuria may develop 10–15 years after onset of diabetes, progress to NS, and then lead to renal failure over 3–5 years. Retinopathy is nearly universal in type 1 diabetics with nephropathy, so much so that the absence of retinopathy should prompt consideration of another glomerular lesion (e.g., membranous nephropathy). In contrast, only ~60% of type 2 diabetics with diabetic nephropathy have retinopathy. Clinical features include proteinuria, progressive hypertension, and progressive renal insufficiency. Pathologic changes include mesangial sclerosis, diffuse, and/or nodular (Kimmelstiel-Wilson) glomerulosclerosis. However, pts rarely undergo renal biopsy; to the extent that yearly measurement of microalbuminuria is routine management for all diabetics, the natural history is an important component of the diagnosis. Pts typically demonstrate progression

TABLE 142-4 EVALUATION OF NEPHROTIC SYNDROME

Random spot urine for protein and creatinine
Serum albumin, cholesterol, complement
Urine protein electrophoresis
Rule out SLE, diabetes mellitus
Review drug exposure
Renal biopsy
Consider malignancy (in elderly pt with membranous GN or minimal change disease)
Consider renal vein thrombosis (if membranous GN or symptoms of pulmonary embolism are present)

Abbreviation: GN, glomerulonephritis.

from microalbuminuria (30–300 mg/24 h) to dipstick-positive proteinuria (>300 mg albuminuria) and then progressively overt proteinuria and chronic kidney disease. However, proteinuria can be quite variable in diabetic nephropathy, with as much as 25 g/24 h in the absence of profound renal insufficiency or alternatively with progressive renal insufficiency and stable, modest proteinuria.

Treatment with ACE inhibitors delays the onset of nephropathy and of ESRD in type 1 diabetics with microalbuminuria and/or declining renal function and should be instituted in all pts tolerant to that class of drug. If a cough develops in a pt treated with an ACE inhibitor, an ARB is the next best choice. Type 2 diabetics with microalbuminuria or proteinuria can be treated with ACE inhibitors or ARBs. Hyperkalemia, hypotension, and/or worsening GFR can limit single or combined therapy with renin-angiotensin-aldosterone (RAA) system inhibitors. If hyperkalemia develops and cannot be controlled with (1) optimizing glucose control, (2) loop diuretics (if otherwise appropriate), or (3) treatment of metabolic acidosis (if present), then tight control of blood pressure with alternative agents is warranted.

Evaluation of NS is shown in Table 142-4.

ASYMPTOMATIC URINARY ABNORMALITIES

Proteinuria in the nonnephrotic range and/or hematuria unaccompanied by edema, reduced GFR, or hypertension can be due to multiple causes (Table 142-5).

Thin Basement Membrane Nephropathy

Also known as benign familial hematuria, may cause up to 25% of isolated, sustained hematuria without proteinuria. Diffuse thinning of the glomerular basement membrane on renal biopsy, with minimal other changes. May be hereditary, caused in some instances by defects in type IV collagen. Pts have persistent glomerular hematuria, with minimal proteinuria. The renal prognosis is controversial but appears to be relatively benign.

IgA Nephropathy

Another very common cause of recurrent hematuria of glomerular origin. Episodes of macroscopic hematuria are present with flulike symptoms, without skin rash, abdominal pain, or arthritis. Renal biopsy shows diffuse mesangial deposition of IgA, often with lesser amounts of IgG, nearly always by C3 and properdin but not by C1q or C4. Prognosis is variable; 50% develop ESRD within 25 years; men with hypertension and heavy proteinuria are at highest risk. Glucocorticoids and other

TABLE 142-5 GLOMERULAR CAUSES OF ASYMPTOMATIC URINARY ABNORMALITIES

I. Hematuria with or without proteinuria
  A. Primary glomerular diseases
    1. Berger's disease (IgA nephropathy)[a]
    2. Mesangiocapillary glomerulonephritis
    3. Other primary glomerular hematurias accompanied by "pure" mesangial proliferation, focal and segmental proliferative glomerulonephritis, or other lesions
    4. "Thin basement membrane" disease (? forme fruste of Alport's syndrome)
  B. Associated with multisystem or hereditary diseases
    1. Alport's syndrome and other "benign" familial hematurias
    2. Fabry's disease
    3. Sickle cell disease
  C. Associated with infections
    1. Resolving poststreptococcal glomerulonephritis
    2. Other postinfectious glomerulonephritides
II. Isolated nonnephrotic proteinuria
  A. Primary glomerular diseases
    1. "Orthostatic" proteinuria
    2. Focal and segmental glomerulosclerosis
    3. Membranous glomerulonephritis
  B. Associated with multisystem or heredofamilial diseases
    1. Diabetes mellitus
    2. Amyloidosis
    3. Nail-patella syndrome

[a]Most common.
Source: RJ Glassock, BM Brenner: HPIM-13.

immunosuppressive agents have not proved successful, except in pts who present with rapidly progressive GN. A randomized clinical trial of fish oil supplementation suggested a modest therapeutic benefit. Rarely recurs in allografts.

Glomerulopathies Associated with Multisystem Disease (Table 142-6)



For a more detailed discussion, see Lewis JB, Neilson EG: Glomerular Diseases, Chap. 338, p. 1831, in HPIM-19.

TABLE 142-6 SEROLOGIC FINDINGS IN SELECTED MULTISYSTEM DISEASES CAUSING GLOMERULAR DISEASE

Disease	C3	Ig	FANA	Anti-dsDNA	Anti-GBM	Cryo-Ig	CIC	ANCA
SLE	↓	↑ IgG	+++	++	–	++	+++	±
Goodpasture's syndrome	–	–	–	–	+++	–	±	+ (10–15%)
Henoch-Schönlein purpura	–	↑IgA	–	–	–	±	++	–
Polyarteritis	↓↑	IgG	+	±	–	++	+++	+++
Granulomatosis with polyangiitis (Wegener's)	↓↑	↑ IgA, IgE	–	–	–	±	++	+++
Cryoglobulinemia	↓	± ↓↑ IgG IgA, IgD	–		–	+++	++	–
Multiple myeloma	–	IgE	–		–	+	–	–
Waldenström's macroglobulinemia	–	↑ IgM	–	–	–	–	–	–
Amyloidosis	–	± Ig	–	–	–	–	–	–

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, antibody to double-stranded (native) DNA; anti-GBM, antibody to glomerular basement membrane antigens; CIC, circulating immune complexes; cryo-Ig, cryoimmunoglobulin; C3, complement component 3; FANA, fluorescent antinuclear antibody assay; Ig, immunoglobulin levels; SLE, systemic lupus erythematosus; –, normal; +, occasionally slightly abnormal; ++, often abnormal; +++, severely abnormal.

Source: RJ Glassock, BM Brenner: HPIM-13.

143 Renal Tubular Disease

Tubulointerstitial diseases constitute a diverse group of acute and chronic, hereditary and acquired disorders involving the renal tubules and supporting structures (Table 143-1). Functionally, they may result in a wide variety of physiologic phenotypes, including nephrogenic diabetes insipidus (DI) with polyuria, non-anion-gap

TABLE 143-1 PRINCIPAL CAUSES OF TUBULOINTERSTITIAL DISEASE OF THE KIDNEY

Toxins	
Exogenous toxins	Metabolic toxins
Analgesic nephropathy[a]	Acute uric acid nephropathy
Lead nephropathy	Gouty nephropathy[a]
Chinese herb nephropathy	Hypercalcemic nephropathy
Balkan endemic nephropathy	Hypokalemic nephropathy
Miscellaneous nephrotoxins (e.g., antibiotics, cyclosporine, radiographic contrast media, heavy metals)[a,b]	Miscellaneous metabolic toxins (e.g., hyperoxaluria, cystinosis, Fabry's disease)
Neoplasia	
Lymphoma	
Leukemia	
Multiple myeloma (cast nephropathy, AL amyloidosis)	
Immune disorders	
Acute (allergic) interstitial nephritis[a,b]	Transplant rejection
Sjögren's syndrome	HIV-associated nephropathy
Amyloidosis	
Vascular disorders	
Arteriolar nephrosclerosis[a]	Sickle cell nephropathy
Atheroembolic disease	Acute tubular necrosis[a,b]
Hereditary renal diseases	
Disorders associated with renal failure	Hereditary tubular disorders
Autosomal dominant polycystic kidney disease	Bartter's syndrome (hereditary hypokalemic alkalosis)
Autosomal recessive polycystic kidney disease	Gitelman's syndrome (hereditary hypokalemic alkalosis)
Medullary cystic kidney disease	Pseudohypoaldosteronism type I (hypotension/salt wasting and hyperkalemia)
Hereditary nephritis (Alport's syndrome)	Pseudohypoaldosteronism type II (hereditary hypertension and hyperkalemia)
	Liddle's syndrome (hypertension and hypokalemia)
	Hereditary hypomagnesemia

(*Continued*)

TABLE 143-1 PRINCIPAL CAUSES OF TUBULOINTERSTITIAL DISEASE OF THE KIDNEY (*CONTINUED*)

Hereditary renal diseases	
	Hereditary nephrogenic diabetes insipidus
	X-linked (AVP receptor dysfunction)
	Autosomal (aquaporin-2 dysfunction)
Infectious injury	
Acute pyelonephritis[a,b]	
Chronic pyelonephritis	
Miscellaneous disorders	
Chronic urinary tract obstruction[a]	
Vesicoureteral reflux[a]	
Radiation nephritis	

[a]Common.
[b]Typically acute.

metabolic acidosis, salt wasting, and hypo- or hyperkalemia. Azotemia is common, owing to associated glomerular fibrosis and/or ischemia. Compared with glomerulopathies, proteinuria and hematuria are less dramatic, and hypertension is less common. The functional consequences of tubular dysfunction are outlined in Table 143-2.

TABLE 143-2 TRANSPORT DYSFUNCTION IN TUBULOINTERSTITIAL DISEASE

Defect	Cause(s)
Reduced GFR[a]	Obliteration of microvasculature and obstruction of tubules
Fanconi syndrome	Damage to proximal tubular reabsorption of solutes, primarily glucose, amino acids, and phosphate; may also exhibit hypouricemia, proximal tubular acidosis, low-molecular-weight proteinuria
Hyperchloremic acidosis[a]	1. Reduced ammonia production (CKD) or excretion (hyperkalemia) 2. Inability to acidify the collecting duct fluid (distal renal tubular acidosis) 3. Proximal bicarbonate wasting (proximal RTA)
Polyuria, isothenuria[a]	Damage to medullary tubules (thick ascending limb and/or collecting duct) and vasculature
Hypokalemic alkalosis	Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubule (Bartter's and Gitelman's syndromes)
Magnesium wasting	Damage or hereditary dysfunction of the thick ascending limb or distal convoluted tubules
Hyperkalemia[a]	Potassium secretory defects including aldosterone resistance
Salt wasting	Distal tubular damage with impaired sodium reabsorption

[a]Common.
Abbreviations: CKD, chronic kidney disease; RTA, renal tubular acidosis.

ACUTE INTERSTITIAL NEPHRITIS (AIN)

Drugs are a leading cause of this type of renal failure, usually identified by a gradual rise in the serum creatinine at least several days after the institution of therapy, occasionally accompanied by fever, eosinophilia, rash, and arthralgias. The onset of renal dysfunction may be very rapid in pts who have previously been sensitized to the offending agent; this is particularly true for rifampin, for which intermittent or interrupted therapy appears to be associated with the development of AIN. In addition to azotemia, there may be evidence of tubular dysfunction (e.g., hyperkalemia, metabolic acidosis). Urinalysis may show hematuria, pyuria, white cell casts, and eosinophiluria on Hansel's or Wright's stain; notably, however, eosinophiluria is not specific for AIN, occurring in other causes of acute kidney injury (AKI), including atheroemboli; "urine for eosinophils" is not a diagnostically useful test.

Drugs that commonly cause AIN are listed in Table 143-3. Some drugs have a particular predilection for causing AIN, e.g., nafcillin; however, less frequent causes may be apparent only from case reports, such that a detailed history and literature review may be required to make the association with AIN. Many drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) in particular, may elicit a glomerular lesion with similarity to minimal change disease, in addition to AIN; these pts typically have nephrotic-range proteinuria, versus the modest proteinuria typically associated with tubulointerstitial disease.

Renal dysfunction in drug-associated AIN usually improves after withdrawal of the offending drug, but complete recovery may be delayed and incomplete. In uncontrolled studies, glucocorticoids have been shown to promote earlier recovery of renal function and reduce fibrosis; this therapy is generally reserved to avoid or reduce the duration of dialytic therapy in pts who fail to respond to medication withdrawal.

AIN may also occur in the context of systemic infections, classically leptospirosis, *Legionella* infection, and streptococcal bacterial infection. Interstitial nephritis characterized by a dense infiltrate of IgG4-expressing plasma cells can occur as part of IgG4-related systemic disease; pancreatitis, retroperitoneal fibrosis, and a chronic

TABLE 143-3 CAUSES OF ACUTE INTERSTITIAL NEPHRITIS

Drugs (70%, antibiotics in one-third)
Antibiotics
Methicillin, nafcillin, oxacillin
Rifampin
Penicillins, cephalosporins
Ciprofloxacin
Sulfamethoxazole and other sulfonamides
Proton pump inhibitors, e.g., omeprazole
H_2 blockers, e.g., cimetidine
Allopurinol
5-Aminosalicylates
NSAIDs, including COX-2 inhibitors
Infections (16%)
Leptospirosis, *Legionella*, streptococcal, tuberculosis
Tubulointerstitial nephritis and uveitis syndrome (TINU) (5%)
Idiopathic (8%)
Sarcoidosis (1%)
IgG4-related systemic disease

Abbreviation: COX-2, cyclooxygenase 2.

sclerosing sialadenitis may variably be present. Sjögren's syndrome can also be associated with acute tubulointerstitial nephritis. Finally, the tubulointerstitial nephritis and uveitis syndrome (TINU) is another increasingly recognized form of AIN. In addition to uveitis, which may precede or follow the AIN in pts with TINU, systemic symptoms and signs are common, e.g., weight loss, fever, malaise, arthralgias, and an elevated erythrocyte sedimentation rate. The renal disease is typically self-limited; those with progressive disease are often treated with prednisone.

CHRONIC INTERSTITIAL NEPHRITIS (IN)

Analgesic nephropathy is an important cause of chronic kidney disease that results from the cumulative (in quantity and duration) effects of combination analgesic agents, usually phenacetin and aspirin. It is thought to be a more common cause of end-stage renal disease (ESRD) in Australia/New Zealand than elsewhere owing to the larger per capita ingestion of analgesic agents in that region of the world. Transitional cell carcinoma may develop. Analgesic nephropathy should be suspected in pts with a history of chronic headache or back pain with chronic kidney disease (CKD) that is otherwise unexplained. Manifestations include papillary necrosis, calculi, sterile pyuria, and azotemia.

A severe form of chronic tubulointerstitial fibrosis has been associated with the ingestion of Chinese herbal medicines, typically employed as part of a dieting regimen; Balkan endemic nephropathy (BEN), geographically restricted to pts from this region of southeastern Europe, shares many similarities with Chinese herbal nephropathy. These disorders are thought to be caused by exposure to aristolochic acid and/or other plant, endemic (in BEN), and medical toxins (the appetite suppressants fenfluramine and diethylpropion, in Chinese herbal nephropathy). Like analgesic nephropathies, these syndromes are both characterized by a high incidence of genitourinary malignancy.

Chronic therapy with lithium can also cause a chronic tubulointerstitial nephritis, often accompanied by nephrogenic DI that persists following discontinuation of the medication. If at all feasible, lithium-treated pts with evolving CKD should be transitioned to alternative medications for their psychiatric disease (e.g., valproic acid). Co-treatment with lithium and amiloride may prevent nephrogenic diabetes insipidus in these pts by blocking entry of lithium into principal cells via the amiloride-sensitive Na+ channel; however, there are no long-term studies on the effect of amiloride co-therapy on the development or progression of CKD.

Metabolic causes of chronic IN include hypercalcemia (with nephrocalcinosis), oxalosis (primary or secondary, e.g., with intestinal disease and hyperabsorption of dietary oxalate), hypokalemia, and hyperuricemia or hyperuricosuria. The renal pathology associated with chronic hypokalemia includes a relatively specific proximal tubular vacuolization, interstitial nephritis, and renal cysts; both chronic and acute renal failure have been described. Chronic IN can occur in association with several systemic diseases, including sarcoidosis, Sjögren's syndrome, and following radiation or chemotherapy exposure (e.g., ifosfamide, cisplatin).

MONOCLONAL IMMUNOGLOBULINS AND RENAL DISEASE

Monoclonal immunoglobulins are associated with a wide variety of renal manifestations (Table 143-4), of which myeloma-associated cast nephropathy is the most common. The physiochemical characteristics of the monoclonal immunoglobulin, or more commonly the monoclonal light or heavy chains, determine the clinical phenotype in individual pts, most commonly cast nephropathy, light chain deposition disease, and AL amyloidosis. In cast nephropathy, filtered light chains aggregate and cause tubular obstruction, tubular damage, and interstitial inflammation. Pts can present with CKD or with AKI; important predisposing factors in acute cast nephropathy include hypercalcemia and volume depletion.

TABLE 143-4 RENAL DISEASES ASSOCIATED WITH MONOCLONAL IMMUNOGLOBULINS

Disease	Notes
Cast nephropathy	Most common cause of CKD in myeloma Tubular obstruction with light chains Interstitial inflammation Acute or chronic renal failure
Light chain deposition disease	Nephrotic syndrome, chronic renal failure, ~40% have associated myeloma
Heavy chain deposition disease	Nephrotic syndrome, chronic renal failure
Monoclonal immunoglobulin deposition disease	Nephrotic syndrome, chronic renal failure
AL amyloidosis	Nephrotic syndrome, cardiac/endocrine/neuropathic involvement ~10% have associated myeloma Renal tubular dysfunction (RTA, nephrogenic DI, etc.)
Hypercalcemia	With myeloma
Hyperviscosity syndrome	With Waldenström's macroglobulinemia
Fanconi syndrome	Glucosuria, aminoaciduria, phosphaturia, ± hypouricemia, proximal RTA, etc.

Abbreviations: CKD, chronic kidney disease; DI, diabetes insipidus; RTA, renal tubular acidosis.

Diagnosis of cast nephropathy relies on the detection of monoclonal light chains in serum and/or urine, typically by protein electrophoresis and immunofixation. Dipstick analysis of the urine for protein is classically negative in cast nephropathy, despite the excretion of up to several grams a day of light chain protein; light chains are not detected by this screening test, which tests only for albuminuria. In contrast, the glomerular deposition of light chains in light chain deposition disease or AL amyloidosis can result in nephrotic-range proteinuria (Table 143-4), with strongly *positive* urine dipstick for protein.

Management of cast nephropathy encompasses aggressive hydration, treatment of hypercalcemia if present, and chemotherapy for the associated multiple myeloma. Some experts advocate the use of plasmapheresis for pts with severe AKI, high levels of serum monoclonal light chains, and a renal biopsy demonstrating cast nephropathy.

Filtered light chains and multiple other low-molecular-weight proteins are also endocytosed and metabolized by the proximal tubule. Rarely, specific light chains generate crystalline depositions within proximal tubule cells, causing a Fanconi syndrome; again, this property appears to be caused by the specific physicochemical characteristics of the associated light chains. Fanconi syndrome or dysfunction of the distal nephron (hyperkalemic acidosis or nephrogenic DI) may also complicate renal amyloidosis.

POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening monogenic genetic disorder, caused by autosomal dominant mutations in the *PKD1* and *PKD2* genes; it is a quantitatively important cause of ESRD.

Autosomal recessive polycystic disease is a less much common cause of renal failure, typically presenting in infancy; hepatic involvement is much more prominent. The massive renal cysts in ADPKD can lead to progressive CKD, episodic flank pain, hematuria (often gross), hypertension, and/or urinary tract infection. The kidneys are often palpable and occasionally of very large size. Hepatic cysts and intracranial aneurysms may also be present; pts with ADPKD and a family history of ruptured intracranial aneurysms should undergo presymptomatic screening. Other common extrarenal features include diverticulosis and mitral valve prolapse.

The expression of ADPKD is highly variable, even within individual families, with the age of onset of ESRD ranging from childhood to old age. The renal phenotype is more severe in pts with mutations in *PKD1*, who on average develop ESRD approximately 15 years earlier than those with *PKD2* mutations. Indeed, some pts with ADPKD discover the disease incidentally in late adult life, having had mild to moderate hypertension earlier.

The diagnosis is usually made by ultrasonography. In a 15- to 29-year-old at-risk individual from a family with ADPKD, the presence of at least two renal cysts (unilateral or bilateral) is sufficient for diagnosis. Notably, however, renal cysts are a common ultrasound finding in older pts without ADPKD, particularly those with CKD. Therefore, in at-risk individuals 30–59 years of age, the presence of at least two cysts in each kidney is required for the diagnosis; this increases to four cysts in each kidney for those older than 60. Conversely, the absence of at least two cysts in each kidney excludes the diagnosis of ADPKD in at-risk individuals between the ages of 30 and 59.

Hypertension is common in ADPKD, often in the absence of an apparent reduction in glomerular filtration rate. Activation of the renin-angiotensin system appears to play a dominant role; angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the recommended antihypertensive agents, with a target blood pressure of <130/80 mmHg. Dual therapy with an angiotensin receptor blocker (ARB) and ACE inhibitor does not confer additional benefit in slowing progression of ADPKD to ESRD. Promising treatment modalities for halting progression of CKD in ADPKD include vasopressin antagonists, somatostatin analogues, and inhibitors of cell proliferation.

Urinary tract infections are also common in ADPKD. In particular, pts may develop cyst infections, often with negative urine cultures and an absence of pyuria. Pts with an infected cyst may have a discrete area of tenderness, as opposed to the more diffuse discomfort of pyelonephritis; however, clinical distinction between these two possibilities can be problematic. Many commonly used antibiotics, including penicillins and aminoglycosides, fail to penetrate cysts and are ineffective; therapy of kidney infections in ADPKD should use an antibiotic that is known to penetrate cysts (e.g., quinolones), guided initially by local antimicrobial susceptibility patterns.

RENAL TUBULAR ACIDOSIS (RTA)

This describes a number of pathophysiologically distinct entities of tubular function whose common feature is the presence of a non-anion-gap metabolic acidosis. Diarrhea, CKD, and RTA together constitute the vast majority of cases of non-anion-gap metabolic acidosis. Pts with earlier stages of CKD (Table 46-1) typically develop a non-anion-gap acidosis, with a superimposed increase in the anion gap at later stages (Chap. 1). Acidosis may develop at an earlier stage of CKD in those with prominent injury to the distal nephron, as for example in reflux nephropathy.

Distal Hypokalemic (Type I) RTA

Pts are unable to acidify the urine despite systemic acidosis; the urinary anion gap is positive, reflective of a decrease in ammonium excretion (Chap. 1). Distal hypokalemic RTA may be inherited (both autosomal dominant and autosomal recessive) or

acquired due to autoimmune and inflammatory diseases (e.g., Sjögren's syndrome, sarcoidosis), urinary tract obstruction, or amphotericin B therapy. Chronic type I RTA is typically associated with hypercalciuria and osteomalacia, a consequence of the long-term buffering of acidosis by bone.

Proximal (Type II) RTA

There is a defect in bicarbonate reabsorption, usually associated with features of Fanconi syndrome, including glycosuria, aminoaciduria, phosphaturia, and uricosuria (indicating proximal tubular dysfunction). Isolated proximal RTA is caused by hereditary dysfunction of the basolateral sodium-bicarbonate cotransporter. Fanconi syndrome may be inherited or acquired due to myeloma, chronic IN (e.g., Chinese herbal nephropathy), or drugs (e.g., ifosfamide, tenofovir). Treatment requires large doses of bicarbonate (5–15 mmol/kg per day), which may aggravate hypokalemia.

Type IV RTA

This may be due to hyporeninemic hypoaldosteronism or to resistance of the distal nephron to aldosterone. Hyporeninemic hypoaldosteronism is typically associated with volume expansion and most commonly seen in elderly and/or diabetic pts with CKD. The hyperkalemia associated with NSAIDs and cyclosporine is at least partially due to hyporeninemic hypoaldosteronism. Pts with hyporeninemic hypoaldosteronism are typically hyperkalemic; they may also exhibit a mild non-anion-gap acidosis, with urine pH <5.5 and a positive urinary anion gap. Acidosis often improves with reduction in serum $[K^+]$; hyperkalemia appears to interfere with medullary concentration of ammonium by the renal countercurrent mechanism. Should reduction in serum $[K^+]$ not improve acidosis, pts should be treated with oral bicarbonate or citrate. Finally, various forms of distal tubular injury and tubulointerstitial disease, e.g., interstitial nephritis, are associated with distal insensitivity to aldosterone; urine pH is classically >5.5, again with a positive urinary anion gap.

For a more detailed discussion, see Beck LH, Salant DJ: Tubulointerstitial Diseases of the Kidney, Chap. 340, p. 1856, in HPIM-19.

144 Urinary Tract Infections and Interstitial Cystitis

URINARY TRACT INFECTIONS

Definitions

The term *urinary tract infection* encompasses a variety of clinical entities: *cystitis* (symptomatic disease of the bladder), *pyelonephritis* (symptomatic disease of the kidney), *prostatitis* (symptomatic disease of the prostate), and asymptomatic bacteriuria (ABU). *Uncomplicated UTI* refers to acute disease in nonpregnant outpatient women

without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* refers to all other types of UTI.

Epidemiology

UTI occurs far more commonly in females than in males, although obstruction from prostatic hypertrophy causes men >50 years old to have an incidence of UTI comparable to that among women of the same age.

- 50–80% of women have at least one UTI during their lifetime, and 20–30% of women have recurrent episodes.
- Risk factors for acute cystitis include recent use of a diaphragm with spermicide, frequent sexual intercourse, a history of UTI, diabetes mellitus, and incontinence; many of these factors also increase the risk of pyelonephritis.

Microbiology

In the United States, *Escherichia coli* accounts for 75–90% of cystitis isolates; *Staphylococcus saprophyticus* for 5–15%; and *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., *Citrobacter* spp., and other organisms for 5–10%.

- The spectrum of organisms causing uncomplicated pyelonephritis is similar, with *E. coli* predominating.
- Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts are also important pathogens in complicated UTI.

Pathogenesis

In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections.

- The pathogenesis of candiduria is distinct in that the hematogenous route is common.
- The presence of *Candida* in the urine of a noninstrumented immunocompetent pt implies either genital contamination or potentially widespread visceral dissemination.

Clinical Manifestations

When a UTI is suspected, the most important issue is to classify it as ABU; as uncomplicated cystitis, pyelonephritis, or prostatitis; or as complicated UTI.

- *Asymptomatic bacteriuria* is diagnosed when a screening urine culture performed for a reason unrelated to the genitourinary tract is incidentally found to contain bacteria, but the pt has no local or systemic symptoms referable to the urinary tract.
- *Cystitis* presents as dysuria, urinary frequency, and urgency; nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain and fever are signs that the upper urinary tract is involved.
- *Pyelonephritis* presents as fever, lower-back or costovertebral-angle pain, nausea, and vomiting. Bacteremia develops in 20–30% of cases.
  - *Papillary necrosis* can occur in pts with obstruction, diabetes, sickle cell disease, or analgesic nephropathy.
  - *Emphysematous pyelonephritis* is particularly severe, is associated with the production of gas in renal and perinephric tissues, and occurs almost exclusively in diabetic pts.
  - *Xanthogranulomatous pyelonephritis* occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue.
- *Prostatitis* can be either infectious or noninfectious; noninfectious cases are far more common. Acute bacterial prostatitis presents as dysuria, urinary frequency,

fever, chills, symptoms of bladder outlet obstruction, and pain in the prostatic, pelvic, or perineal area.
- *Complicated UTI* presents as symptomatic disease in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

Diagnosis

The clinical history itself has a high predictive value in diagnosing uncomplicated cystitis; the likelihood of UTI is 96% in a pt presenting with both dysuria and urinary frequency in the absence of vaginal discharge.

- A urine dipstick test positive for nitrite or leukocyte esterase can confirm the diagnosis of uncomplicated cystitis in pts with a high pretest probability of disease.
- The detection of bacteria in a urine culture is the diagnostic gold standard for UTI. A colony count threshold of $>10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women with symptoms of cystitis.

TREATMENT URINARY TRACT INFECTIONS

- **Uncomplicated cystitis in women** See Table 144-1 for effective therapeutic regimens.
  - Trimethoprim-sulfamethoxazole (TMP-SMX) has been recommended as first-line treatment for acute cystitis but should be avoided in regions with resistance rates >20%.
  - Nitrofurantoin is another first-line agent with low rates of resistance.

TABLE 144-1 TREATMENT STRATEGIES FOR ACUTE UNCOMPLICATED CYSTITIS

Drug and Dose	Estimated Clinical Efficacy, %	Estimated Bacterial Efficacy,[a] %	Common Side Effects
Nitrofurantoin, 100 mg bid × 5–7 d	84–95	86–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	90–100	91–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	70–91	78–83	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	85–95	81–98	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimen	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

[a]Microbial response as measured by reduction of bacterial counts in the urine.
Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases Guideline for Treatment of Uncomplicated UTI. TMP-SMX, trimethoprim-sulfamethoxazole; DS, double-strength.

- Fluoroquinolones should be used only when other antibiotics are not suitable because of increasing resistance or their role in prompting nosocomial outbreaks of *Clostridium difficile* infection.
- Except for pivmecillinam, β-lactam agents are associated with lower rates of pathogen eradication and higher rates of relapse.

- **Pyelonephritis** Given high rates of TMP-SMX-resistant *E. coli*, fluoroquinolones (e.g., ciprofloxacin, 500 mg PO bid for 7 days) are first-line agents for the treatment of acute uncomplicated pyelonephritis. Oral TMP-SMX (one double-strength tablet bid for 14 days) is effective against susceptible uropathogens.
- **UTI in pregnant women** Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy.
- **UTI in men** In men with apparently uncomplicated UTI, a 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended.
  - If acute bacterial prostatitis is suspected, antibiotics should be initiated after urine and blood are obtained for cultures.
  - Therapy can be tailored to urine culture results and should be continued for 2–4 weeks; a 4- to 6-week course is often necessary for chronic bacterial prostatitis.
- **Asymptomatic bacteriuria** ABU should be treated only in pregnant women, in pts undergoing urologic surgery, and perhaps in neutropenic pts and renal transplant recipients. Antibiotic choice is guided by culture results.
- **Catheter-associated UTI** Urine culture results are essential to guide therapy.
  - Replacing the catheter during treatment is generally necessary. Candiduria, a common complication of indwelling catheterization, resolves in ~1/3 of asymptomatic cases with catheter removal.
  - Treatment of candiduria (fluconazole, 200–400 mg/d for 14 days) is recommended for pts who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease.

Prevention of Recurrent UTI

Women experiencing symptomatic UTIs ≥2 times a year are candidates for prophylaxis—either continuous or postcoital—or pt-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. Pt-initiated therapy involves supplying the pt with materials for urine culture and for self-medication with a course of antibiotics at the first symptoms of infection.

Prognosis

In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure.

INTERSTITIAL CYSTITIS

Interstitial cystitis (painful bladder syndrome) is a chronic condition characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia.

Epidemiology

In the United States, 3–6% of women and 2–4% of men have interstitial cystitis. Among women, the average age at onset is the early forties, but the range is from childhood through the early sixties.

Etiology

The etiology remains unknown.

- Theoretical possibilities include chronic bladder infection, inflammatory factors such as mast cells, autoimmunity, increased permeability of the bladder mucosa, and unusual pain sensitivity.
- However, few data support any of these factors as an inciting cause.

Clinical Manifestations

The cardinal symptoms of pain (often at ≥2 sites), urinary urgency and frequency, and nocturia occur in no consistent order. Symptoms can begin acutely or gradually.

- Unlike pelvic pain arising from other sources, pain caused by interstitial cystitis is exacerbated by bladder filling and relieved by bladder emptying.
- 85% of pts void >10 times per day; some do so as often as 60 times per day.
- Many pts with interstitial cystitis have comorbid functional somatic syndromes (e.g., fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, migraine).

Diagnosis

The diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation (e.g., diseases that manifest with pelvic pain and/or urinary symptoms; functional somatic syndromes with urinary symptoms); physical exam and laboratory findings are insensitive and/or nonspecific. Cystoscopy may reveal an ulcer (10% of pts) or petechial hemorrhages after bladder distension, but neither of these findings is specific.

TREATMENT **INTERSTITIAL CYSTITIS**

The goal of therapy is the relief of symptoms, which often requires a multifaceted approach (e.g., education, stress reduction, dietary changes, medications such as nonsteroidal anti-inflammatory drugs or amitriptyline, pelvic-floor physical therapy, and treatment of associated functional somatic syndromes).



For a more detailed discussion, see Warren JW: Dysuria, Bladder Pain, and the Interstitial Cystitis/Bladder Pain Syndrome, Chap. 60e; and Gupta K, Trautner BW: Urinary Tract Infections, Pyelonephritis, and Prostatitis, Chap. 162, p. 861, in HPIM-19.

145 Nephrolithiasis

Renal calculi are common, affecting ~1% of the population, and recurrent in more than half of pts. Stone formation begins when urine becomes supersaturated with insoluble components due to (1) low urinary volume, (2) excessive or insufficient excretion of selected compounds, or (3) other factors (e.g., urinary pH) that diminish

solubility. Approximately 75% of stones are Ca-based (the majority Ca oxalate; also Ca phosphate and other mixed stones), 15% struvite (magnesium-ammonium-phosphate), 5% uric acid, and 1% cystine, reflecting the metabolic disturbance(s) from which they arise.

SIGNS AND SYMPTOMS

Stones in the renal pelvis may be asymptomatic or cause hematuria alone; with passage, obstruction may occur at any site along the collecting system. Obstruction related to the passing of a stone leads to severe pain, often radiating to the groin, sometimes accompanied by intense visceral symptoms (i.e., nausea, vomiting, diaphoresis, light-headedness), hematuria, pyuria, urinary tract infection (UTI), and, rarely, hydronephrosis. In contrast, staghorn calculi, associated with recurrent UTI with urea-splitting organisms (*Proteus*, *Klebsiella*, *Providencia*, *Morganella*, and others), may be completely asymptomatic, presenting with loss of renal function.

STONE COMPOSITION

Most stones are composed of Ca oxalate. These may be associated with hypercalciuria and/or hyperoxaluria. Hypercalciuria can be seen in association with a very high-Na diet, loop diuretic therapy, distal (type I) renal tubular acidosis (RTA), sarcoidosis, Cushing's syndrome, aldosterone excess, or conditions associated with hypercalcemia (e.g., primary hyperparathyroidism, vitamin D excess, milk-alkali syndrome), or it may be idiopathic.

Hyperoxaluria may be seen with intestinal (especially ileal) malabsorption syndromes (e.g., inflammatory bowel disease, pancreatitis), due to reduced intestinal secretion of oxalate and/or the binding of intestinal Ca by fatty acids within the bowel lumen, with enhanced absorption of free oxalate and hyperoxaluria. Ca oxalate stones may also form due to (1) a deficiency of urinary citrate, an inhibitor of stone formation that is underexcreted with metabolic acidosis; and (2) hyperuricosuria (see below). Ca phosphate stones are much less common and tend to occur in the setting of an abnormally high urinary pH (7–8), usually in association with a complete or partial distal RTA.

Struvite stones form in the collecting system when infection with urea-splitting organisms is present. Struvite is the most common component of staghorn calculi and obstruction. Risk factors include previous UTI, nonstruvite stone disease, urinary catheters, neurogenic bladder (e.g., with diabetes or multiple sclerosis), and instrumentation.

Uric acid stones develop when the urine is saturated with uric acid in the presence of an acid urine pH; pts typically have underlying metabolic syndrome and insulin resistance, often with clinical gout, associated with a relative defect in ammoniagenesis and urine pH that is <5.4 and often <5.0. Pts with myeloproliferative disorders and other causes of secondary hyperuricemia and hyperuricosuria due to increased purine biosynthesis and/or urate production are at risk for stones if the urine volume diminishes. Hyperuricosuria without hyperuricemia may be seen in association with certain drugs (e.g., probenecid, high-dose salicylates).

Cystine stones are the result of a rare inherited defect in renal and intestinal transport of several dibasic amino acids; the overexcretion of cystine (cysteine disulfide), which is relatively insoluble, leads to nephrolithiasis. Stones begin in childhood and are a rare cause of staghorn calculi; they occasionally lead to end-stage renal disease. Cystine stones are more likely to form in acidic urinary pH.

WORKUP

Although some have advocated a complete workup after a first stone episode, others would defer that evaluation until there has been evidence of recurrence or if

TABLE 145-1 WORKUP FOR AN OUTPATIENT WITH A RENAL STONE

1. Dietary and fluid intake history
2. Careful medical history and physical examination, focusing on systemic diseases
3. Noncontrast helical CT, with 5-mm CT cuts
4. Routine UA; presence of crystals, hematuria, measurement of urine pH
5. Serum chemistries: BUN, Cr, uric acid, calcium, phosphate, chloride, bicarbonate, PTH
6. Timed urine collections (at least 1 day during week, 1 day on weekend): Cr, Na, K, urea nitrogen, uric acid, calcium, phosphate, oxalate, citrate, pH

Abbreviations: Cr, creatinine; PTH, parathyroid hormone.

there is no obvious cause (e.g., low fluid intake during the summer months with obvious dehydration). Table 145-1 outlines a reasonable workup for an outpatient with an uncomplicated kidney stone. On occasion, a stone is recovered and can be analyzed for content, yielding important clues to pathogenesis and management. For example, a predominance of Ca phosphate suggests underlying distal RTA or hyperparathyroidism.

TREATMENT NEPHROLITHIASIS

Treatment of renal calculi is often empirical, based on odds (Ca oxalate stones most common), clinical history, and/or the metabolic workup. An increase in fluid intake to at least 2.5–3 L/d is perhaps the single most effective intervention, regardless of the type of stone. Con servative recommendations for pts with Ca oxalate stones (i.e., low-salt, low-fat, moderate-protein diet) are thought to be healthful in general and therefore advisable in pts whose condition is otherwise uncomplicated. In contrast to prior assumptions, dietary calcium intake does not contribute to stone risk; rather, dietary calcium may help to reduce oxalate absorption and reduce stone risk. Table 145-2 outlines stone-specific therapies for pts with complex or recurrent nephrolithiasis.

TABLE 145-2 SPECIFIC THERAPIES FOR NEPHROLITHIASIS

Stone Type	Dietary Modifications	Other
Calcium oxalate	Increase fluid intake Moderate sodium intake	Citrate supplementation (calcium or potassium salts > sodium)
	Moderate oxalate intake Moderate protein intake Moderate fat intake	Cholestyramine or other therapy for fat malabsorption Thiazides if hypercalciuric Allopurinol if hyperuricosuric
Calcium phosphate	Increase fluid intake	Thiazides if hypercalciuric
	Moderate sodium intake	Treat hyperparathyroidism if present Alkali for distal renal tubular acidosis

(*Continued*)

TABLE 145-2 SPECIFIC THERAPIES FOR NEPHROLITHIASIS (*CONTINUED*)

Struvite	Increase fluid intake; same as calcium oxalate if evidence of calcium oxalate nidus for struvite	Methenamine and vitamin C or daily suppressive antibiotic therapy (e.g., trimethoprim-sulfamethoxazole)
Uric acid	Increase fluid intake	Allopurinol
	Moderate dietary protein intake	Alkali therapy (K^+ citrate) to raise urine pH to 6.0–6.5
Cystine	Increase fluid intake	Alkali therapy
		Penicillamine

Note: Sodium excretion correlates with calcium excretion.

For a more detailed discussion, see Curhan, GC: Nephrolithiasis, Chap. 342, p. 1866, in HPIM-19.

146 Urinary Tract Obstruction

Urinary tract obstruction (UTO), a potentially reversible cause of renal failure (RF), should be considered in all cases of acute or abrupt worsening of chronic RF. Consequences depend on duration and severity and whether the obstruction is unilateral or bilateral. UTO may occur at any level from collecting tubule to urethra. It is preponderant in women (pelvic tumors), elderly men (prostatic disease), diabetic pts (papillary necrosis), pts with neurologic diseases (spinal cord injury or multiple sclerosis, with neurogenic bladder), and individuals with retroperitoneal lymphadenopathy or fibrosis, vesicoureteral reflux, nephrolithiasis, or other causes of functional urinary retention (e.g., anticholinergic drugs).

CLINICAL MANIFESTATIONS

Pain can occur in some settings (obstruction due to stones) but is not common. In men, there is frequently a history of lower urinary tract symptoms, e.g., hesitancy, urgency, or frequent nocturia. Physical examination may reveal an enlarged bladder by percussion over the lower abdominal wall; bedside ultrasound assessment ("bladder scan") can be helpful to assess the postvoid bladder volume. Other findings depend on the clinical scenario. Prostatic hypertrophy can be determined by digital rectal examination. A bimanual examination in women may show a pelvic or rectal mass. The workup of pts with RF suspected of having UTO is shown in Fig. 146-1. Laboratory studies may show marked elevations of blood urea nitrogen and creatinine; if the obstruction has been of sufficient duration, there may be evidence of tubulointerstitial disease (e.g., hyperkalemia, non-anion-gap metabolic acidosis, mild hypernatremia). Urinalysis is most often benign or with a small number of

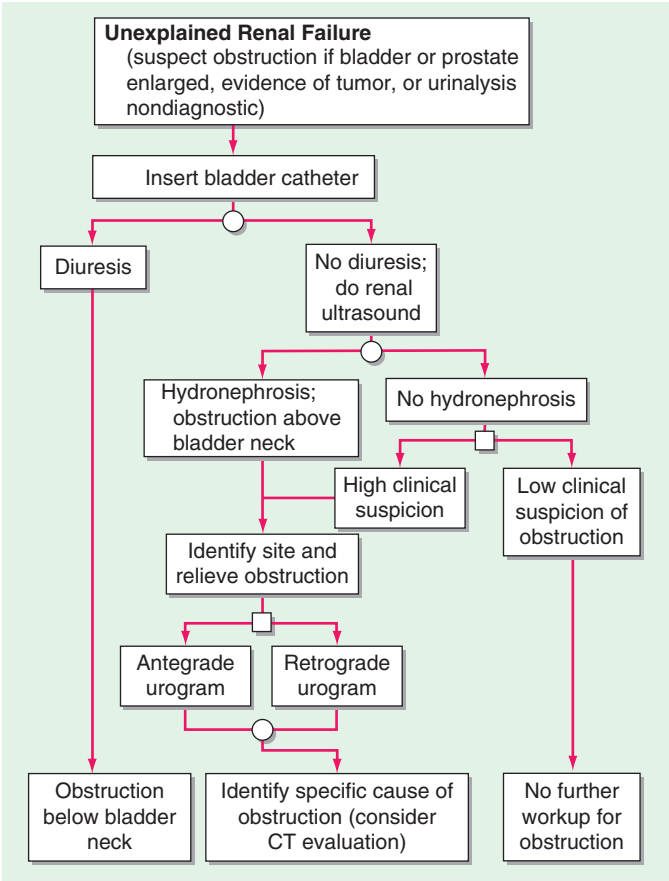


FIGURE 146-1 Diagnostic approach for urinary tract obstruction in unexplained renal failure. Circles represent diagnostic procedures, and squares indicate clinical decisions based on available data.

cells; heavy proteinuria is rare. An obstructing stone may be visualized on abdominal radiography or helical noncontrast CT with 5-mm cuts.

Ultrasonography can be used to assess the degree of hydronephrosis and the integrity of the renal parenchyma; CT or IV urography may be required to localize the level of obstruction. Calyceal dilation is commonly seen; it may be absent with hyperacute obstruction, upper tract encasement by tumor or retroperitoneal fibrosis, or indwelling staghorn calculi. A nuclear renal scan to assess excretion of the radioisotope technetium Tc-99m mertiatide (Tc-99m MAG3), before and after administration of a loop diuretic may be helpful for functional assessment of obstruction; it can also identify a difference in function between the two kidneys. Imaging in retroperitoneal fibrosis with associated periaortitis classically reveals a periaortic, confluent mass encasing the anterior and lateral sides of the aorta. Kidney size may indicate the duration of obstruction. It should be noted that unilateral obstruction may be prolonged and severe (ultimately leading to loss of renal function in the obstructed kidney), with no hint of abnormality on physical examination and laboratory survey.

TREATMENT URINARY TRACT OBSTRUCTION

Management of acute RF associated with UTO is dictated by (1) the level of obstruction (upper vs lower tract), and (2) the acuity of the obstruction and its clinical consequences, including renal dysfunction and infection. Benign causes of UTO, including bladder outlet obstruction and nephrolithiasis, should be ruled out because conservative management, including Foley catheter placement and IV fluids, respectively, will usually relieve the obstruction in most cases.

Among more seriously ill pts, ureteral obstruction due to tumor is the most common and concerning cause of UTO. If technically feasible, ureteral obstruction due to tumor is best managed by cystoscopic placement of a ureteral stent. Otherwise, the placement of nephrostomy tubes with external drainage may be required. IV antibiotics should also be given if there are signs of pyelonephritis or urosepsis. In addition to ureteral stenting, pts with idiopathic retroperitoneal fibrosis are typically treated with immunosuppression (prednisone, mycophenolate mofetil, and/or tamoxifen).

Fluid and electrolyte status should be carefully monitored after obstruction is relieved. There may be a physiologic natriuresis/diuresis related to volume overload. However, there may be an "inappropriate" natriuresis/diuresis related to (1) elevated urea nitrogen, leading to an osmotic diuresis; and (2) acquired nephrogenic diabetes insipidus. Hypernatremia, sometimes of a severe degree, may develop.

For a more detailed discussion, see Seifter JL: Urinary Tract Obstruction, Chap. 343, p. 1871, in HPIM-19.

147 Peptic Ulcer and Related Disorders

PEPTIC ULCER DISEASE

Peptic ulcer disease (PUD) occurs most commonly in duodenal bulb (duodenal ulcer, DU) and stomach (gastric ulcer, GU). It may also occur in esophagus, pyloric channel, duodenal loop, jejunum, and Meckel's diverticulum. PUD results when "aggressive" factors (gastric acid, pepsin) overwhelm "defensive" factors involved in mucosal resistance (gastric mucus, bicarbonate, microcirculation, prostaglandins, mucosal "barrier") and from effects of *Helicobacter pylori*.

CAUSES AND RISK FACTORS

General

H. pylori is a spiral urease-producing organism that colonizes gastric antral mucosa in up to 100% of persons with DU and 80% with GU. It is also found in normals (increasing prevalence with age) and in those of low socioeconomic status. *H. pylori* is invariably associated with histologic evidence of active chronic gastritis, which over years can lead to atrophic gastritis and gastric cancer. The other major cause of ulcers (those not due to *H. pylori*) is nonsteroidal anti-inflammatory drugs (NSAIDs). Fewer than 1% are due to gastrinoma (Zollinger-Ellison [Z-E] syndrome). Other risk factors and associations: hereditary (? increased parietal cell number), smoking, hypercalcemia, mastocytosis, blood group O (antigens may bind *H. pylori*). Unproven: stress, coffee, alcohol.

Duodenal Ulcer

Mild gastric acid hypersecretion resulting from (1) increased release of gastrin, presumably due to (a) stimulation of antral G cells by cytokines released by inflammatory cells and (b) diminished production of somatostatin by D cells, both resulting from *H. pylori* infection; and (2) an exaggerated acid response to gastrin due to an increased parietal cell mass resulting from gastrin stimulation. These abnormalities reverse rapidly with eradication of *H. pylori*. However, a mildly elevated maximum gastric acid output in response to exogenous gastrin persists in some pts long after eradication of *H. pylori*, suggesting that gastric acid hypersecretion may be, in part, genetically determined. *H. pylori* may also result in elevated serum pepsinogen levels. Mucosal defense in duodenum is compromised by toxic effects of *H. pylori* infection on patches of gastric metaplasia that result from gastric acid hypersecretion or rapid gastric emptying. Other risk factors include glucocorticoids, NSAIDs, chronic renal failure, renal transplantation, cirrhosis, and chronic lung disease.

Gastric Ulcer

H. pylori is also principal cause. Gastric acid secretory rates are usually normal or reduced, possibly reflecting earlier age of infection by *H. pylori* than in DU pts. Gastritis due to reflux of duodenal contents (including bile) may play a role. Chronic salicylate or NSAID use may account for 15–30% of GUs and increase risk of associated bleeding, perforation.

CLINICAL FEATURES

Duodenal Ulcer

Burning epigastric pain 90 min to 3 h after meals, often nocturnal, relieved by food.

Gastric Ulcer

Burning epigastric pain made worse by or unrelated to food; anorexia, food aversion, weight loss (in 40%). Great individual variation. Similar symptoms may occur in persons without demonstrated peptic ulcers ("nonulcer dyspepsia"); less responsive to standard therapy.

COMPLICATIONS

Bleeding, obstruction, penetration causing acute pancreatitis, perforation, intractability.

DIAGNOSIS

Duodenal Ulcer

Upper endoscopy or upper gastrointestinal (GI) barium radiography.

Gastric Ulcer

Upper endoscopy preferable to exclude possibility that ulcer is malignant (brush cytology, ≥6 pinch biopsies of ulcer margin). Radiographic features suggesting malignancy: ulcer within a mass, folds that do not radiate from ulcer margin, a large ulcer (>2.5–3 cm).

DETECTION OF *H. PYLORI*

Detection of antibodies in serum (inexpensive, preferred when endoscopy is not required); rapid urease test of antral biopsy (when endoscopy is required). Urea breath test generally used to confirm eradication of *H. pylori*, if necessary. The fecal antigen test is sensitive, specific, and inexpensive (Table 147-1).

TABLE 147-1 TESTS FOR DETECTION OF *H. PYLORI*

Test	Sensitivity/ Specificity, %	Comments
Invasive (endoscopy/biopsy required)		
Rapid urease	80–95/95–100	Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds
Histology	80–90/>95	Requires pathology processing and staining; provides histologic information
Culture	—/—	Time consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility
Noninvasive		
Serology	>80/>90	Inexpensive, convenient; not useful for early follow-up
Urea breath test	>90/>90	Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test); exposure to low-dose radiation with ^{14}C test
Stool antigen	>90/>90	Inexpensive, convenient; not established for eradication but promising

Abbreviation: PPIs, proton pump inhibitors.

TREATMENT PEPTIC ULCER DISEASE

MEDICAL Objectives: pain relief, healing, prevention of complications, prevention of recurrences. For GU, exclude malignancy (follow endoscopically to healing). Dietary restriction unnecessary with contemporary drugs; discontinue NSAIDs; smoking may prevent healing and should be stopped. Eradication of *H. pylori* markedly reduces rate of ulcer relapse and is indicated for all DUs and GUs associated with *H. pylori* (Table 147-2). Acid suppression is generally included in regimen. Reinfection rates are <1%/year. Standard drugs (H_2 receptor blockers, sucralfate, antacids) heal 80–90% of DUs and 60% of GUs in 6 weeks; healing is more rapid with omeprazole (20 mg/d).

SURGERY Used for complications (persistent or recurrent bleeding, obstruction, perforation) or, uncommonly, intractability (first screen for surreptitious NSAID use and gastrinoma). For DU, see Table 147-3. For GU, perform subtotal gastrectomy.

COMPLICATIONS OF SURGERY (1) Obstructed afferent loop (Billroth II), (2) bile reflux gastritis, (3) dumping syndrome (rapid gastric emptying with abdominal distress + postprandial vasomotor symptoms), (4) postvagotomy diarrhea, (5) bezoar, (6) anemia (iron, B_{12}, folate malabsorption), (7) malabsorption (poor mixing of gastric contents, pancreatic juices, bile; bacterial overgrowth), (8) osteomalacia and osteoporosis (vitamin D and Ca malabsorption), (9) gastric remnant carcinoma.

APPROACH TO THE PATIENT: **Peptic Ulcer Disease**

Optimal approach is uncertain. Serologic testing for *H. pylori* and treating, if present, may be cost-effective. Other options include trial of acid-suppressive therapy, endoscopy only in treatment failures, or initial endoscopy in all cases.

TABLE 147-2 REGIMENS RECOMMENDED FOR ERADICATION OF *H. PYLORI* INFECTION

Drug	Dose
Triple therapy	
1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline[a]	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin or metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole[b] *or*	500 mg bid
Amoxicillin[c]	1 g bid
Quadruple therapy	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

[a]Alternative: use prepacked Helidac.
[b]Alternative: use prepacked Prevpac.
[c]Use either metronidazole or amoxicillin, not both.

TABLE 147-3 SURGICAL TREATMENT OF DUODENAL ULCER

Operation	Recurrence Rate	Complication Rate
Vagotomy + antrectomy (Billroth I or II)[a]	1%	Highest
Vagotomy and pyloroplasty	10%	Intermediate
Parietal cell (proximal gastric, superselective) vagotomy	≥10%	Lowest

[a]Billroth I, gastroduodenostomy; Billroth II, gastrojejunostomy.

GASTROPATHIES

EROSIVE GASTROPATHIES

Hemorrhagic gastritis, multiple gastric erosions may be caused by aspirin and other NSAIDs (lower risk with newer agents, e.g., nabumetone and etodolac, which do not inhibit gastric mucosal prostaglandins) or severe stress (burns, sepsis, trauma, surgery, shock, or respiratory, renal, or liver failure). Pt may be asymptomatic or experience epigastric discomfort, nausea, hematemesis, or melena. Diagnosis is made by upper endoscopy.

TREATMENT EROSIVE GASTROPATHIES

Removal of offending agent and maintenance of O_2 and blood volume as required. For prevention of stress ulcers in critically ill pts, hourly oral administration of liquid antacids (e.g., Maalox 30 mL), IV H_2 receptor antagonist (e.g., cimetidine, 300-mg bolus + 37.5–50 mg/h IV), or both is recommended to maintain gastric pH > 4. Alternatively, sucralfate slurry, 1 g PO q6h, can be given; does not raise gastric pH and may thus avoid increased risk of aspiration pneumonia associated with liquid antacids. Pantoprazole can be administered IV to suppress gastric acid in the critically ill. Misoprostol, 200 μg PO qid, or profound acid suppression (e.g., famotidine, 40 mg PO bid) can be used with NSAIDs to prevent NSAID-induced ulcers.

CHRONIC GASTRITIS

Identified histologically by an inflammatory cell infiltrate dominated by lymphocytes and plasma cells with scant neutrophils. In its early stage, the changes are limited to the lamina propria (*superficial gastritis*). When the disease progresses to destroy glands, it becomes *atrophic gastritis*. The final stage is *gastric atrophy*, in which the mucosa is thin and the infiltrate sparse. Chronic gastritis can be classified based on predominant site of involvement.

Type A Gastritis

This is the body-predominant and less common form. Generally asymptomatic, common in elderly; autoimmune mechanism may be associated with achlorhydria, pernicious anemia, and increased risk of gastric cancer (value of screening endoscopy uncertain). Antibodies to parietal cells present in >90%.

Type B Gastritis

This is antral-predominant disease and caused by *H. pylori*. Often asymptomatic but may be associated with dyspepsia. Atrophic gastritis, gastric atrophy, gastric lymphoid follicles, and gastric B cell lymphomas may occur. Infection early in life or in setting of malnutrition or low gastric acid output is associated with gastritis of entire stomach (including body) and increased risk of gastric cancer. Eradication of

H. pylori (Table 147-2) not routinely recommended unless PUD or gastric mucosa-associated lymphoid tissue (MALT) lymphoma is present.

SPECIFIC TYPES OF GASTROPATHY OR GASTRITIS

Alcoholic gastropathy (submucosal hemorrhages), Ménétrier's disease (hypertrophic gastropathy), eosinophilic gastritis, granulomatous gastritis, Crohn's disease, sarcoidosis, infections (tuberculosis, syphilis, fungi, viruses, parasites), pseudolymphoma, radiation, corrosive gastritis.

ZOLLINGER-ELLISON (Z-E) SYNDROME (GASTRINOMA)

Consider when ulcer disease is severe, refractory to therapy, associated with ulcers in atypical locations, or associated with diarrhea. Tumors are usually pancreatic or in duodenum (submucosal, often small), may be multiple, slowly growing; >60% malignant; 25% associated with MEN 1, i.e., multiple endocrine neoplasia type 1 (gastrinoma, hyperparathyroidism, pituitary neoplasm), often duodenal, small, multicentric, less likely to metastasize to liver than pancreatic gastrinomas but often metastasize to local lymph nodes.

DIAGNOSIS

Suggestive

Basal acid output >15 mmol/h; basal/maximal acid output >60%; large mucosal folds on endoscopy or upper GI radiograph.

Confirmatory

Serum gastrin >1000 ng/L or rise in gastrin of 200 ng/L following IV secretin and, if necessary, rise of 400 ng/L following IV calcium (Table 147-4).

DIFFERENTIAL DIAGNOSIS

Increased Gastric Acid Secretion

Z-E syndrome, antral G-cell hyperplasia or hyperfunction (? due to *H. pylori*), post-gastrectomy retained antrum, renal failure, massive small bowel resection, chronic gastric outlet obstruction.

Normal or Decreased Gastric Acid Secretion

Pernicious anemia, chronic gastritis, gastric cancer, vagotomy, pheochromocytoma.

TREATMENT ZOLLINGER-ELLISON SYNDROME

Omeprazole (or lansoprazole), beginning at 60 mg PO q A.M. and increasing until maximal gastric acid output is <10 mmol/h before next dose, is drug of choice during evaluation and in pts who are not surgical candidates; dose can often be reduced over time. Radiolabeled octreotide scanning has emerged as the

TABLE 147-4 DIFFERENTIAL DIAGNOSTIC TESTS

Condition	Fasting Gastrin	Gastrin Response to	
		IV Secretin	Food
DU	N (≤150 ng/L)	NC	Slight ↑
Z-E	↑↑↑	↑↑↑	NC
Antral G (gastrin) cell hyperplasia	↑	↑, NC	↑↑↑

Abbreviations: DU, duodenal ulcer; N, normal; NC, no change; Z-E, Zollinger-Ellison syndrome.

most sensitive test for detecting primary tumors and metastases; may be supplemented by endoscopic ultrasonography. Exploratory laparotomy with resection of primary tumor and solitary metastases is done when possible. In pts with MEN 1, tumor is often multifocal and unresectable; treat hyperparathyroidism first (hypergastrinemia may improve). For unresectable tumors, parietal cell vagotomy may enhance control of ulcer disease by drugs. Chemotherapy is used for metastatic tumor to control symptoms (e.g., streptozocin, 5-fluorouracil, doxorubicin, or interferon α); 40% partial response rate. Newer agents effective in pancreatic neuroendocrine tumors have not been evaluated.

For a more detailed discussion, see Del Valle J: Peptic Ulcer Disease and Related Disorders, Chap. 348, p. 1911, in HPIM-19.

148 Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of unknown etiology involving the gastrointestinal (GI) tract. Peak occurrence is between ages 15 and 30 and between ages 60 and 80, but onset may occur at any age. Epidemiologic features are shown in Table 148-1. Pathogenesis of IBD involves activation of immune cells by unknown inciting agent (? microorganism, dietary component, bacterial or self-antigen) leading to release of cytokines and inflammatory mediators. Genetic component suggested by increased risk in first-degree relatives of pts with IBD and concurrence of type of IBD, location of Crohn's disease (CD), and clinical

TABLE 148-1 EPIDEMIOLOGY OF IBD

	Ulcerative Colitis	Crohn's Disease
Incidence (North America) per person-years	0–19.2 per 100,000	0–20.2 per100,000
Age of onset	15–30 and 60–80	15–30 and 60–80
Ethnicity	Jewish > non-Jewish white > African American > Hispanic > Asian	
Male/female ratio	0.51–1.58	0.34–1.65
Smoking	May prevent disease (OR 0.58)	May cause disease (OR 1.76)
Oral contraceptives	No increased risk	OR 1.4
Appendectomy	Protective (risk 13–26% lower)	Not protective
Monozygotic twins	6–18% concordance	38–58% concordance
Dizygotic twins	0–2% concordance	4% concordance

Abbreviation: IBD, inflammatory bowel disease; OR, odds ratio.

course. Reported associations include HLA-DR2 in Japanese pts with ulcerative colitis (UC) and a CD-related gene called *CARD15* on chromosome 16p. *CARD15* mutations may account for 10% of CD risk. Other potential pathogenic factors include serum antineutrophil cytoplasmic antibodies (ANCA) in 70% of pts with UC (also in 5–10% of CD pts) and antibodies to *Saccharomyces cerevisiae* (ASCA) in 60–70% of CD pts (also in 10–15% of UC pts and 5% of normal controls). Granulomatous angiitis (vasculitis) may occur in CD. Acute flares may be precipitated by infections, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress. Onset of UC often follows cessation of smoking.

ULCERATIVE COLITIS (UC)

PATHOLOGY

Colonic mucosal inflammation; rectum almost always involved, with inflammation extending continuously (no skip areas) proximally for a variable extent; histologic features include epithelial damage, inflammation, crypt abscesses, loss of goblet cells.

CLINICAL MANIFESTATIONS

Bloody diarrhea, mucus, fever, abdominal pain, tenesmus, weight loss; spectrum of severity (majority of cases are mild, limited to rectosigmoid). In severe cases, dehydration, anemia, hypokalemia, hypoalbuminemia.

COMPLICATIONS

Toxic megacolon, colonic perforation; cancer risk related to extent and duration of colitis; often preceded by or coincident with dysplasia, which may be detected on surveillance colonoscopic biopsies.

DIAGNOSIS

Sigmoidoscopy/colonoscopy: mucosal erythema, granularity, friability, exudate, hemorrhage, ulcers, inflammatory polyps (pseudopolyps). Barium enema: loss of haustrations, mucosal irregularity, ulcerations.

CROHN'S DISEASE (CD)

PATHOLOGY

Any part of GI tract, usually terminal ileum and/or colon; transmural inflammation, bowel wall thickening, linear ulcerations, and submucosal thickening leading to cobblestone pattern; discontinuous (skip areas); histologic features include transmural inflammation, granulomas (often absent), fissures, fistulas.

CLINICAL MANIFESTATIONS

Fever, abdominal pain, diarrhea (often without blood), fatigue, weight loss, growth retardation in children; acute ileitis mimicking appendicitis; anorectal fissures, fistulas, abscesses. Clinical course falls into three broad patterns: (1) inflammatory, (2) stricturing, and (3) fistulizing.

COMPLICATIONS

Intestinal obstruction (edema vs. fibrosis); rarely toxic megacolon or perforation; intestinal fistulas to bowel, bladder, vagina, skin, soft tissue, often with abscess formation; bile salt malabsorption leading to cholesterol gallstones and/or oxalate kidney stones; intestinal malignancy; amyloidosis.

DIAGNOSIS

Sigmoidoscopy/colonoscopy, barium enema, upper GI and small-bowel series: nodularity, rigidity, ulcers that may be deep or longitudinal, cobblestoning, skip areas, strictures, fistulas. CT may show thickened, matted bowel loops or an abscess.

DIFFERENTIAL DIAGNOSIS

INFECTIOUS ENTEROCOLITIS

Shigella, *Salmonella*, *Campylobacter*, *Yersinia* (acute ileitis), *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Escherichia coli* serotype O157:H7, *Gonorrhea*, *Lymphogranuloma venereum*, *Clostridium difficile* (pseudomembranous colitis), tuberculosis, amebiasis, cytomegalovirus, AIDS.

OTHERS

Ischemic bowel disease, appendicitis, diverticulitis, radiation enterocolitis, bile salt–induced diarrhea (ileal resection), drug-induced colitis (e.g., NSAIDs), bleeding colonic lesion (e.g., neoplasm), irritable bowel syndrome (no bleeding), microscopic (lymphocytic) or collagenous colitis (chronic watery diarrhea)—normal colonoscopy, but biopsies show superficial colonic epithelial inflammation and, in collagenous colitis, a thick subepithelial layer of collagen; response to aminosalicylates and glucocorticoids variable.

EXTRAINTESTINAL MANIFESTATIONS OF UC AND CD

1. *Joint:* peripheral arthritis—parallels activity of bowel disease; ankylosing spondylitis and sacroiliitis (associated with HLA-B27)—activity independent of bowel disease
2. *Skin:* erythema nodosum, aphthous ulcers, pyoderma gangrenosum, cutaneous CD
3. *Eye:* conjunctivitis, episcleritis, iritis, uveitis
4. *Liver:* fatty liver, "pericholangitis" (intrahepatic sclerosing cholangitis), primary sclerosing cholangitis, cholangiocarcinoma, chronic hepatitis
5. *Others:* autoimmune hemolytic anemia, phlebitis, pulmonary embolus (hypercoagulable state), kidney stones, metabolic bone disease

TREATMENT INFLAMMATORY BOWEL DISEASES (FIG. 48-1)

SUPPORTIVE Antidiarrheal agents (diphenoxylate and atropine, loperamide) in mild disease; IV hydration and blood transfusions in severe disease; parenteral nutrition or defined enteral formulas—effective as primary therapy in CD, although high relapse rate when oral feeding is resumed; should not replace drug therapy; important role in preoperative preparation of malnourished pt; emotional support.

SULFASALAZINE AND AMINOSALICYLATES Active component of sulfasalazine is 5-aminosalicylic acid (5-ASA) linked to sulfapyridine carrier; useful in colonic disease of mild to moderate severity (1–1.5 g PO qid); efficacy in maintaining remission demonstrated only for UC (500 mg PO qid). Toxicity (generally due to sulfapyridine component): dose related—nausea, headache, rarely hemolytic anemia—may resolve when drug dose is lowered; idiosyncratic—fever, rash, neutropenia, pancreatitis, hepatitis, etc.; miscellaneous—oligospermia. Newer aminosalicylates are as effective as sulfasalazine but with fewer side effects. Enemas containing 4 g of 5-ASA (mesalamine) may be used in distal UC, one nightly retained qhs until remission, then q2hs or q3hs. Suppositories containing 500 mg of 5-ASA may be used in proctitis.

GLUCOCORTICOIDS Useful in severe disease and ileal or ileocolonic CD. Prednisone, 40–60 mg PO qd, then taper; IV hydrocortisone, 100 mg tid or equivalent, in hospitalized pts; IV adrenocorticotropic hormone drip (120 U qd) may be preferable in first attacks of UC. Nightly hydrocortisone retention enemas in proctosigmoiditis. Numerous side effects make long-term use problematic.

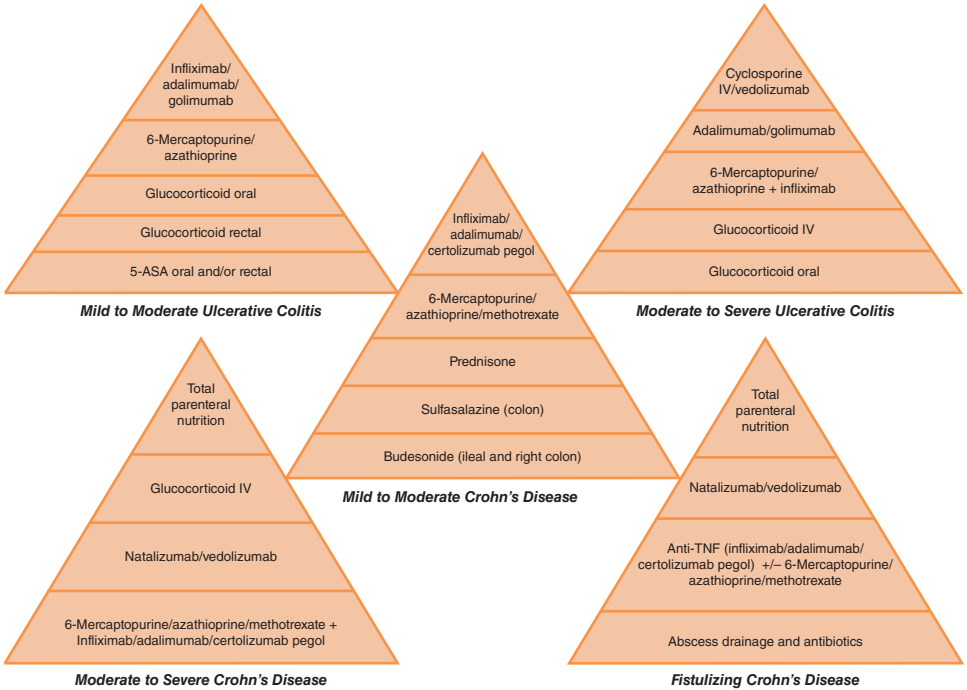


FIGURE 148-1 Medical management of IBD. 5-ASA, 5-aminosalicylic acid.

IMMUNOSUPPRESSIVE AGENTS Azathioprine, 6-mercaptopurine—50 mg PO qd up to 2.0 or 1.5 mg/kg qd, respectively. Useful as steroid-sparing agents and in intractable or fistulous CD (may require 2- to 6-month trial before efficacy seen). Toxicity—immunosuppression, pancreatitis, ?carcinogenicity. Avoid in pregnancy.

METRONIDAZOLE Appears effective in colonic CD (500 mg PO bid) and refractory perineal CD (10–20 mg/kg PO qd). Toxicity—peripheral neuropathy, metallic taste, ?carcinogenicity. Avoid in pregnancy. Other antibiotics (e.g., ciprofloxacin 500 mg PO bid) may be of value in terminal ileal and perianal CD, and broad-spectrum IV antibiotics are indicated for fulminant colitis and abscesses.

OTHERS Cyclosporine (potential value in a dose of 4 [mg/kg]/d IV for 7–14 days in severe UC and possibly intractable Crohn's fistulas); experimental—tacrolimus, methotrexate, chloroquine, fish oil, nicotine, others. Infliximab (monoclonal antibody to tumor necrosis factor [TNF]) 5 mg/kg IV induces responses in 65% (complete in 33%) of CD pts refractory to 5-ASA, glucocorticoids, and 6-mercaptopurine. In UC, 27–49% of pts respond.

Adalimumab is a humanized version of the anti-TNF antibody that is less likely to elicit neutralizing antibodies in the pt. Pegylated versions of anti-TNF antibody may be used once monthly.

Natalizumab is an anti-integrin antibody with activity against CD, but some pts develop progressive multifocal leukoencephalopathy. Vedolizumab is specific for α4β7 integrin and is more gut selective in its effects.

SURGERY UC: Colectomy (curative) for intractability, toxic megacolon (if no improvement with aggressive medical therapy in 24–48 h), cancer, dysplasia. Ileal pouch—anal anastomosis is operation of choice in UC, but contraindicated in CD and in elderly. CD: Resection for fixed obstruction (or stricturoplasty), abscesses, persistent symptomatic fistulas, intractability.

For a more detailed discussion, see Friedman S, Blumberg RS: Inflammatory Bowel Disease, Chap. 351, p. 1947, in HPIM-19.

149 Colonic and Anorectal Diseases

IRRITABLE BOWEL SYNDROME (IBS)

Characterized by altered bowel habits, abdominal pain, and absence of detectable organic pathology. Most common GI disease in clinical practice. Three types of clinical presentations: (1) spastic colon (chronic abdominal pain and constipation), (2) alternating constipation and diarrhea, or (3) chronic, painless diarrhea.

PATHOPHYSIOLOGY

Visceral hyperalgesia to mechanoreceptor stimuli is common. Reported abnormalities include altered colonic motility at rest and in response to stress, cholinergic drugs, cholecystokinin; altered small-intestinal motility; enhanced visceral sensation

TABLE 149-1 DIAGNOSTIC CRITERIA FOR IRRITABLE BOWEL SYNDROME[a]

Recurrent abdominal pain or discomfort[b] at least 3 days per month in the last 3 months associated with *two or more* of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.
[b]Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation is required for subject eligibility.
Source: Adapted from Longstreth GF et al: Functional bowel disorders. *Gastroenterology* 130:1480, 2006.

(lower pain threshold in response to gut distention); and abnormal extrinsic innervation of the gut. Pts presenting with IBS to a physician have an increased frequency of psychological disturbances—depression, hysteria, obsessive-compulsive disorder. Specific food intolerances and malabsorption of bile acids by the terminal ileum may account for a few cases.

CLINICAL MANIFESTATIONS

Onset often before age 30; females:males = 2:1. Abdominal pain and irregular bowel habits. Additional symptoms often include abdominal distention, relief of abdominal pain with bowel movement, increased frequency of stools with pain, loose stools with pain, mucus in stools, and sense of incomplete evacuation. Associated findings include pasty stools, ribbony or pencil-thin stools, heartburn, bloating, back pain, weakness, faintness, palpitations, and urinary frequency.

DIAGNOSIS

IBS is a diagnosis of exclusion. Rome criteria for diagnosis are shown in Table 149-1. Consider sigmoidoscopy and barium radiographs to exclude inflammatory bowel disease or malignancy; consider excluding giardiasis, intestinal lactase deficiency, and hyperthyroidism.

TREATMENT IRRITABLE BOWEL SYNDROME (TABLE 149-2)

Reassurance and supportive physician-pt relationship, avoidance of stress or precipitating factors, dietary bulk (fiber, psyllium extract, e.g., Metamucil one tbsp daily or bid); for diarrhea, trials of loperamide (2-mg tabs PO q A.M. then 1 PO after each loose stool to a maximum of 8/d, then titrate), diphenoxylate (Lomotil) (up to 2-mg tabs PO qid), or cholestyramine (up to 1-g packet mixed in water PO qid); for pain, anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid) or hyoscyamine as Levsin 1–2 PO q4h prn. Amitriptyline 25–50 mg PO qhs or other antidepressants in low doses may relieve pain. Selective serotonin reuptake inhibitors such as paroxetine are being evaluated in constipation-dominant pts, and serotonin receptor antagonists such as alosetron are being evaluated in diarrhea-dominant pts. Altering gut flora with probiotics (*Bifidobacterium infantis* 35624) or oral nonabsorbable antibiotics (rifaximin) is being evaluated with some promising early results. Psychotherapy, hypnotherapy of possible benefit in severe refractory cases. Some pts respond to dietary changes to eliminate or severely reduce fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS).

TABLE 149-2 POSSIBLE DRUGS FOR A DOMINANT SYMPTOM IN IBS

Symptom	Drug	Dose
Diarrhea	Loperamide	2–4 mg when necessary/ maximum 12 g/d
	Cholestyramine resin	4 g with meals
	Alosetron[a]	0.5–1 mg bid (for severe IBS, women)
Constipation	Psyllium husk	3–4 g bid with meals, then adjust
	Methylcellulose	2 g bid with meals, then adjust
	Calcium polycarbophil	1 g qd to qid
	Lactulose syrup	10–20 g bid
	70% sorbitol	15 mL bid
	Polyethylene glycol 3350	17 g in 250 mL water qd
	Lubiprostone (Amitiza)	24 mg bid
	Magnesium hydroxide	30–60 mL qd
Abdominal pain	Smooth-muscle relaxant	qd to qid ac
	Tricyclic antidepressants	Start 25–50 mg hs, then adjust
	Selective serotonin reuptake inhibitors	Begin small dose, increase as needed

[a]Available only in the United States.
Abbreviation: IBS, irritable bowel syndrome.
Source: Adapted from Longstreth GF et al: Functional bowel disorders. *Gastroenterology* 130:1480, 2006.

DIVERTICULAR DISEASE

Herniations or saclike protrusions of the mucosa through the muscularis at points of nutrient artery penetration; possibly due to increased intraluminal pressure, low-fiber diet; most common in sigmoid colon.

CLINICAL PRESENTATION

1. *Asymptomatic* (detected by barium enema or colonoscopy).
2. *Pain*: recurrent left lower quadrant pain relieved by defecation; alternating constipation and diarrhea. Diagnosis by barium enema.
3. *Diverticulitis*: pain, fever, altered bowel habits, tender colon, leukocytosis. Best confirmed and staged by CT after opacification of bowel. (In pts who recover with medical therapy, perform elective barium enema or colonoscopy in 4–6 weeks to exclude cancer.) Complications: pericolic abscess, perforation, fistula (to bladder, vagina, skin, soft tissue), liver abscess, stricture. Frequently require surgery or, for abscesses, percutaneous drainage.
4. *Hemorrhage*: usually in absence of diverticulitis, often from ascending colon and self-limited. If persistent, manage with mesenteric arteriography and intra-arterial infusion of vasopressin, or surgery (Chap. 41).

TREATMENT DIVERTICULAR DISEASE

PAIN High-fiber diet, psyllium extract (e.g., Metamucil 1 tbsp PO qd or bid), anticholinergics (e.g., dicyclomine HCl 10–40 mg PO qid).

DIVERTICULITIS NPO, IV fluids, antibiotics for 7–10 d (e.g., trimethoprim/sulfamethoxazole or ciprofloxacin and metronidazole; add ampicillin to cover enterococci in

nonresponders); for ambulatory pts, ampicillin/clavulanate (clear liquid diet); surgical resection in refractory or frequently recurrent cases, young persons (<age 50), immunosuppressed pts, or when there is inability to exclude cancer.

Pts who have had at least two documented episodes and those who respond slowly to medical therapy should be offered surgical options to achieve removal of the diseased colonic segment, controlling sepsis, eliminating obstructions or fistulas, and restoring intestinal continuity.

INTESTINAL PSEUDOOBSTRUCTION

Recurrent attacks of nausea, vomiting, and abdominal pain and distention mimicking mechanical obstruction; may be complicated by steatorrhea due to bacterial overgrowth.

CAUSES

Primary: Familial visceral neuropathy, familial visceral myopathy, idiopathic. *Secondary:* Scleroderma, amyloidosis, diabetes, celiac disease, parkinsonism, muscular dystrophy, drugs, electrolyte imbalance, postsurgical.

TREATMENT INTESTINAL PSEUDOOBSTRUCTION

For acute attacks: intestinal decompression with long tube. Oral antibiotics for bacterial overgrowth (e.g., metronidazole 250 mg PO tid, tetracycline 500 mg PO qid, or ciprofloxacin 500 mg bid 1 week out of each month, usually in an alternating rotation of at least two antibiotics). Avoid surgery. In refractory cases, consider long-term parenteral hyperalimentation.

VASCULAR DISORDERS (SMALL AND LARGE INTESTINE)

MECHANISMS OF MESENTERIC ISCHEMIA

(1) Occlusive: embolus (atrial fibrillation, valvular heart disease); arterial thrombus (atherosclerosis); venous thrombosis (trauma, neoplasm, infection, cirrhosis, oral contraceptives, antithrombin-III deficiency, protein S or C deficiency, lupus anticoagulant, factor V Leiden mutation, idiopathic); vasculitis (systemic lupus erythematosus, polyarteritis, rheumatoid arthritis, Henoch-Schönlein purpura); (2) nonocclusive: hypotension, heart failure, arrhythmia, digitalis (vasoconstrictor).

ACUTE MESENTERIC ISCHEMIA

Periumbilical pain out of proportion to tenderness; nausea, vomiting, distention, GI bleeding, altered bowel habits. Abdominal x-ray shows bowel distention, air-fluid levels, thumbprinting (submucosal edema), but may be normal early in course. Peritoneal signs indicate infarcted bowel requiring surgical resection. Early celiac and mesenteric arteriography is recommended in all cases following hemodynamic resuscitation (avoid vasopressors, digitalis). Intra-arterial vasodilators (e.g., papaverine) can be administered to reverse vasoconstriction. Laparotomy indicated to restore intestinal blood flow obstructed by embolus or thrombosis or to resect necrotic bowel. Postoperative anticoagulation indicated in mesenteric venous thrombosis, controversial in arterial occlusion.

CHRONIC MESENTERIC INSUFFICIENCY

"Abdominal angina": dull, crampy periumbilical pain 15–30 min after a meal and lasting for several hours; weight loss; occasionally diarrhea. Evaluate with mesenteric arteriography for possible bypass graft surgery.

ISCHEMIC COLITIS

Usually due to nonocclusive disease in pts with atherosclerosis. Severe lower abdominal pain, rectal bleeding, hypotension. Abdominal x-ray shows colonic dilation, thumbprinting. Sigmoidoscopy shows submucosal hemorrhage, friability, ulcerations; rectum often spared. Conservative management (NPO, IV fluids); surgical resection for infarction or postischemic stricture.

COLONIC ANGIODYSPLASIA

In persons over age 60, vascular ectasias, usually in right colon, account for up to 40% of cases of chronic or recurrent lower GI bleeding. May be associated with aortic stenosis. Diagnosis is by arteriography (clusters of small vessels, early and prolonged opacification of draining vein) or colonoscopy (flat, bright red, fernlike lesions). For bleeding, treat by colonoscopic electro- or laser coagulation, band ligation, arteriographic embolization, or, if necessary, right hemicolectomy (Chap. 41).

ANORECTAL DISEASES

HEMORRHOIDS

Due to increased hydrostatic pressure in hemorrhoidal venous plexus (associated with straining at stool, pregnancy). May be external, internal, thrombosed, acute (prolapsed or strangulated), or bleeding. Treat pain with bulk laxative and stool softeners (psyllium extract, dioctyl sodium sulfosuccinate 100–200 mg/d), sitz baths one to four per day, witch hazel compresses, analgesics as needed. Bleeding may require rubber band ligation or injection sclerotherapy. Operative hemorrhoidectomy in severe or refractory cases.

ANAL FISSURES

Medical therapy as for hemorrhoids. Relaxation of the anal canal with nitroglycerin ointment (0.2%) applied tid or botulinum toxin type A up to 20 U injected into the internal sphincter on each side of the fissure. Internal anal sphincterotomy in refractory cases.

PRURITUS ANI

Often of unclear cause; may be due to poor hygiene, fungal or parasitic infection. Treat with thorough cleansing after bowel movement, topical glucocorticoid, and antifungal agent if indicated.

ANAL CONDYLOMAS (GENITAL WARTS)

Wartlike papillomas due to sexually transmitted papillomavirus. Treat with cautious application of liquid nitrogen or podophyllotoxin or with intralesional interferon α. Tend to recur. May be prevented by vaccination with human papilloma virus (HPV) vaccine.



For a more detailed discussion, see Owyang C: Irritable Bowel Syndrome, Chap. 352, p. 1965; Ahmed R, Gearhart SL: Diverticular Disease and Common Anorectal Disorders, Chap. 353, p. 1971; Ahmed R, Malas M: Mesenteric Vascular Insufficiency, Chap. 354, p. 1978, in HPIM-19.

150 Cholelithiasis, Cholecystitis, and Cholangitis

CHOLELITHIASIS

There are two major types of gallstones: cholesterol and pigment stones. Cholesterol gallstones contain >50% cholesterol monohydrate. Pigment stones have <20% cholesterol and are composed primarily of calcium bilirubinate. In the United States, 80% of stones are cholesterol and 20% are pigment.

EPIDEMIOLOGY

One million new cases of cholelithiasis per year in the United States. Predisposing factors include demographic/genetics (increased prevalence in North American Indians), obesity, weight loss, female sex hormones, age, ileal disease, pregnancy, type IV hyperlipidemia, and cirrhosis.

SYMPTOMS AND SIGNS

Many gallstones are "silent," i.e., present in asymptomatic pts. Symptoms occur when stones trigger inflammation or cause obstruction of the cystic or common bile ducts (CBDs). Major symptoms: (1) biliary colic—a severe steady ache in the RUQ or epigastrium that begins suddenly; often occurs 30–90 min after meals, lasts for several hours, and occasionally radiates to the right scapula or back; (2) nausea, vomiting. Physical examination may be normal or show epigastric or RUQ tenderness.

LABORATORY

Occasionally, mild and transient elevations in bilirubin (<85 μmol/L [<5 mg/dL]) accompany biliary colic.

IMAGING

Only 10% of cholesterol gallstones are radiopaque. Ultrasonography is best diagnostic test. The oral cholecystogram has been largely replaced by ultrasound, but may be used to assess the patency of the cystic duct and gallbladder emptying function (Table 150-1).

DIFFERENTIAL DIAGNOSIS

Includes peptic ulcer disease (PUD), gastroesophageal reflux, irritable bowel syndrome, and hepatitis.

COMPLICATIONS

Cholecystitis, pancreatitis, cholangitis.

TREATMENT CHOLELITHIASIS

In asymptomatic pts, risk of developing complications requiring surgery is small. Elective cholecystectomy should be reserved for: (1) symptomatic pts (i.e., biliary colic despite low-fat diet); (2) persons with previous complications of cholelithiasis (see below); and (3) presence of an underlying condition predisposing to an increased risk of complications (calcified or porcelain gallbladder). Pts with gallstones >3 cm or with an anomalous gallbladder containing stones should also

TABLE 150-1 DIAGNOSTIC EVALUATION OF THE BILE DUCTS

Diagnostic Advantages	Diagnostic Limitations
Hepatobiliary ultrasound	
Rapid	Bowel gas
Simultaneous scanning of GB, liver, bile ducts, pancreas	Massive obesity
	Ascites
Accurate identification of dilated bile ducts	Barium
Not limited by jaundice, pregnancy	Partial bile duct obstruction
Guidance for fine-needle biopsy	Poor visualization of distal CBD
Computed tomography	
Simultaneous scanning of GB, liver, bile ducts, pancreas	Extreme cachexia
	Movement artifact
Accurate identification of dilated bile ducts, masses	Ileus
	Partial bile duct obstruction
Not limited by jaundice, gas, obesity, ascites	
High-resolution image	
Guidance for fine-needle biopsy	
Magnetic resonance cholangiopancreatography	
Useful modality for visualizing pancreatic and biliary ducts	Cannot offer therapeutic intervention
Has excellent sensitivity for bile duct dilation, biliary stricture, and intraductal abnormalities	High cost
Can identify pancreatic duct dilation or stricture, pancreatic duct stenosis, and pancreas divisum	
Endoscopic retrograde cholangiopancreatography	
Simultaneous pancreatography	Gastroduodenal obstruction
Best visualization of distal biliary tract	?Roux-en-Y biliary-enteric anastomosis
Bile or pancreatic cytology	
Endoscopic sphincterotomy and stone removal	
Biliary manometry	
Percutaneous transhepatic cholangiogram	
Extremely successful when bile ducts dilated	Nondilated or sclerosed ducts
Best visualization of proximal biliary tract	
Bile cytology/culture	
Percutaneous transhepatic drainage	
Endoscopic ultrasound	
Most sensitive method to detect ampullary stones	

Abbreviations: CBD, common bile duct; GB, gallbladder.

be considered for surgery. Laparoscopic cholecystectomy is minimally invasive and is the procedure of choice for most pts undergoing elective cholecystectomy. Oral dissolution agents (ursodeoxycholic acid) partially or completely dissolve small radiolucent stones in 50% of selected pts within 6–24 months. Because of the frequency of stone recurrence and the effectiveness of laparoscopic surgery,

the role of oral dissolution therapy has been largely confined to pts who are not candidates for elective cholecystectomy.

ACUTE CHOLECYSTITIS

Acute inflammation of the gallbladder is usually caused by cystic duct obstruction by an impacted stone. Inflammatory response is evoked by (1) mechanical inflammation from increased intraluminal pressure; (2) chemical inflammation from release of lysolecithin; (3) bacterial inflammation, which plays a role in 50–85% of pts with acute cholecystitis.

ETIOLOGY

Approximately 90% calculous; 10% acalculous. Acalculous cholecystitis is associated with higher complication rate and acute illness (i.e., burns, trauma, major surgery), fasting, hyperalimentation leading to gallbladder stasis, vasculitis, carcinoma of gallbladder or CBD, some gallbladder infections (*Leptospira*, *Streptococcus*, *Salmonella*, or *Vibrio cholerae*), but in >50% of cases an underlying explanation is not found.

SYMPTOMS AND SIGNS

(1) Biliary colic (RUQ or epigastric pain) that progressively worsens; (2) nausea, vomiting, anorexia; and (3) fever. Examination typically reveals RUQ tenderness; palpable RUQ mass found in 20% of pts. *Murphy's sign* is present when deep inspiration or cough during palpation of the RUQ produces increased pain or inspiratory arrest.

LABORATORY

Mild leukocytosis; serum bilirubin, alkaline phosphatase, and aspartate aminotransferase (AST) may be mildly elevated.

IMAGING

Ultrasonography is useful for demonstrating gallstones and occasionally a phlegmonous mass surrounding the gallbladder. Radionuclide scans (HIDA, DIDA, DISIDA, etc.) may identify cystic duct obstruction.

DIFFERENTIAL DIAGNOSIS

Includes acute pancreatitis, appendicitis, pyelonephritis, PUD, hepatitis, and hepatic abscess.

COMPLICATIONS

Empyema, hydrops, gangrene, perforation, fistulization, gallstone ileus, porcelain gallbladder.

TREATMENT ACUTE CHOLECYSTITIS

No oral intake, nasogastric suction, IV fluids and electrolytes, analgesia (meperidine or NSAIDs), and antibiotics (ureidopenicillins, ampicillin sulbactam, ciprofloxacin, third-generation cephalosporins; anaerobic coverage should be added if gangrenous or emphysematous cholecystitis is suspected; imipenem/meropenem covers the spectrum of bacteria causing ascending cholangitis but should be reserved for the most life-threatening infections when other antibiotics have failed). Acute symptoms will resolve in 70% of pts. Optimal timing of surgery depends on pt stabilization and should be performed as soon as feasible. Urgent cholecystectomy is appropriate in most pts with a suspected or confirmed complication. Delayed surgery is reserved for pts with high risk of emergent surgery and where the diagnosis is in doubt.

CHRONIC CHOLECYSTITIS

ETIOLOGY

Chronic inflammation of the gallbladder; almost always associated with gallstones. Results from repeated acute/subacute cholecystitis or prolonged mechanical irritation of gallbladder wall.

SYMPTOMS AND SIGNS

May be asymptomatic for years, may progress to symptomatic gallbladder disease or to acute cholecystitis, or present with complications.

LABORATORY

Tests are usually normal.

IMAGING

Ultrasonography preferred; usually shows gallstones within a contracted gallbladder (Table 150-1).

DIFFERENTIAL DIAGNOSIS

PUD, esophagitis, irritable bowel syndrome.

TREATMENT CHRONIC CHOLECYSTITIS

Surgery indicated if pt is symptomatic.

CHOLEDOCHOLITHIASIS/CHOLANGITIS

ETIOLOGY

In pts with cholelithiasis, passage of gallstones into CBD occurs in 10–15%; increases with age. At cholecystectomy, undetected stones are left behind in 1–5% of pts.

SYMPTOMS AND SIGNS

Choledocholithiasis may present as an incidental finding, biliary colic, obstructive jaundice, cholangitis, or pancreatitis. Cholangitis usually presents as fever, RUQ pain, and jaundice (*Charcot's triad*).

LABORATORY

Elevations in serum bilirubin, alkaline phosphatase, and aminotransferases. Leukocytosis usually accompanies cholangitis; blood cultures are frequently positive. Amylase is elevated in 15% of cases.

IMAGING

Diagnosis usually made by cholangiography either preoperatively by endoscopic retrograde cholangiopancreatography (ERCP) or intraoperatively at the time of cholecystectomy. Ultrasonography may reveal dilated bile ducts but is not sensitive for detecting CBD stones (Table 150-1).

DIFFERENTIAL DIAGNOSIS

Acute cholecystitis, renal colic, perforated viscus, pancreatitis.

COMPLICATIONS

Cholangitis, obstructive jaundice, gallstone-induced pancreatitis, and secondary biliary cirrhosis.

TREATMENT CHOLEDOCHOLITHIASIS/CHOLANGITIS

Laparoscopic cholecystectomy and ERCP have decreased the need for choledocholithotomy and T-tube drainage of the bile ducts. When CBD stones are suspected prior to laparoscopic cholecystectomy, preoperative ERCP with endoscopic papillotomy and stone extraction is the preferred approach. CBD stones should be suspected in gallstone pts with (1) history of jaundice or pancreatitis, (2) abnormal LFT, and (3) ultrasound evidence of a dilated CBD or stones in the duct. Cholangitis treated like acute cholecystitis; no oral intake, hydration, analgesia, and antibiotics are the mainstays; stones should be removed surgically or endoscopically.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

PSC is a sclerosing, inflammatory, and obliterative process involving the biliary tree.

ETIOLOGY

Associations: inflammatory bowel disease (75% of cases of PSC—especially ulcerative colitis), AIDS, rarely retroperitoneal fibrosis.

SYMPTOMS AND SIGNS

Pruritus, RUQ pain, jaundice, fever, weight loss, and malaise. Approximately 44% may be asymptomatic at diagnosis. May progress to cirrhosis with portal hypertension.

LABORATORY

Evidence of cholestasis (elevated bilirubin and alkaline phosphatase) common.

RADIOLOGY/ENDOSCOPY

Transhepatic or endoscopic cholangiograms reveal stenosis and dilation of the intra- and extrahepatic bile ducts.

DIFFERENTIAL DIAGNOSIS

Cholangiocarcinoma, Caroli disease (cystic dilation of bile ducts), *Fasciola hepatica* infection, echinococcosis, and ascariasis. IgG4-associated cholangitis.

TREATMENT PRIMARY SCLEROSING CHOLANGITIS

No satisfactory therapy. Cholangitis should be treated as outlined above. Cholestyramine may control pruritus. Supplemental vitamin D and calcium may retard bone loss. Glucocorticoids, methotrexate, and cyclosporine have not been shown to be effective. Ursodeoxycholic acid improves liver tests but has not been shown to affect survival. Surgical relief of biliary obstruction may be appropriate but has a high complication rate. Liver transplantation should be considered in pts with end-stage cirrhosis. Median survival: 9–12 years after diagnosis, with age, bilirubin level, histologic stage, and splenomegaly being predictors of survival.



For a more detailed discussion, see Greenberger NJ, Paumgartner G: Diseases of the Gallbladder and Bile Ducts, Chap. 369, p. 2075, in HPIM-19.

151 Pancreatitis

ACUTE PANCREATITIS

Any severe acute pain in the abdomen or back should suggest the possibility of acute pancreatitis. The diagnosis is established by two of the following three criteria: (1) typical abdominal pain in the epigastrium that may radiate to the back, (2) threefold or greater elevation in serum lipase and/or amylase, and (3) confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging. The pathologic spectrum of acute pancreatitis varies from *interstitial pancreatitis*, which is usually a mild and self-limited disorder, to *necrotizing pancreatitis*, in which the degree of necrosis may correlate with the severity of the attack and its systemic manifestations.

ETIOLOGY

Most common causes in the United States are cholelithiasis and alcohol. Others are listed in Table 151-1.

CLINICAL FEATURES

Can vary from mild abdominal pain to shock. *Common symptoms:* (1) steady, boring pain in the epigastricand periumbilical region may radiate to the back, chest, flanks, and lower abdomen; (2) nausea, vomiting, abdominal distention.

Physical examination: (1) low-grade fever, tachycardia, hypotension; (2) erythematous skin nodules due to subcutaneous fat necrosis; (3) basilar rales, pleural effusion (often on the left); (4) abdominal tenderness and rigidity, diminished bowel sounds, palpable upper abdominal mass; (5) Cullen's sign: blue discoloration in the periumbilical area due to hemoperitoneum; (6) Turner's sign: blue-red-purple or green-brown discoloration of the flanks due to tissue catabolism of hemoglobin.

LABORATORY

1. *Serum amylase:* Large elevations (>3 × normal) virtually assure the diagnosis if salivary gland disease and intestinal perforation/infarction are excluded. However, normal serum amylase does not exclude the diagnosis of acute pancreatitis, and the degree of elevation does not predict severity of pancreatitis. Amylase levels typically return to normal in 3–7 days.
2. *Serum lipase level:* Serum lipase is the preferred test for diagnosis of acute pancreatitis. Increases in parallel with amylase level and measurement of both tests increases the diagnostic yield.
3. *Other tests: Hypocalcemia* occurs in ~25% of pts. *Leukocytosis* (15,000–20,000/μL) occurs frequently. *Hypertriglyceridemia* occurs in 15–20% of cases and can cause a spuriously normal serum amylase level. *Hyperglycemia* is common. *Serum bilirubin, alkaline phosphatase*, and *aspartame aminotransferase* can be transiently elevated. *Hypoalbuminemia* and marked elevations of *serum lactic dehydrogenase* (LDH) are associated with an increased mortality rate. *Hypoxemia* is present in 25% of pts. Arterial pH <7.32 may spuriously elevate serum amylase.

IMAGING

1. *Abdominal radiographs* can be abnormal but are not specific for pancreatitis and are infrequently used.
2. *Ultrasound* often fails to visualize the pancreas because of overlying intestinal gas but may detect gallstones, pseudocysts, mass lesions, or edema or enlargement of the pancreas.

TABLE 151-1 CAUSES OF ACUTE PANCREATITIS

Common Causes
Gallstones (including microlithiasis)
Alcohol (acute and chronic alcoholism)
Hypertriglyceridemia
Endoscopic retrograde cholangiopancreatography (ERCP), especially after biliary manometry
Drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid [5-ASA])
Trauma (especially blunt abdominal trauma)
Postoperative (abdominal and nonabdominal operations)
Uncommon Causes
Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery)
Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP)
Cancer of the pancreas
Hypercalcemia
Periampullary diverticulum
Pancreas divisum
Hereditary pancreatitis
Cystic fibrosis
Renal failure
Infections (mumps, coxsackievirus, cytomegalovirus, echovirus, parasites)
Autoimmune (e.g., type 1 and type 2)
Causes to Consider in Pts with Recurrent Bouts of Acute Pancreatitis Without an Obvious Etiology
Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis, biliary sludge
Drugs
Alcohol abuse
Metabolic: Hypertriglyceridemia, hypercalcemia
Anatomic: Pancreas divisum
Pancreatic cancer
Intraductal papillary mucinous neoplasm (IPMN)
Hereditary pancreatitis
Cystic fibrosis
Autoimmune
Idiopathic

3. *CT* can confirm the clinical impression of acute pancreatitis. It can also be helpful in evaluating the complications of acute pancreatitis.

DIFFERENTIAL DIAGNOSIS

Intestinal perforation (especially peptic ulcer), cholecystitis, acute intestinal obstruction, mesenteric vascular occlusion, renal colic, inferior myocardial infarction, aortic dissection, connective tissue disorders, pneumonia, and diabetic ketoacidosis.

TREATMENT ACUTE PANCREATITIS

Most (90%) cases subside over a period of 3–7 days. Severity should be assessed to determine if ICU care is required. The most important treatment is safe, aggressive IV fluid resuscitation. Other conventional measures: no oral alimentation and analgesics for abdominal pain. Precipitating factors (alcohol, medications) must be eliminated. In mild or moderate pancreatitis, a clear liquid diet can usually be started after 3–6 days.

COMPLICATIONS

Risk factors and markers of severe acute pancreatitis are listed in Table 151-2. The median prevalence of organ failure is 54% in necrotizing pancreatitis. With single-organ system failure, the mortality is 3–10% but increases to 47% with multisystem organ failure.

TABLE 151-2 SEVERE ACUTE PANCREATITIS

Risk Factors for Severity
• Age >60 years
• Obesity, BMI >30
• Comorbid disease (Charlson Comorbidity Index)
Markers of Severity at Admission or Within 24 h
• SIRS—defined by presence of 2 or more criteria:
• Core temperature <36° or>38°C
• Heart rate >90 beats/min
• Respirations >20/min or Pco_2 <32 mmHg
• White blood cell count >12,000/μL, <4000/μL, or 10% bands
• APACHE II
• Hemoconcentration (hematocrit >44%)
• Admission BUN (>22 mg/dL)
• BISAP Score
– (B) BUN >25 mg/dL
– (I) Impaired mental status
– (S) SIRS: ≥2 of 4 present
– (A) Age >60 years
– (P) Pleural effusion
• Organ failure (Modified Marshall Score)
• Cardiovascular: systolic bp <90 mmHg, heart rate >130 beats/min
• Pulmonary: Pao_2 <60 mmHg
• Renal: serum creatinine >2.0 mg%
Markers of Severity During Hospitalization
• Persistent organ failure
• Pancreatic necrosis

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BISAP, Bedside Index of Severity in Acute Pancreatitis; SIRS, systemic inflammatory response syndrome.

Systemic

Shock, GI bleeding, common duct obstruction, ileus, splenic infarction or rupture, disseminated intravascular coagulation, subcutaneous fat necrosis, acute respiratory distress syndrome, pleural effusion, acute renal failure, sudden blindness.

Local

1. Sterile or infected *pancreatic necrosis*—necrosis may become secondarily infected in 40–60% of pts, typically within 1–2 weeks after the onset of pancreatitis. Percutaneous aspiration of necrosis with Gram stain and culture should be performed if there are ongoing signs of possible pancreatic infection such as sustained leukocytosis, fever, or organ failure. Repeated fine-needle aspiration and Gram stain with culture of pancreatic necrosis may be done every 5–7 days in the presence of persistent fever. Repeated CT or MRI imaging should also be considered with any change in clinical course to monitor for complications. *Sterile necrosis* is most often managed conservatively unless complications arise. Once a diagnosis of *infected necrosis* is established and an organism identified, targeted antibiotics should be instituted. Pancreatic debridement (necrosectomy) should be considered for definitive management of *infected necrosis*, but clinical decisions are generally influenced by response to antibiotic treatment and overall clinical condition. A step-up approach (percutaneous or endoscopic transgastric drainage followed, if necessary, by open necrosectomy) has been successfully reported by some pancreatic centers.
2. *Pancreatic pseudocysts* develop over 1–4 weeks in 15% of pts. Abdominal pain is the usual complaint, and a tender upper abdominal mass may be present. Can be detected by abdominal ultrasound or CT. In pts who are stable and uncomplicated, treatment is supportive; pseudocysts that are >5 cm in diameter and persist for >6 weeks should be considered for drainage. In pts with an expanding pseudocyst or one complicated by hemorrhage, rupture, or abscess, surgery should be performed.
3. *Pancreatic ascites* and *pancreatic duct disruption*. Diagnosis can be confirmed on MRCP or ERCP. Placement of a bridging pancreatic stent for at least 6 weeks is >90% effective at resolving the leak.

CHRONIC PANCREATITIS

Chronic pancreatitis is a disease process characterized by irreversible damage to the pancreas.

ETIOLOGY

Alcoholism is most frequent cause of clinically apparent chronic pancreatitis; in 25% of adults, etiology is unknown. Other causes are listed in Table 151-3.

SYMPTOMS AND SIGNS

Pain is cardinal symptom. Weight loss, steatorrhea, and other signs and symptoms of malabsorption common. Physical examination often unremarkable.

LABORATORY

No specific laboratory test for chronic pancreatitis. Serum amylase and lipase levels are often normal. Serum bilirubin and alkaline phosphatase may be elevated. The fecal elastase-1 and small-bowel biopsy are useful in the evaluation of pts with suspected pancreatic steatorrhea. Impaired glucose tolerance is present in >50% of pts. Secretin stimulation test is a relatively sensitive test for pancreatic exocrine deficiency and becomes abnormal when ≥60% of the pancreatic exocrine function has been lost.

IMAGING

Plain films of the abdomen reveal pancreatic calcifications in 30–60%. *CT scan* is the imaging modality of choice followed by MRI, endoscopic ultrasound, and pancreas function testing.

TABLE 151-3 CHRONIC PANCREATITIS AND PANCREATIC EXOCRINE INSUFFICIENCY: TIGAR-O CLASSIFICATION SYSTEM

Toxic-metabolic	**Autoimmune**
Alcoholic	Type 1 autoimmune chronic pancreatitis
Tobacco smoking	IgG4 systemic
Hypercalcemia	Type 2 autoimmune chronic pancreatitis
Hyperlipidemia	**Recurrent and severe acute pancreatitis**
Chronic renal failure	Postnecrotic (severe acute pancreatitis)
Medications—phenacetin abuse	Recurrent acute pancreatitis
Toxins—organotin compounds (e.g., dibutylin dichloride, DBTC)	Vascular diseases/ischemia
Idiopathic	Radiation induced
Early onset	**Obstructive**
Late onset	Pancreas divisum
Tropical	Duct obstruction (e.g., tumor)
Genetic	Preampullary duodenal wall cysts
Cationic trypsinogen (*PRSS1*)	Posttraumatic pancreatic duct scars
Cystic fibrosis transmembrane conductance regulator gene (*CFTR*)	
Calcium-sensing receptor (*CASR*)	
Chymotrypsin C gene (*CTRC*)	
Pancreatic secretory trypsin inhibitor gene (*SPINK1*)	

Abbreviations: DBTC, dibutylin dichloride; TIGAR-O, toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive.

DIFFERENTIAL DIAGNOSIS

Important to distinguish from pancreatic carcinoma; may require radiographically guided biopsy.

TREATMENT CHRONIC PANCREATITIS

Aimed at controlling pain and malabsorption. The management of pain in pts with chronic pancreatitis is problematic. Recent meta-analyses have shown no consistent benefit of enzyme therapy at reducing pain in chronic pancreatitis. A recent prospective study reported that pregabalin can improve pain in chronic pancreatitis and lower pain medication requirement. Surgery with ductal decompression may control pain if there is a large-duct disease. Subtotal pancreatectomy may also control pain but at the cost of exocrine insufficiency and diabetes. Malabsorption is managed with a low-fat diet and pancreatic enzyme replacement. Because pancreatic enzymes are inactivated by acid, agents that reduce acid production (e.g., omeprazole or sodium bicarbonate) may improve their efficacy (but should not be given with enteric-coated preparations). Insulin may be necessary to control serum glucose.

COMPLICATIONS

Chronic abdominal pain, gastroparesis, malabsorption/maldigestion, impaired glucose tolerance. Nondiabetic retinopathy due to vitamin A and/or zinc deficiency. GI bleeding, icterus, effusions, subcutaneous fat necrosis, and metabolic bone disease. Increased risk for pancreatic carcinoma. Narcotic addiction common.



For a more detailed discussion, see Conwell DL, Greenberger NJ, Banks PA: Approach to the Patient with Pancreatic Disease, Chap. 370, p. 2086; Conwell DL, Banks PA, Greenberger NJ: Acute and Chronic Pancreatitis, Chap. 371, p. 2090, in HPIM-19.

152 Acute Hepatitis

VIRAL HEPATITIS

Acute viral hepatitis is a systemic infection predominantly affecting the liver. Clinically characterized by malaise, nausea, vomiting, diarrhea, and low-grade fever followed by dark urine, jaundice, and tender hepatomegaly; may be subclinical and detected on basis of elevated aspartate and alanine aminotransferase (AST and ALT) levels. Hepatitis B may be associated with immune-complex phenomena, including arthritis, serum sickness-like illness, glomerulonephritis, and a polyarteritis nodosa–like vasculitis. Hepatitis-like illnesses may be caused not only by hepatotropic viruses (A, B, C, D, E) but also by other viruses (Epstein-Barr, CMV, coxsackievirus, etc.), alcohol, drugs, hypotension and ischemia, and biliary tract disease (Table 152-1).

HEPATITIS A (HAV)

27-nm picornavirus (hepatovirus) with single-stranded RNA genome.

Clinical Course See Fig. 152-1.

Outcome

Recovery within 6–12 months, usually with no clinical sequelae; a small proportion will have one or two apparent clinical and serologic relapses; in some cases, pronounced cholestasis suggesting biliary obstruction may occur; rare fatalities (fulminant hepatitis), no chronic carrier state.

Diagnosis

IgM anti-HAV in acute or early convalescent serum sample.

Epidemiology

Fecal-oral transmission; endemic in underdeveloped countries; food-borne and waterborne epidemics; outbreaks in day-care centers, residential institutions.

TABLE 152-1 CLINICAL AND EPIDEMIOLOGIC FEATURES OF VIRAL HEPATITIS

Feature	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Epidemic cases: young adults (20–40 years); sporadic cases: older adults (>60)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]	+	–
Sexual	±	++	±[a]	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common[d]	None[f]
Carrier	None	0.1–30%*c*	1.5–3.2%	Variable[g]	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute good, Chronic poor	Good

Prophylaxis	Ig, inactivated vaccine	HBIG, recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine

[a]Primarily with HIV co-infection and high-level viremia in index case; risk ~5%.
[b]Up to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.
[c]Varies considerably throughout the world and in subpopulations within countries; see text.
[d]In acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable.
[e]10–20% in pregnant women.
[f]Except as observed in immunosuppressed liver allograft recipients or other immunosuppressed hosts.
[g]Common in Mediterranean countries; rare in North America and western Europe.
Abbreviation: HBIG, hepatitis B immunoglobulin. See text for other abbreviations.

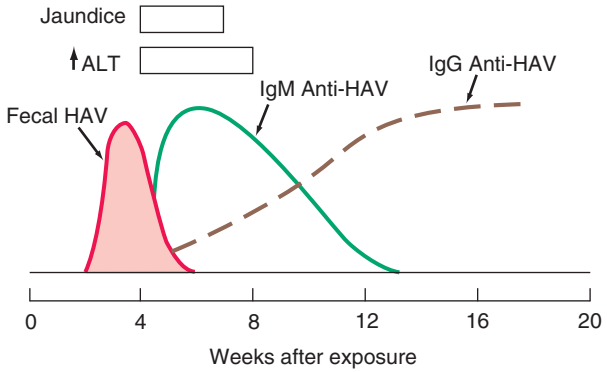


FIGURE 152-1 Scheme of typical clinical and laboratory features of HAV. ALT, alanine aminotransferase.

Prevention

After exposure: immune globulin 0.02 mL/kg IM within 2 weeks to household and institutional contacts (not casual contacts at work). *Before exposure*: inactivated HAV vaccine 1 mL IM (unit dose depends on formulation); half dose to children; repeat at 6–12 months; target travelers, military recruits, animal handlers, day-care personnel, laboratory workers, and pts with chronic liver disease (especially hepatitis C).

HEPATITIS B (HBV)

42-nm hepadnavirus with outer surface coat (HBsAg), inner nucleocapsid core (HBcAg), DNA polymerase, and partially double-stranded DNA genome of 3200 nucleotides. Circulating form of HBcAg is HBeAg, a marker of viral replication and infectivity. Multiple serotypes and genetic heterogeneity.

Clinical Course See Fig. 152-2.

Outcome

Recovery >90%, fulminant hepatitis (<1%), chronic hepatitis or carrier state (only 1–2% of immunocompetent adults; higher in neonates, elderly, immunocompromised), cirrhosis, and hepatocellular carcinoma (especially following chronic infection beginning in infancy or early childhood) (Chap. 154). Reactivation of HBV has been observed with immunosuppression, particularly with rituximab.

Diagnosis

HBsAg in serum (acute or chronic infection); IgM anti-HBc (early anti-HBc indicative of acute or recent infection). Most sensitive test is detection of HBV DNA in serum; not generally required for routine diagnosis.

Epidemiology

Percutaneous (needle stick), sexual, or perinatal transmission. Endemic in sub-Saharan Africa and Southeast Asia, where up to 20% of population acquire infection, usually early in life.

Prevention

After exposure in unvaccinated persons: hepatitis B immune globulin (HBIG) 0.06 mL/kg IM immediately after needle stick to within 14 days of sexual exposure in

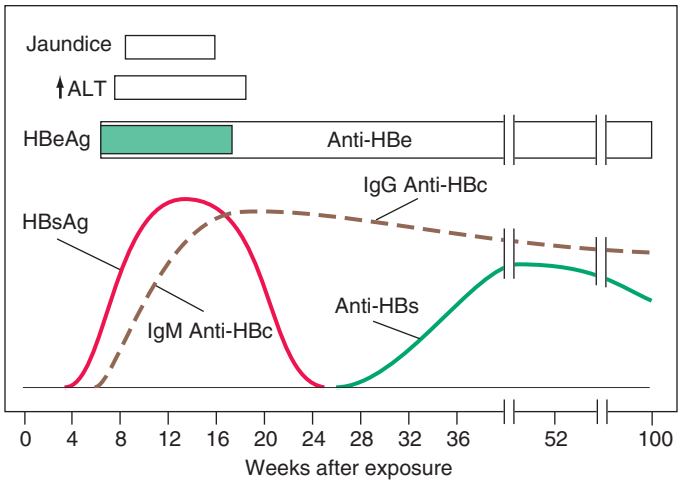


FIGURE 152-2 Scheme of typical clinical and laboratory features of HBV. ALT, alanine aminotransferase.

combination with vaccine series. For perinatal exposure (HbsAg+ mother) HBIG 0.05 mL in the thigh immediately after birth with the vaccine series started within the first 12 h of life. *Before exposure*: recombinant hepatitis B vaccine IM (dose depends on formulation as well as adult or pediatric and hemodialysis); at 0, 1, and 6 months; deltoid, not gluteal injection. Has been targeted to high-risk groups (e.g., health workers, persons with multiple sexual partners, IV drug users, hemodialysis pts, hemophiliacs, household and sexual contacts of HBsAg carriers, persons traveling in endemic areas, unvaccinated children <18). Universal vaccination of all children is now recommended in the United States.

HEPATITIS C (HCV)

Caused by flavi-like virus in the genus Hepacivirus with RNA genome of >9000 nucleotides; genetic heterogeneity. Incubation period 7–8 weeks.

Clinical Course

Often clinically mild and marked by fluctuating elevations of serum aminotransferase levels; >50% likelihood of chronicity, leading to cirrhosis in >20%.

Diagnosis

Anti-HCV in serum. Current third-generation immunoassay incorporates proteins from the core, NS3, and NS5 regions. The most sensitive indicator of HCV infection is HCV RNA (Fig. 152-3).

Epidemiology

HCV accounts for >90% of transfusion-associated hepatitis cases. IV drug use accounts >50% of reported cases of hepatitis C. Little evidence for frequent sexual or perinatal transmission.

Prevention

Exclusion of paid blood donors, testing of donated blood for anti-HCV. Anti-HCV detected by enzyme immunoassay in blood donors with normal ALT is often falsely positive (30%); result should be confirmed by HCV RNA in serum.

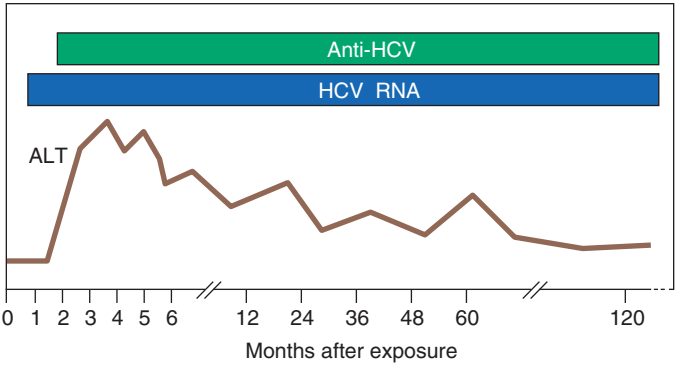


FIGURE 152-3 Scheme of typical laboratory features during acute hepatitis C progressing to chronicity. HCV RNA is the first detectable event, preceding alanine aminotransferase (ALT) elevation and the appearance of anti-HCV.

HEPATITIS D (HDV, DELTA AGENT)

Defective 37-nm RNA virus that requires HBV for its replication; either co-infects with HBV or superinfects a chronic HBV carrier. Enhances severity of HBV infection (acceleration of chronic hepatitis to cirrhosis, occasionally fulminant acute hepatitis).

Diagnosis

Anti-HDV in serum (acute hepatitis D—often in low titer, is transient; chronic hepatitis D—in higher titer, is sustained).

Epidemiology

Endemic among HBV carriers in Mediterranean Basin, where it is spread predominantly by nonpercutaneous means. In nonendemic areas (e.g., northern Europe, United States) HDV is spread percutaneously among HBSAg+ IV drug users or by transfusion in hemophiliacs.

Prevention

Hepatitis B vaccine (noncarriers only).

HEPATITIS E (HEV)

Caused by 29- to 32-nm agent resembling caliciviruses but considered within its own genus, Hepevirus. Enterically transmitted and responsible for waterborne epidemics of hepatitis in India, parts of Asia and Africa, and Central America. Self-limited illness with high (10–20%) mortality rate in pregnant women.

TREATMENT VIRAL HEPATITIS

Activity as tolerated, high-calorie diet (often tolerated best in morning), IV hydration for severe vomiting, cholestyramine up to 4 g PO four times daily for severe pruritus, avoid hepatically metabolized drugs; no role for glucocorticoids. Liver transplantation for fulminant hepatic failure. In rare instances of severe acute HBV, treatment with a nucleoside analogue has been used successfully. Most authorities would recommend antiviral therapy for severe acute HBV (Chap. 153). For acute HCV, in places where directly acting antivirals are available, delay in treatment initiation for up to 6 months with counseling and monitoring of HCV RNA levels are recommended. The same regimens that are recommended for

treatment naïve pts with chronic HCV infection can then be used for acute infection (Chap. 153).

TOXIC AND DRUG-INDUCED HEPATITIS

DOSE-DEPENDENT (DIRECT HEPATOTOXINS)

Onset is within 48 h, predictable, necrosis around terminal hepatic venule–e.g., carbon tetrachloride, benzene derivatives, mushroom poisoning, acetaminophen, or microvesicular steatosis (e.g., tetracyclines, valproic acid).

IDIOSYNCRATIC

Variable dose and time of onset; small number of exposed persons affected; may be associated with fever, rash, arthralgias, eosinophilia. In many cases, mechanism may actually involve toxic metabolite, possibly determined on genetic basis—e.g., isoniazid, halothane, phenytoin, methyldopa, carbamazepine, diclofenac, oxacillin, sulfonamides.

TREATMENT TOXIC AND DRUG-INDUCED HEPATITIS

Supportive as for viral hepatitis; withdraw suspected agent, and include use of gastric lavage and oral administration of charcoal or cholestyramine. Liver transplantation if necessary. In acetaminophen overdose, more specific therapy is available in the form of sulfhydryl compounds (e.g., *N*-acetylcysteine). These agents appear to act by providing a reservoir of sulfhydryl groups to bind the toxic metabolites or by stimulating synthesis of hepatic glutathione. Therapy should be begun within 8 h of ingestion but may be effective even if given as late as 24–36 h after overdose.

FULMINANT HEPATITIS

Massive hepatic necrosis with impaired consciousness occurring within 8 weeks of the onset of illness.

CAUSES

Infections (viral, including HAV, HBV, HCV [rarely], HDV, HEV; bacterial, rickettsial, parasitic), drugs and toxins, ischemia (shock), Budd-Chiari syndrome, idiopathic chronic active hepatitis, acute Wilson's disease, microvesicular fat syndromes (Reye's syndrome, acute fatty liver of pregnancy).

CLINICAL MANIFESTATIONS

Pts usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the pt has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (>80% in pts with deep coma).

TREATMENT FULIMINANT HEPATITIS

The goal of therapy is to support the pt by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver

regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Meticulous intensive care that includes prophylactic antibiotic coverage is the one factor that does appear to improve survival. Liver transplantation should be considered.



For a more detailed discussion, see Dienstag JL: Acute Viral Hepatitis, Chap. 360, p.2004, and Lee WM, Dienstag JL: Toxic and Drug-Induced Hepatitis, Chap. 361, p. 2023, in HPIM-19.

153 Chronic Hepatitis

A group of disorders characterized by a chronic inflammatory reaction in the liver for at least 6 months.

OVERVIEW

ETIOLOGY

Hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta agent), drugs (methyldopa, nitrofurantoin, isoniazid, dantrolene), autoimmune hepatitis, Wilson's disease, hemochromatosis, α_1-antitrypsin deficiency.

HISTOLOGIC CLASSIFICATION

Chronic hepatitis can be classified by *grade* and *stage*. The grade is a histologic assessment of necrosis and inflammatory activity and is based on examination of the liver biopsy. The stage of chronic hepatitis reflects the level of disease progression and is based on the degree of fibrosis (see Table 362-2, p. 2032, HPIM-19).

PRESENTATION

Wide clinical spectrum ranging from asymptomatic serum aminotransferase elevations to apparently acute, even fulminant, hepatitis. Common symptoms include fatigue, malaise, anorexia, low-grade fever; jaundice is frequent in severe disease. Some pts may present with complications of cirrhosis: ascites, variceal bleeding, encephalopathy, coagulopathy, and hypersplenism. In chronic HBV or HCV and autoimmune hepatitis, extrahepatic features may predominate.

CHRONIC HEPATITIS B

Follows up to 1–2% of cases of acute hepatitis B in immunocompetent hosts; more frequent in immunocompromised hosts. Spectrum of disease: asymptomatic antigenemia, chronic hepatitis, cirrhosis, hepatocellular cancer; early phase often

associated with continued symptoms of hepatitis, elevated aminotransferase levels, presence in serum of HBeAg and HBV DNA, and presence in liver of replicative form of HBV; later phase in some pts may be associated with clinical and biochemical improvement, disappearance of HBeAg and HBV DNA and appearance of anti-HBeAg in serum, and integration of HBV DNA into host hepatocyte genome. In Mediterranean and European countries as well as in Asia, a frequent variant is characterized by readily detectable HBV DNA, but without HBeAg (anti-HBeAg-reactive). Most of these cases are due to a mutation in the pre-C region of the HBV genome that prevents HBeAg synthesis (may appear during course of chronic wild-type HBV infection as a result of immune pressure and may also account for some cases of fulminant hepatitis B). Chronic hepatitis B ultimately leads to cirrhosis in 25–40% of cases (particularly in pts with HDV superinfection or the pre-C mutation) and hepatocellular carcinoma in many of these pts (particularly when chronic infection is acquired early in life).

EXTRAHEPATIC MANIFESTATIONS (IMMUNE COMPLEX–MEDIATED)

Rash, urticaria, arthritis, polyarteritis nodosa–like vasculitis, polyneuropathy, glomerulonephritis.

TREATMENT CHRONIC HEPATITIS B

There are currently seven approved drugs for the treatment of chronic HBV: interferon α (IFN-α), pegylated interferon (PEG IFN), lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir (see Table 153-1).Use of IFN-α has been supplanted by PEG-IFN. Table 153-2 summarizes recommendations for treatment of chronic HBV.

CHRONIC HEPATITIS C

Follows 50–70% of cases of transfusion-associated and sporadic hepatitis C. Clinically mild, often waxing and waning aminotransferase elevations; mild chronic hepatitis on liver biopsy. Extrahepatic manifestations include cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, and lymphocytic sialadenitis. Diagnosis confirmed by detecting anti-HCV in serum. May lead to cirrhosis in ≥20% of cases after 20 years.

TREATMENT CHRONIC HEPATITIS C

Therapy for chronic HCV is currently stratified based on HCV genotype and the presence of treatment naïve or treatment experienced disease in addition to pt-specific factors (see Tables 153-3 and Table 153-4). Therapeutic options for chronic HCV have evolved rapidly such that current recommendations as established by leading expert panels should be reviewed prior to deciding on the most appropriate treatment regimen.

HEPATITIS A

Although hepatitis A rarely causes fulminant hepatic failure, it may do so more frequently in pts with chronic liver disease—especially those with chronic hepatitis B or C. The hepatitis A vaccine is immunogenic and well tolerated in pts with chronic hepatitis. Thus, pts with chronic liver disease, especially those with chronic hepatitis B or C, should be vaccinated against hepatitis A.

TABLE 153-1 COMPARISON OF PEGYLATED INTERFERON (PEG IFN), LAMIVUDINE, ADEFOVIR, ENTECAVIR, TELBIVUDINE, AND TENOFOVIR THERAPY FOR CHRONIC HEPATITIS B[a]

Feature	PEG IFN[b]	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Route of administration	Subcutaneous injection	Oral	Oral	Oral	Oral	Oral
Duration of therapy[c]	48–52 weeks	≥52 weeks	≥48 weeks	≥48 weeks	≥52 weeks	≥48 weeks
Tolerability	Poorly tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended	Well tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended
HBeAg seroconversion						
1 yr Rx	18–20%	16–18%	12%	21%	22%	21%
>1 yr Rx	NA	up to 50% @ 5 yrs	43% @ 3 yrs[d]	31% @ 2 yrs 44% @ 6 yrs	30% @ 2 yrs	40% @ 5 yrs
Log_{10} HBV DNA reduction (mean copies/mL)						
HBeAg-reactive	4.5	5.5	median 3.5–5	6.235.0	6.4	6.2
HBeAg-negative	4.1	4.4–4.7	median 3.5–3.9		5.2	4.6
HBV DNA PCR negative (<300–400 copies/mL; <1000 copies/mL for adefovir) at end of yr 1						
HBeAg-reactive	10–25%	36–44%	13–21%	67% (91% @ 4 yrs)	60%	76%
HBeAg-negative	63%	60–70%	48–77%	90%	88%	93%
ALT normalization at end of yr 1						

HBeAg-reactive	39%	41–75%	48–61%	68%	77%	68%
HBeAg-negative	34–38%	62–79%	48–77%	78%	74%	76%
HBsAg loss yr 1	3–4%	≤1%	0%	2%	<1%	3%
>yr 1	12% 5 yr after 1 yr of Rx	No data	5% at yr 5	6% at yr 6	No data	8% at yr 5
Histologic improvement (≥2 point reduction in HAI) at yr 1						
HBeAg-reactive	38% 6 months after	49–56%	53–68%	72%	65%	74%
HBeAg-negative	48% 6 months after	61–66%	64%	70%	67%	72%
Viral resistance	None	15–30% @ 1 yr	None @ 1 yr	≤1% @ 1 yr[e]	Up to 5% @ yr 1	0% @ yr 1
		70% @ 5 yrs	29% @ 5 yrs	1.2% @ 6 yrs[e]	Up to 22% @ yr 2	0% through yr 5
Pregnancy category	C	C[f]	C	C	B	B
Cost (US$) for 1 yr	~$18,000	~$2,500	~$6,500	~$8,700[g]	~$6,000	~$6,000

[a]Generally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously.
[b]Although standard interferon α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN.
[c]Duration of therapy in clinical efficacy trials; use in clinical practice may vary.
[d]Because of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly.
[e]7% during a year of therapy (43% at year 4) in lamivudine-resistant pts.
[f]Despite its Class C designation, lamivudine has an extensive pregnancy safety record in women with HIV/AIDS.
[g]Approximately $17,400 for lamivudine-refractory pts.
Abbreviations: ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; Rx, therapy; yr, year.

TABLE 153-2 RECOMMENDATIONS FOR TREATMENT OF CHRONIC HEPATITIS B[a]

HBeAg status	Clinical	HBV DNA (IU/mL)	ALT	Recommendation
HBeAg-reactive	[b]	$>2 \times 10^4$	≤2 × ULN[c,d]	No treatment; monitor. In pts >40, with family history of hepatocellular carcinoma, and/or ALT persistently at the high end of the twofold range, liver biopsy may help in decision to treat
	Chronic hepatitis	$>2 \times 10^{4d}$	>2 × ULN[d]	Treat[e]
	Cirrhosis compensated	$>2 \times 10^3$	< or > ULN	Treat[e] with oral agents, not PEG IFN
	Cirrhosis decompensated	$<2 \times 10^3$	>ULN	Consider treatment[f]
		Detectable	< or > ULN	Treat[e] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation
HBeAg-negative	[b]	$\leq 2 \times 10^3$	≤ULN	Inactive carrier; treatment not necessary
	Chronic hepatitis	$>10^3$	1 to >2 × ULN[d]	Consider liver biopsy; treat[h] if biopsy shows moderate to severe inflammation or fibrosis
	Chronic hepatitis	$>10^4$	>2 × ULN[d]	Treat[h,i]
	Cirrhosis compensated	$>2 \times 10^3$	< or > ULN	Treat[e] with oral agents, not PEG IFN
		$<2 \times 10^3$	>ULN	Consider treatment[f]
	Cirrhosis decompensated	Detectable	< or > ULN	Treat[h] with oral agents[g], not PEG IFN; refer for liver transplantation
		Undetectable	< or > ULN	Observe; refer for liver transplantation

[a]Based on practice guidelines of the American Association for the Study of Liver Diseases (AASLD). Except as indicated in footnotes, these guidelines are similar to those issued by the European Association for the Study of the Liver (EASL).
[b]Liver disease tends to be mild or inactive clinically; most such pts do not undergo liver biopsy.
[c]This pattern is common during early decades of life in Asian pts infected at birth.
[d]According to the EASL guidelines, treat if HBV DNA is $>2 \times 10^3$ IU/mL and ALT >ULN.
[e]One of the potent oral drugs with a high barrier to resistance (entecavir or tenofovir) or PEG IFN can be used as first-line therapy (see text). These oral agents, but not PEG IFN, should be used for interferon-refractory/intolerant and immunocompromised pts. PEG IFN is administered weekly by subcutaneous injection for a year; the oral agents are administered daily for at least a year and continued indefinitely or until at least 6 months after HBeAg seroconversion.
[f]According to EASL guidelines, pts with compensated cirrhosis and detectable HBV DNA at any level, even with normal ALT, are candidates for therapy. Most authorities would treat indefinitely, even in HBeAg-positive disease after HBeAg seroconversion.
[g]Because the emergence of resistance can lead to loss of antiviral benefit and further deterioration in decompensated cirrhosis, a low-resistance regimen is recommended—entecavir or tenofovir monotherapy or combination therapy with the more resistance-prone lamivudine (or telbivudine) plus adefovir. Therapy should be instituted urgently.
[h]Because HBeAg seroconversion is not an option, the goal of therapy is to suppress HBV DNA and maintain a normal ALT. PEG IFN is administered by subcutaneous injection weekly for a year; caution is warranted in relying on a 6-month posttreatment interval to define a sustained response, because the majority of such responses are lost thereafter. Oral agents, entecavir or tenofovir, are administered daily, usually indefinitely or until, as very rarely occurs, virologic and biochemical responses are accompanied by HBsAg seroconversion.
[i]For older pts and those with advanced fibrosis, consider lowering the HBV DNA threshold to $>2 \times 10^3$ IU/mL.
Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PEG IFN, pegylated interferon; ULN, upper limit of normal.

TABLE 153-3 PEGYLATED INTERFERON (PEG IFN) α2a AND α2b FOR CHRONIC HEPATITIS C

	PEG IFN-α2b	PEG IFN-α2a
PEG size	12 kD linear	40 kD branched
Elimination half-life	54 h	65 h
Clearance	725 mL/h	60 mL/h
Dose	1.5 μg/kg (weight-based)	180 μg
Storage	Room temperature	Refrigerated
Ribavirin dose		
Genotype 1	800–1400 mg[a]	1000–1200 mg[b]
Genotype 2/3	800 mg	800 mg
Duration of therapy		
Genotype 1	48 weeks	48 weeks
Genotype 2/3	48 weeksc	24 weeks
Efficacy of combination therapy[d]	54%	56%
Genotype 1	40–42%	41–51%
Genotype 2/3	82%	76–78%

[a]In the registration trial for PEG IFN-α2b plus ribavirin, the optimal regimen was 1.5 μg of PEG IFN plus 800 mg of ribavirin; however, a post hoc analysis of this study suggested that higher ribavirin doses are better. In subsequent trials of PEG IFN-α2b with ribavirin in pts with genotype 1, the following daily ribavirin doses have been validated: 800 mg for pts weighing <65 kg, 1000 mg for pts weighing >65–85 kg, 1200 for pts weighing >85–105 kg, and 1400 mg for pts weighing >105 kg.
[b]1000 mg for pts weighing <75 kg; 1200 mg for pts weighing ≥75 kg.
[c]In the registration trial for PEG IFN-α2b plus ribavirin, all pts were treated for 48 weeks; however, data from other trials of standard interferons and the other PEG IFN demonstrated that 24 weeks suffices for pts with genotypes 2 and 3. For pts with genotype 3 who have advanced fibrosis/cirrhosis and/or high-level HCV RNA, a full 48 weeks is preferable.
[d]Attempts to compare the two PEG IFN preparations based on the results of registration clinical trials are confounded by differences between trials of the two agents in methodologic details (different ribavirin doses, different methods for recording depression, and other side effects) and study-population composition (different proportion with bridging fibrosis/cirrhosis, proportion from the United States versus international, mean weight, proportion with genotype 1, and proportion with high-level HCV RNA). In the head-to-head comparison of the two PEG IFN preparations in the IDEAL trial reported in 2009, the two drugs were comparable in tolerability and efficacy. PEG IFN-α2b was administered at a weekly weight-based dose of 1.0 μg/kg or 1.5 μg/kg, and PEG IFN-α2a at a weekly fixed dose of 180 μg. For PEG IFN-α2b, daily ribavirin weight-based doses ranged between 800 and 1400 mg based on weight criteria (see footnote [a], above), whereas for PEG IFN-α2a, daily ribavirin weight-based doses ranged between 1000 and 1200 mg (see footnote [b], above). For the two PEG IFN-α2b study arms, ribavirin dose reductions for ribavirin-associated adverse effects were done in 200- to 400-mg decrements; for PEG IFN-α2a, the ribavirin dose was reduced to 600 mg for intolerability. Sustained virologic responses occurred in 38.0% of the low-dose PEG IFN-α2b group, 39.8% of the standard, full-dose PEG IFN-α2b group, and 40.9% of the PEG IFN-α2a group.
Abbreviations: HCV RNA, hepatitis C virus RNA; PEG, polyethylene glycol.

TABLE 153-4 INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY OF CHRONIC HEPATITIS C[a]

Standard Indications for Therapy[a]

AASLD and EASL 2015 Guidelines recommend treatment for all with advanced fibrosis and differ regarding therapy for those with earlier stage fibrosis as follows:

AASLD

- Treatment is recommended for all pts with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.
- Immediate treatment is assigned the highest priority for those pts with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and pts with severe extrahepatic hepatitis C.

EASL

- All treatment-naïve and treatment-experienced pts with compensated and decompensated liver disease.
- Treatment should be prioritized for pts with significant fibrosis (METAVIR score F3 or F4)
- In pts with less severe disease, the indication for and timing of therapy can be individualized.

Antiviral Therapy Management Decisions Made on an Individual Basis

Children (age <18 years)—protease inhibitors not recommended.

Age >70 (in protease inhibitor trials, telaprevir trials included pts age 18–70; boceprevir trials included pts >18 years of age [no upper age cutoff])

Mild hepatitis on liver biopsy

Persons with severe renal insufficiency (require reduced doses of PEG IFN and ribavirin)

Concurrent HIV treated similarly, but with extra attention to interactions.

Long-Term Maintenance Therapy Recommended: None

Long-Term Maintenance Therapy in Nonresponders: Not Recommended

Antiviral Therapy Not Recommended

Decompensated cirrhosis (contraindicated with IFN based regimens)

Pregnancy (teratogenicity of ribavirin, unknown effects DAAs)

Contraindications to use of antiviral medications

Therapeutic Regimens

TREATMENT-NAÏVE

Genotype 1a:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 (no cirrhosis) or 24 weeks +/- weight-based ribavirin (cirrhosis)
- Ledipasvir 90 mg and sofosbuvir 400 mg daily for 12 weeks
- Daily paritaprevir 150mg and ritonavir 100mg/ombitasvir 25mg + twice daily dasabuvir 250mg + weight-based ribavirin for 12 (no cirrhosis) or 24 weeks (cirrhosis)
- Simepravir 150 mg and sofosbuvir 400 mg daily for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without q80K mutation) +/- weight-based ribavirin

(*Continued*)

TABLE 153-4 INDICATIONS AND RECOMMENDATIONS FOR ANTIVIRAL THERAPY OF CHRONIC HEPATITIS C[a] (*CONTINUED*)

Genotype 1b:

- Same as genotype 1a with the exception of daily paritaprevir 150 mg/ritonavir 100mg/ombitasvir 25 mg + twice daily dasabuvir 250 mg is used without ribavirin

Genotype 2:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 weeks in pts who cannot tolerate ribavirin
- Sofosbuvir 400 mg daily + weight-based ribavirin for 12 weeks in noncirrhotic pts, 16 weeks if cirrhotic.

Genotype 3:

- Daclatasvir 60 mg and sofosbuvir 400 mg daily for 12 weeks (no cirrhosis) or 24 weeks +/- weight-based ribavirin (cirrhosis).
- Sofosbuvir 400 mg daily and weight-based ribavirin + weekly PEG-IFN for IFN eligible pts
- Alternative: sofosbuvir 400 mg daily and weight-based ribavirin for 24 weeks

Genotype 4:

- Ledipasvir 90 mg and sofosbuvir 400 mg daily for 12 weeks
- Daily paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg + weight-based ribavirin for 12 weeks
- Sofosbuvir 400 mg daily + weight-based ribavirin for 24 weeks
- Alternative: sofosbuvir 400 mg daily + weight-based ribavirin + weekly PEG-IFN for 12 weeks

Genotype 5 and 6:

- Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks
- Alternative: sofosbuvir 400 mg + weight-based ribavirin + weekly PEG-IFN for 12 weeks

TREATMENT-EXPERIENCED

For the latest guidelines:

- AASLD Guidelines; http://www.hcvguidelines.org
- EASL guidelines: http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015

Features Associated with Reduced Responsiveness

Genotype and subtype

Treatment experience

Extent of fibrosis

[a]Recommendations for the treatment of hepatitis C are rapidly evolving and new recommendations continue to supplant those listed in this table. Before making any therapeutic decisions, the most recent guidelines should be reviewed which can be found at the website locations provided within the table.

Abbreviations: AASLD, American Society for the Study of Liver Diseases; ALT, alanine aminotransferase; DAA, directly acting antivirals; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; IFN, interferon; PEG IFN, pegylated interferon; IU, international units (1 IU/mL is equivalent to ~2.5 copies/mL).

AUTOIMMUNE HEPATITIS

CLASSIFICATION

Type I: classic autoimmune hepatitis, anti–smooth-muscle and/or antinuclear antibodies (ANA). *Type II:* associated with anti-liver/kidney microsomal (anti-LKM) antibodies, which are directed against cytochrome P450IID6 (seen primarily in southern Europe). *Type III* pts lack ANA and anti-LKM, have antibodies reactive with hepatocyte cytokeratins; clinically similar to type I. Criteria have been suggested by an international group for establishing a diagnosis of autoimmune hepatitis.

CLINICAL MANIFESTATIONS

Classic autoimmune hepatitis (type I): 80% women, third to fifth decades. Abrupt onset (acute hepatitis) in a third. Insidious onset in two-thirds: progressive jaundice, anorexia, hepatomegaly, abdominal pain, epistaxis, fever, fatigue, amenorrhea. Leads to cirrhosis; >50% 5-year mortality if untreated.

EXTRAHEPATIC MANIFESTATIONS

Rash, arthralgias, keratoconjunctivitis sicca, thyroiditis, hemolytic anemia, nephritis.

SEROLOGIC ABNORMALITIES

Hypergammaglobulinemia, positive rheumatoid factor, smooth-muscle antibody (40–80%), ANA (20–50%), antimitochondrial antibody (10–20%), false-positive anti-HCV enzyme immunoassay but usually not HCV RNA, atypical p-ANCA. Type II: anti-LKM antibody.

TREATMENT AUTOIMMUNE HEPATITIS

Indicated for symptomatic disease with biopsy evidence of severe chronic hepatitis (bridging necrosis), marked aminotransferase elevations (5- to 10-fold), and hypergammaglobulinemia. Prednisone or prednisolone 30–60 mg/d PO tapered to 10–15 mg/d over several weeks; often azathioprine 50 mg/d PO is also administered to permit lower glucocorticoid doses and avoid steroid side effects. Monitor liver function tests monthly. Symptoms may improve rapidly, but biochemical improvement may take weeks or months and subsequent histologic improvement (to lesion of mild chronic hepatitis or normal biopsy) up to 18–24 months. Therapy should be continued for at least 12–18 months. Relapse occurs in at least 50% of cases (re-treat). For frequent relapses, consider maintenance therapy with low-dose glucocorticoids or azathioprine 2 (mg/kg)/d.

For a more detailed discussion, see Dienstag JL: Chronic Hepatitis, Chap. 362, p. 2031, in HPIM-19.

154 Cirrhosis and Alcoholic Liver Disease

CIRRHOSIS

Cirrhosis is defined histopathologically and has a variety of causes, clinical features, and complications. In cirrhosis, there is the development of liver fibrosis to the point that there is architectural distortion with the formation of regenerative nodules, which results in decreased liver function.

CAUSES (SEE TABLE 154-1)

CLINICAL MANIFESTATIONS

May be absent, with cirrhosis being incidentally found at surgery.

Symptoms

Anorexia, nausea, vomiting, diarrhea, vague RUQ pain, fatigue, weakness, fever, jaundice, amenorrhea, impotence, infertility.

Signs

Spider telangiectases, palmar erythema, jaundice, scleral icterus, parotid and lacrimal gland enlargement, clubbing, Dupuytren's contracture, gynecomastia, testicular atrophy, hepatosplenomegaly, ascites, gastrointestinal bleeding (e.g., varices), hepatic encephalopathy.

Laboratory Findings

Anemia (microcytic due to blood loss, macrocytic due to folate deficiency; hemolytic called *Zieve's syndrome*), pancytopenia (hypersplenism), prolonged PT, rarely overt DIC; hyponatremia, hypokalemic alkalosis, glucose disturbances, hypoalbuminemia.

DIAGNOSTIC STUDIES

Depend on clinical setting. Serum: HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HDV, Fe, total iron-binding capacity, ferritin, antimitochondrial antibody (AMA), smooth-muscle antibody (SMA), anti-liver/kidney microsomal (anti-LKM) antibody, ANA, ceruloplasmin, α_1 antitrypsin (and phenotyping); abdominal ultrasound with Doppler study, CT or MRI (may show cirrhotic liver, splenomegaly, collaterals, venous thrombosis). Definitive diagnosis often depends on liver biopsy (percutaneous, transjugular, or open).

TABLE 154-1 CAUSES OF CIRRHOSIS

Alcoholism	Cardiac cirrhosis
Chronic viral hepatitis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	α_1-Antitrypsin deficiency
Nonalcoholic steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	

TABLE 154-2 COMPLICATIONS OF CIRRHOSIS

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Hepatorenal syndrome	Osteoporosis
Type 1	Osteomalacia
Type 2	Hematologic abnormalities
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia

COMPLICATIONS (SEE TABLE 154-2 AND CHAPS. 42, 43, AND 155)

The Child-Pugh scoring system has been used to predict the severity of cirrhosis and the risk of complications (Table 154-3).

ALCOHOLIC LIVER DISEASE

Excessive alcohol use can cause fatty liver, alcoholic hepatitis, cirrhosis. Alcoholic cirrhosis accounts for about 40% of the deaths due to cirrhosis. History of excessive alcohol use often denied. Severe forms (hepatitis, cirrhosis) associated with ingestion of 160 g/d for 10–20 years; women more susceptible than men and develop advanced liver disease with less alcohol intake. Hepatitis B and C may be cofactors in the development of liver disease. Malnutrition may contribute to development of cirrhosis.

FATTY LIVER

Often presents as asymptomatic hepatomegaly and mild elevations in biochemical liver tests. Reverses on withdrawal of ethanol; does not lead to cirrhosis.

TABLE 154-3 CHILD-PUGH CLASSIFICATION OF CIRRHOSIS

Factor	Units	1	2	3
Serum bilirubin	μmol/L	<34	34–51	>51
	mg/dL	<2.0	2.0–3.0	>3.0
Serum albumin	g/L	>35	30–35	<30
	g/dL	>3.5	3.0–3.5	<3.0
Prothrombin time	Seconds prolonged	0–4	4–6	>6
	INR	<1.7	1.7–2.3	>2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

Note: The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5–15. Child-Pugh class is either A (a score of 5–6), B (7–9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (class B). This level has been the accepted criterion for listing for liver transplantation.

ALCOHOLIC HEPATITIS

Clinical presentation ranges from asymptomatic to severe liver failure with jaundice, ascites, GI bleeding, and encephalopathy. Typically anorexia, nausea, vomiting, fever, jaundice, tender hepatomegaly. Occasional cholestatic picture mimicking biliary obstruction. Aspartate aminotransferase (AST) usually <400 U/L and more than twofold higher than alanine aminotransferase (ALT). Bilirubin and WBC may be elevated. Diagnosis defined by liver biopsy findings: hepatocyte swelling, alcoholic hyaline (Mallory-Denk bodies), infiltration of PMNs, necrosis of hepatocytes, pericentral venular fibrosis.

OTHER METABOLIC CONSEQUENCES OF ALCOHOLISM

Increased NADH/NAD ratio leads to lactic acidemia, ketoacidosis, hyperuricemia, hypoglycemia, hypomagnesemia, hypophosphatemia. Also mitochondrial dysfunction, induction of microsomal enzymes resulting in altered drug metabolism, lipid peroxidation leading to membrane damage, hypermetabolic state; many features of alcoholic hepatitis are attributable to toxic effects of acetaldehyde and cytokines (interleukins 1 and 6, and TNF, released because of impaired detoxification of endotoxin).

ADVERSE PROGNOSTIC FACTORS

Critically ill pts with alcoholic hepatitis have 30-day mortality rates >50%. Severe alcoholic hepatitis characterized by PT >5 × above control, bilirubin >137 μmol/L (>8 mg/dL), hypoalbuminemia, azotemia. A discriminant function can be calculated as 4.6 × (pt's PT in seconds) (control PT in seconds) + serum bilirubin (mg/dL). Values ≥32 are associated with poor prognosis. A Model for End-Stage Liver Disease (MELD) score > 21 is also associated with significant mortality in alcoholic hepatitis. Ascites, variceal hemorrhage, encephalopathy, hepatorenal syndrome predict a poor prognosis.

TREATMENT ALCOHOLIC LIVER DISEASE

Abstinence is essential; 8500- to 12,500-kJ (2000- to 3000-kcal) diet with 1 g/kg protein (less if encephalopathy). Daily multivitamin, thiamine 100 mg, folic acid 1 mg. Correct potassium, magnesium, and phosphate deficiencies. Transfusions of packed red cells, plasma as necessary. Monitor glucose (hypoglycemia in severe liver disease). Pts with severe alcoholic hepatitis defined as a discriminant function >32 or MELD >20 should be given prednisone 40 mg/d or prednisolone 32 mg/d PO for 4 weeks followed by a taper. Pentoxifylline demonstrated improved survival, primarily due to a decrease in hepatorenal syndrome and led to the inclusion of this agent as an alternative to glucocorticoids in the treatment of severe alcoholic hepatitis. Liver transplantation may be an option in carefully selected pts with end-stage cirrhosis.

PRIMARY BILIARY CIRRHOSIS (PBC)

PBC is a progressive nonsuppurative destructive intrahepatic cholangitis. Strong female predominance, median age of 50 years. Presents as asymptomatic elevation in alkaline phosphatase (better prognosis) or with pruritus, progressive jaundice, consequences of impaired bile excretion, and ultimately cirrhosis and liver failure.

CLINICAL MANIFESTATIONS

Pruritus, fatigue, jaundice, xanthelasma, xanthomata, osteoporosis, steatorrhea, skin pigmentation, hepatosplenomegaly, portal hypertension; elevations in serum alkaline phosphatase, bilirubin, cholesterol, and IgM levels.

ASSOCIATED DISEASES

Sjögren's syndrome, collagen vascular diseases, thyroiditis, glomerulonephritis, pernicious anemia, renal tubular acidosis.

DIAGNOSIS

Antimitochondrial antibodies (AMA) in 90% (directed against enzymes of the pyruvate dehydrogenase complex and other 2-oxo-acid dehydrogenase mitochondrial enzymes). Liver biopsy most important in AMA-negative PBC. Biopsies identify 4 stages: stage 1—destruction of interlobular bile ducts, granulomas; stage 2—ductular proliferation; stage 3—fibrosis; stage 4—cirrhosis.

PROGNOSIS

Correlates with age, serum bilirubin, serum albumin, prothrombin time, edema.

TREATMENT PRIMARY BILIARY CIRRHOSIS

Ursodeoxycholic acid 13–15 mg/kg per day has been shown to improve the biochemical and histologic features of disease. Response is greatest when given early. Cholestyramine 4 g PO with meals for pruritus; in refractory cases consider rifampin, naltrexone, plasmapheresis. Calcium, vitamin D, and bisphosphonates are given for osteoporosis. Liver transplantation for end-stage disease.

LIVER TRANSPLANTATION

Consider in the absence of contraindications for chronic, irreversible, progressive liver disease or fulminant hepatic failure when no alternative therapy is available (Table 154-4).

TABLE 154-4 INDICATIONS FOR LIVER TRANSPLANTATION

Children	Adults
Biliary atresia	Primary biliary cirrhosis
Neonatal hepatitis	Secondary biliary cirrhosis
Congenital hepatic fibrosis	Primary sclerosing cholangitis
Alagille syndrome[a]	Autoimmune hepatitis
Byler disease[b]	Caroli disease[c]
α_1-Antitrypsin deficiency	Cryptogenic cirrhosis
Inherited disorders of metabolism	Chronic hepatitis with cirrhosis
Wilson's disease	Hepatic vein thrombosis
Tyrosinemia	Fulminant hepatitis
Glycogen storage diseases	Alcoholic cirrhosis
Lysosomal storage diseases	Chronic viral hepatitis
Protoporphyria	Primary hepatocellular malignancies
Crigler-Najjar disease type I	Hepatic adenomas
Familial hypercholesterolemia	Nonalcoholic steatohepatitis
Primary hyperoxaluria type I	Familial amyloid polyneuropathy
Hemophilia	

[a]Arteriohepatic dysplasia, with paucity of bile ducts, and congenital malformations, including pulmonary stenosis.
[b]Intrahepatic cholestasis, progressive liver failure, mental and growth retardation.
[c]Multiple cystic dilatations of the intrahepatic biliary tree.

TABLE 154-5 CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Absolute	Relative
Uncontrolled extrahepatobiliary infection	Age >70
Active, untreated sepsis	Prior extensive hepatobiliary surgery
Uncorrectable, life-limiting congenital anomalies	Portal vein thrombosis
Active substance or alcohol abuse	Renal failure not attributable to liver disease
Advanced cardiopulmonary disease	Previous extrahepatic malignancy (not including nonmelanoma skin cancer)
Extrahepatobiliary malignancy (not including nonmelanoma skin cancer)	Severe obesity
Metastatic malignancy to the liver	Severe malnutrition/wasting
Cholangiocarcinoma	Medical noncompliance
AIDS	HIV seropositivity with failure to control HIV viremia or CD4 <100/μL
Life-threatening systemic diseases	Intrahepatic sepsis
	Severe hypoxemia secondary to right-to-left intrapulmonary shunts (Po_2<50 mmHg)
	Severe pulmonary hypertension (mean pulmonary artery pressure >35 mmHg)
	Uncontrolled psychiatric disorder

CONTRAINDICATIONS (SEE TABLE 154-5)

SELECTION OF DONOR

Matched for ABO blood group compatibility and liver size (reduced-size grafts may be used, esp. in children). Should be negative for HIV, HBV, and HCV. Living-donor transplant has gained increased popularity with transplantation of the right hepatic lobe from a healthy adult donor to an adult. Living-donor transplant of the left lobe accounts for one-third of all liver transplants in children.

IMMUNOSUPPRESSION

Various combinations of tacrolimus or cyclosporine and glucocorticoids, sirolimus, everolimus, mycophenolate mofetil, or OKT3 (monoclonal antithymocyte globulin).

MEDICAL COMPLICATIONS AFTER TRANSPLANTATION

Liver graft dysfunction (primary nonfunction, acute or chronic rejection, ischemia, hepatic artery thrombosis, biliary obstruction or leak, recurrence of primary disease); infections (bacterial, viral, fungal, opportunistic); renal dysfunction; neuropsychiatric disorders, cardiovascular instability, pulmonary compromise.

SUCCESS RATE

Currently, 5-year survival rates exceed 60%; less for certain conditions (e.g., chronic hepatitis B, hepatocellular carcinoma).

For a more detailed discussion, see Mailliard ME, Sorrell MF: Alcoholic Liver Disease, Chap. 363, p. 2052; Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058; Chung RT, Dienstag JL,: Liver Transplantation, Chap. 368, p. 2067, in HPIM-19.

155 Portal Hypertension

Portal hypertension is defined as elevation of the hepatic venous pressure gradient to >5 mmHg, which occurs as a consequence of cirrhosis (Chap. 154). It is caused by increased intrahepatic resistance to the passage of blood flow through the liver due to cirrhosis together with increased splanchnic blood flow due to vasodilatation within the splanchnic vascular bed.

CLASSIFICATION (SEE TABLE 155-1)

CONSEQUENCES

The primary complications of portal hypertension are gastroesophageal varices with hemorrhage, ascites (Chap. 43), hypersplenism, hepatic encephalopathy,

TABLE 155-1 CLASSIFICATION OF PORTAL HYPERTENSION

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Massive splenomegaly (Banti's syndrome)
Hepatic
Presinusoidal
Schistosomiasis
Congenital hepatic fibrosis
Sinusoidal
Cirrhosis—many causes
Alcoholic hepatitis
Postsinusoidal
Hepatic sinusoidal obstruction (venoocclusive syndrome)
Posthepatic
Budd-Chiari syndrome
Inferior vena caval webs
Cardiac causes
Restrictive cardiomyopathy
Constrictive pericarditis
Severe congestive heart failure

spontaneous bacterial peritonitis (Chap. 43), hepatorenal syndrome (Chap. 43), hepatocellular carcinoma (Chap. 71).

ESOPHAGOGASTRIC VARICES

About one-third of pts with cirrhosis have varices, and one-third of pts with varices will develop bleeding. Bleeding is a life-threatening complication; risk of bleeding correlates with variceal size and location, the degree of portal hypertension (portal venous pressure >12 mmHg), and the severity of cirrhosis, e.g., Child-Pugh classification (see Table 154-3).

DIAGNOSIS

Esophagogastroscopy: procedure of choice for evaluation of upper GI hemorrhage in pts with known or suspected portal hypertension. *Celiac* and *mesenteric arteriography* are alternatives when massive bleeding prevents endoscopy and to evaluate portal vein patency (portal vein may also be studied by ultrasound with Doppler and MRI).

TREATMENT ESOPHAGOGASTRIC VARICES

See Chap. 41 for general measures to treat GI bleeding.

CONTROL OF ACUTE BLEEDING

Choice of approach depends on clinical setting and availability.

1. Endoscopic intervention is employed as first-line treatment to control bleeding acutely. Endoscopic variceal ligation (EVL) is used to control acute bleeding in >90% of cases. EVL is less successful when varices extend into proximal stomach. Some endoscopists will use variceal injection (sclerotherapy) as initial therapy, particularly when bleeding is vigorous.
2. Vasoconstricting agents: somatostatin or octreotide (50–100 μg/h by continuous infusion).
3. Balloon tamponade (Sengstaken-Blakemore- or Minnesota tube). Can be used when endoscopic therapy is not immediately available or in pts who need stabilization prior to endoscopic therapy. Complications—obstruction of pharynx, asphyxiation, aspiration, esophageal ulceration. Generally reserved for massive bleeding, failure of vasopressin and/or endoscopic therapy.
4. Transjugular intrahepatic portosystemic shunt (TIPS)—portacaval shunt placed by interventional radiologic technique, reserved for failure of other approaches; risk of hepatic encephalopathy (20–30%), shunt stenosis or occlusion, infection.

PREVENTION OF RECURRENT BLEEDING

1. EVL should be repeated until obliteration of all varices is accomplished.
2. Propranolol or nadolol—nonselective beta blockers that act as portal venous antihypertensives; may decrease the risk of variceal hemorrhage and mortality due to hemorrhage.
3. TIPS—regarded as useful "bridge" to liver transplantation in pt who has failed pharmacologic therapy and is awaiting a donor liver.
4. Portosystemic shunt surgery used less commonly with the advent of TIPS; could be considered for pts with good hepatic synthetic function.

PREVENTION OF INITIAL BLEED

For pts at high risk of variceal bleeding, consider prophylaxis with EVL and/or nonselective beta blockers.

HEPATIC ENCEPHALOPATHY

An alteration in mental status and cognitive function occurring in the presence of liver failure; may be acute and reversible or chronic and progressive.

CLINICAL FEATURES

Confusion, slurred speech, change in personality that can include being violent and hard to manage, being sleepy and difficult to arouse, asterixis (flapping tremor). Can progress to coma; initially responsive to noxious stimuli, later unresponsive.

PATHOPHYSIOLOGY

Gut-derived neurotoxins that are not removed by the liver because of vascular shunting and decreased hepatic mass reach the brain and cause the symptoms of hepatic encephalopathy. Ammonia levels are typically elevated in encephalopathy, but the correlation between the severity of liver disease and height of ammonia levels is often poor. Other compounds that may contribute include false neurotransmitters and mercaptans.

PRECIPITANTS

GI bleeding, azotemia, constipation, high-protein meal, hypokalemic alkalosis, CNS depressant drugs (e.g., benzodiazepines and barbiturates), hypoxia, hypercarbia, sepsis.

TREATMENT HEPATIC ENCEPHALOPATHY

Remove precipitants; correct electrolyte imbalances. Lactulose (nonabsorbable disaccharide) results in colonic acidification and diarrhea and is the mainstay of treatment; goal is to produce 2–3 soft stools per day. Poorly absorbed antibiotics are often used in pts who do not tolerate lactulose, with alternating administration of neomycin and metronidazole being used to reduce the individual side effects of each. Rifaximin has recently also been used; zinc supplementation is sometimes helpful. Liver transplantation when otherwise indicated.

For a more detailed discussion, see Bacon BR: Cirrhosis and Its Complications, Chap. 365, p. 2058; in HPIM-19.

This page intentionally left blank

156 Diseases of Immediate-Type Hypersensitivity

DEFINITION

These diseases result from IgE-dependent release of mediators from sensitized basophils and mast cells upon contact with an offending antigen (allergen). Associated disorders include anaphylaxis, allergic rhinitis, urticaria, asthma, and eczematous (atopic) dermatitis.

PATHOPHYSIOLOGY

IgE binds to the surface of mast cells and basophils through a high-affinity receptor. Cross-linking of this IgE by antigen causes cellular activation with subsequent release of preformed and newly synthesized mediators (Fig. 156-1). These mediators have been implicated in many pathophysiologic events associated with immediate-type hypersensitivity, such as vasodilation, increased vasopermeability, smooth-muscle contraction, and chemotaxis of neutrophils and other inflammatory cells. The clinical manifestations of each allergic reaction depend largely on the anatomic site(s) and time course of mediator release.

URTICARIA AND ANGIOEDEMA

DEFINITION

May occur together or separately. *Urticaria* involves only the superficial dermis and presents as circumscribed wheals with raised serpiginous borders and blanched

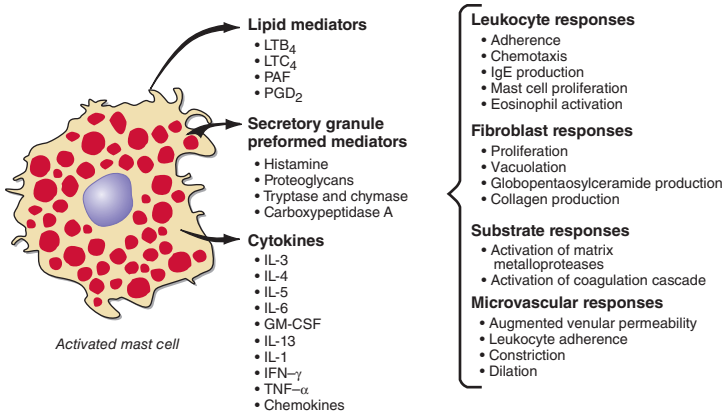


FIGURE 156-1 Bioactive mediators of three categories generated by IgE-dependent activation of murine mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; LT, leukotriene; PAF, platelet-activating factor; PGD_2, prostaglandin D_2.

TABLE 156-1 CLASSIFICATION OF URTICARIA AND/OR ANGIOEDEMA

1. IgE-dependent
   a. Specific antigen sensitivity (pollens, foods, drugs, fungi, molds, Hymenoptera venom, helminths)
   b. Physical: dermographism, cold, solar, pressure, cholinergic
   c. Autoimmune
2. Bradykinin-mediated
   a. Hereditary angioedema: C1 inhibitor deficiency: null (type 1) and dysfunctional (type 2), mutated factor XII (type 3)
   b. Acquired angioedema: C1 inhibitor deficiency: anti-idiotype and anti-C1 inhibitor
   c. Angiotensin-converting enzyme inhibitors
3. Complement-mediated
   a. Necrotizing vasculitis
   b. Serum sickness
   c. Reactions to blood products
4. Nonimmunologic
   a. Direct mast cell–releasing agents (opiates, antibiotics, curare, D-tubocurarine, radiocontrast media)
   b. Agents that alter arachidonic acid metabolism (aspirin and nonsteroidal anti-inflammatory agents, azo dyes, and benzoates)
5. Idiopathic

centers; wheals may coalesce. *Angioedema* involves deeper layers of skin and may include subcutaneous tissue. Recurrent episodes of urticaria and/or angioedema of <6 weeks duration are considered acute, whereas attacks persisting beyond this period are chronic.

CLASSIFICATION AND ETIOLOGY

The classification of urticaria-angioedema focuses on mechanisms that elicit clinical disease and can be useful for differential diagnosis, but most cases of chronic urticaria are idiopathic (Table 156-1).

Urticaria-angioedema can occur secondary to inhalation, physical contact, or more commonly ingestion (fruits, shellfish, fish, milk products, chocolate, legumes including peanuts, drugs) that may elicit urticaria alone or the anaphylactic syndrome (Chap. 26).

PATHOPHYSIOLOGY

Characterized by edema in the superficial dermis in urticaria and subcutaneous tissue and deep dermis in angioedema. Up to 40% of pts with chronic urticaria have an autoimmune cause including autoantibodies to IgE (5–10%) or, more commonly, to the α chain of FcεRI (35–45%).

DIAGNOSIS

History, with special attention to possible offending exposures and/or ingestion as well as the duration of lesions. Urticarial vasculitis typically persists >72 h, whereas conventional urticaria often lasts <48 h.

- Skin testing to food and/or inhalant antigens.
- Physical provocation, e.g., challenge with vibratory or cold stimuli.

- Laboratory examination: complement levels, erythrocyte sedimentation rate (ESR) (neither an elevated ESR nor hypocomplementemia is observed in IgE-mediated urticaria or angioedema); C1 inhibitor (C1INH) testing for deficiency of C1INH antigen (type 1) or a nonfunctional protein (type 2) if history suggests hereditary angioedema; cryoglobulins, hepatitis B antigen, and antibody studies; autoantibody screen.
- Skin biopsy may be necessary.

DIFFERENTIAL DIAGNOSIS

Atopic dermatitis, contact sensitivity, cutaneous mastocytosis (urticaria pigmentosa), systemic mastocytosis.

PREVENTION

Identification and avoidance of offending agent(s), if possible.

TREATMENT URTICARIA AND ANGIOEDEMA

- H_1 antihistamines may be helpful: e.g., chlorpheniramine up to 24 mg PO daily; diphenhydramine 25–50 mg PO qid; hydroxyzine 40–200 mg PO daily; cyproheptadine 8–32 mg PO daily; or the low or nonsedating class, e.g., loratidine 10 mg PO daily; desloratidine 5 mg PO daily; fexofenadine up to 180 mg PO daily; cetirizine 5–10 mg PO daily; levocetirizine 5 mg PO daily.
- H_2 antihistamines: e.g., ranitidine 150 mg PO bid may add benefit.
- Doxepin, a tricyclic compound with H_1 and H_2 receptor antagonist activity, has been used.
- Leukotriene receptor antagonists can be add-on therapy: e.g., montelukast 10 mg daily or zafirlukast 20 mg bid.
- Topical glucocorticoids are of no value in the management of urticaria and/or angioedema. Systemic glucocorticoids should not be used in the treatment of idiopathic, allergen-induced, or physical urticaria because of their long-term toxicity.

ALLERGIC RHINITIS

DEFINITION

Characterized by sneezing; rhinorrhea; obstruction of the nasal passages; conjunctival, nasal, and pharyngeal itching; and lacrimation, all occurring in a temporal relationship to allergen exposure. Prevalence in North America is ~20% with a peak prevalence ~40% occurring in childhood and adolescence. Perennial allergic rhinitis occurs in response to allergens that are present throughout the year such as house dust (containing dust mite antigens) and animal danders.

PATHOPHYSIOLOGY

Deposition of pollens and other allergens on nasal mucosa of sensitized individuals results in IgE-dependent triggering of mast cells with subsequent release of mediators that cause development of mucosal hyperemia, swelling, and fluid transudation.

DIAGNOSIS

Accurate history of symptoms correlated with time of seasonal pollination of plants in a given locale; special attention must be paid to other potentially sensitizing antigens such as materials associated with pets, e.g., dander.

- Physical examination: nasal mucosa may be boggy or erythematous; nasal polyps may be present; conjunctivae may be inflamed or edematous; manifestations of other allergic conditions (e.g., asthma, eczema) may be present.
- Skin tests to inhalant and/or food antigens.
- Nasal smear may reveal large numbers of eosinophils; presence of neutrophils may suggest infection.
- Total and specific serum IgE (as assessed by immunoassay) may be elevated.

DIFFERENTIAL DIAGNOSIS

Vasomotor rhinitis, upper respiratory infection (URI), irritant exposure, pregnancy with nasal mucosal edema, rhinitis medicamentosa, nonallergic rhinitis with eosinophilia, rhinitis due to α-adrenergic agents.

PREVENTION

Identification and avoidance of offending antigen(s).

TREATMENT ALLERGIC RHINITIS

- Older antihistamines (e.g., chlorpheniramine, diphenhydramine) are effective but cause sedation and psychomotor impairment including reduced hand-eye coordination and impaired automobile driving skills. Newer antihistamines (e.g., fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine, olopatadine, bilastine, and azelastine) are equally effective but are less sedating and more H_1 specific.
- Oral sympathomimetics, e.g., pseudoephedrine 30–60 mg PO qid; may aggravate hypertension; combination antihistamine/decongestant preparations may balance side effects and provide improved pt convenience.
- Topical vasoconstrictors—should be used sparingly due to rebound congestion and chronic rhinitis associated with prolonged use.
- Topical nasal glucocorticoids, e.g., beclomethasone, two sprays in each nostril bid, or fluticasone, two sprays in each nostril once daily.
- Topical nasal cromolyn sodium, one to two sprays in each nostril qid.
- Montelukast 10 mg PO daily is approved for seasonal and perennial rhinitis.
- Hyposensitization therapy, if more conservative therapy is unsuccessful.

SYSTEMIC MASTOCYTOSIS

DEFINITION

A systemic disorder defined by a clonal expansion of mast cells that in most instances is indolent and nonmalignant. Generally involves bone marrow, skin, gastrointestinal (GI) mucosa, liver, and spleen. Classified as cutaneous mastocytosis with variants and four systemic forms: indolent, associated with concomitant hematologic disorder, aggressive, and mast cell leukemia. Mast cell sarcoma and extracutaneous mastocytomas are rare solid mast cell tumors.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The clinical manifestations of systemic mastocytosis are due to tissue occupancy by the mast cell mass, the tissue response to that mass (fibrosis), and the release of bioactive substances acting both locally (urticaria pigmentosa, crampy abdominal pain, gastritis, peptic ulcer) and at distal sites (headache, pruritus, flushing, vascular

TABLE 156-2 DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS[a]

Major: Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous tissues with confirmation by immunodetection of tryptase or metachromasia
Minor: Abnormal mast cell morphology with a spindle shape and/or multilobed or eccentric nucleus
Aberrant mast cell surface phenotype with expression of CD25 and CD2 (IL-2 receptor) in addition to C117 (*c-kit*)
Detection of codon 816 mutation in peripheral blood cells, bone marrow cells, or lesional tissue
Total serum tryptase (mostly alpha) >20 ng/mL

[a]Diagnosis requires either the major and one minor or three minor criteria.

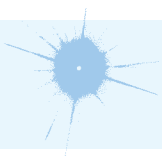
collapse). Clinical manifestations may be aggravated by alcohol, use of narcotics (e.g., codeine), and ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs).

DIAGNOSIS

Although the diagnosis of mastocytosis may be suspected on the basis of clinical and laboratory findings, it can be established only by tissue biopsy (usually bone marrow biopsy). The diagnostic criteria for systemic mastocytosis are shown in Table 156-2. Laboratory studies that can help support a diagnosis of systemic mastocytosis include measurement of urinary or blood levels of mast cell products such as histamine, histamine metabolites, prostaglandin D_2 (PGD_2) metabolites, or mast cell tryptase. Other studies including bone scan, skeletal survey, and GI contrast studies may be helpful. Other flushing disorders (e.g., carcinoid syndrome, pheochromocytoma) should be excluded.

TREATMENT SYSTEMIC MASTOCYTOSIS

- H_1 and H_2 antihistamines.
- Proton pump inhibitors for gastric hypersecretion.
- Oral cromolyn sodium for diarrhea and abdominal pain.
- Aspirin for severe flushing to block PGD_2.
- Systemic glucocorticoids may help, but frequently are associated with complications.
- Mast cell cytoreductive therapy with interferon α (IFN-α) or cladribine is generally reserved for advanced, nonindolent variants of systemic mastocytosis.
- Chemotherapy for frank leukemias.



For a more detailed discussion, see Boyce JA, Austen KF: Allergies, Anaphylaxis, and Systemic Mastocytosis, Chap. 376, p. 2113, in HPIM-19.

157 Primary Immune Deficiency Diseases

DEFINITION

Primary immunodeficiencies are genetic diseases that can involve all possible aspects of immune responses, from innate through adaptive, as well as cell differentiation, effector function, and immune regulation (Table 157-1). The consequences of primary immunodeficiencies vary widely as a function of the molecules that are defective and include vulnerability to infection by pathogenic and opportunistic infection, immunopathologic responses such as allergy, lymphoproliferations, and autoimmunity, and increased risk of cancers. The locations and sites of infection and the causal microorganisms often aid the physician in diagnosis.

DIAGNOSIS (SEE TABLE 157-2)

CLASSIFICATION (TABLE 157-1)

DEFICIENCIES OF THE INNATE IMMUNE SYSTEM

Account for ~10% of all primary immunodeficiencies (Table 157-1).

DEFICIENCES OF THE ADAPTIVE IMMUNE SYSTEM

T-Lymphocyte Deficiency Syndromes

Severe Combined Immunodeficiency (SCID) Group of rare primary immunodeficiencies characterized by a profound block in T-cell development as a consequence of an intrinsic deficiency. Clinical consequences occur within 3–6 months following birth. The most frequent clinical manifestations are recurrent oral candidiasis, failure to thrive, protracted diarrhea, *Pneumocystis jirovecii* infections. Six distinct causative mechanisms have been identified:

- *Cytokine signaling deficiency:* Most frequent SCID accounting for 40–50% of cases with the absence of T and NK cells. These pts have a deficiency in the gamma chain receptor shared by several cytokine receptors (interleukins 2, 4, 7, 9, 15, 21). The same phenotype seen in X-linked SCID can be inherited as an autosomal recessive disease due to mutations in the JAK3 protein kinase gene.
- *Purine metabolism deficiency:* About 20% of SCID pts are deficient in adenosine deaminase (ADA) due to mutations in the *ADA* gene.
- *Defective rearrangements of T- and B-cell receptors:* Account for ~20–30% of SCID cases. Main deficiencies involve recombinase activating genes (RAG-1, RAG-2) DNA-dependent protein kinase, DNA ligase 4, and Cernunnos deficiencies.
- *Defective (pre-) T-cell receptor signaling in the thymus:* Rare deficiencies in CD3 subunits associated with the (pre) TCR and CD45.
- *Reticular dysgenesis:* Extremely rare. Results from adenylate kinase 2 deficiency.
- *Defective egress of lymphocytes:* Defective egress of T cells from the thymus resulting from deficiency in coronin-1A.

TREATMENT SEVERE COMBINED IMMUNODEFICIENCY

Curative treatment relies on hematopoietic stem cell transplant (HSCT).

TABLE 157-1 CLASSIFICATION OF PRIMARY IMMUNE DEFICIENCY DISEASES

Deficiencies of the Innate Immune System	
• Phagocytic cells	
– Impaired production: SCN	
– Asplenia	
– Impaired adhesion: LAD	
– Impaired killing: CGD	
• Innate immunity receptors and signal transduction	
– Defects in toll-like receptor signaling	
– Mendelian susceptibility to mycobacterial disease	
• Complement deficiencies	
– Classical, alternative, and lectin pathways	
– Lytic phase	
Deficiencies of the Adaptive Immune System	
• T lymphocytes	
– Impaired development	SCIDs, DiGeorge syndrome
– Impaired survival, migration, function	Severe combined immunodeficiencies
	Hyper-IgE syndrome (autosomal dominant)
	DOK8 deficiency
	CD40 ligand deficiency
	Wiskott-Aldrich syndrome
	Ataxia-telangiectasia and other DNA repair deficiencies
• B lymphocytes	
– Impaired development	XL and AR agammaglobulinemia
– Impaired function	Hyper-IgM syndrome
	CVID
	IgA deficiency
Regulatory Defects	
• Innate immunity	Autoinflammatory syndromes (outside the scope of this chapter)
	Severe colitis
• Adaptive immunity	HLH
	ALPS
	Autoimmunity and inflammatory diseases (IPEX, APECED)

Abbreviations: ALPS, autoimmune lymphoproliferation syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; HLH, hemophagocytic lymphohistiocytosis; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; LAD, leukocyte adhesion deficiency; SCIDs, severe combined immune deficiencies; SCN, severe congenital neutropenia; XL, X-linked.

TABLE 157-2 TEST MOST FREQUENTLY USED TO DIAGNOSE A PRIMARY IMMUNE DEFICIENCY

Test	Information	PID Disease
Blood cell counts and cell morphology	Neutrophil counts	↓Severe congenital neutropenia, ↑↑ LAD
	Lymphocyte counts[a]	T-cell ID
	Eosinophilia	WAS, hyper-IgE syndrome
	Howell-Jolly bodies	Asplenia
Chest x-ray	Thymic shadow	SCID, DiGeorge syndrome
	Costochondral junctions	Adenosine deaminase deficiency
Bone x-ray	Metaphyseal ends	Cartilage hair hypoplasia
Immunoglobulin serum levels	IgG, IgA, IgM	B-cell ID
	IgE	Hyper-IgE syndrome, WAS, T-cell ID
Lymphocyte phenotype	T-, B-lymphocyte counts	T-cell ID, agammaglobulinemia
DHR assay NBT assay	Reactive oxygen species production by PMN	Chronic granulomatous disease
CH50, AP50	Classic and alternative complement pathways	Complement deficiencies
Ultrasonography of the abdomen	Spleen size	Asplenia

[a]Normal counts vary with age. For example, the lymphocyte count is between 3000 and 9000/μL of blood below the age of 3 months and between 1500 and 2500/μL in adults.
Abbreviations: DHR, dihydrorhodamine fluorescence; ID, immunodeficiency; LAD, leukocyte adhesion deficiency; NBT, nitroblue tetrazolium; PID, primary immune deficiency; PMNs, polymorphonuclear leukocytes; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome.

Other T Cell–Related Primary Immunodeficiencies

- *DiGeorge syndrome:* Maldevelopment of the thymus
- *Hyper-IgE syndrome*
- *CD40 ligand deficiency*
- *Wiskott-Aldrich syndrome*
- *Ataxia-telangiectasia and other DNA repair deficiencies*

TREATMENT OTHER T CELL–RELATED PRIMARY IMMUNODEFICIENCIES

Treatment is complex and largely investigational. HSCT plays a role in some diseases. Live vaccines and blood transfusions containing viable T cells should be strictly avoided. Prophylaxis for *P. jirovecii* pneumonia should be considered in selected pts with severe T-cell deficiency.

B-Lymphocyte Deficiency Syndromes

Deficiencies that affect B cells are the most common primary immunodeficiencies and account for ~60–70% of all cases. Defective antibody production predisposes to invasive pyogenic bacterial infections as well as recurrent sinus and pulmonary infections. Complete lack of antibody production (agammaglobulinemia) predisposes to disseminated enteroviral infections causing meningoencephalitis, hepatitis, and a dermatomyositis-like disease. Diagnosis relies on the determination of serum Ig level.

- *Agammaglobulinemia:* Due to an X-linked mutation in the Bruton's tyrosine kinase (Btk) gene in 85% of cases.
- *Hyper IgM:* In most pts this syndrome results from an X-linked defect in the gene encoding CD40 ligand. Pts exhibit normal or increased serum IgM with low or absent IgG and IgA.
- *Common variable immunodeficiency (CVID):* Heterogeneous group of syndromes characterized by low serum levels of one or more Ig isotypes. Prevalence estimated to be 1 in 20,000. Besides infections, pts may develop lymphoproliferation, granulomatous lesions, colitis, antibody-mediated autoimmune diseases, and lymphomas.
- *Isolated IgA deficiency:* Most common immunodeficiency; affects 1 in 600 people. The majority of affected individuals do not have increased infections; antibodies against IgA may lead to anaphylaxis during transfusion of blood or plasma; may progress to CVID.
- *Selective antibody deficiency to polysaccharide antigens.*

TREATMENT B CELL/IMMUNOGLOBULIN DEFICIENCY SYNDROMES

IV immunoglobulin administration (only for pts who have recurrent bacterial infections and are deficient in IgG):

- Starting dose 400–500 mg/kg given every 3–4 weeks
- Adjust dose to keep trough IgG level 800 mg/dL
- SC administration usually once a week can be considered in selected pts.

REGULATORY DEFECTS

Rare but increasingly described primary immunodeficiencies that cause homeostatic dysregulation of the immune system either alone or in association with increased vulnerability to infection (Table 157-1).

For a more detailed discussion, see Fischer A: Primary Immune Deficiency Diseases, Chap. 374, p. 2103, in HPIM-19.

158 Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Other Connective Tissue Diseases

CONNECTIVE TISSUE DISEASE

DEFINITION

Heterogeneous disorders that share certain common features, including inflammation of skin, joints, and other structures rich in connective tissue; as well as altered patterns of immunoregulation, including production of autoantibodies and abnormalities of cell-mediated immunity. While distinct clinical entities can be defined,

manifestations may vary considerably from one pt to the next, and overlap of clinical features between and among specific diseases can occur.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

DEFINITION AND PATHOGENESIS

Disease of unknown etiology in which tissues and cells undergo damage mediated by tissue-binding autoantibodies and immune complexes. Genetic, environmental, and sex hormonal factors are likely of pathogenic importance. T- and B-cell hyperactivity, production of autoantibodies with specificity for nuclear antigenic determinants, and abnormalities of T-cell function occur.

CLINICAL MANIFESTATIONS

Approximately 90% of pts are women, usually of child-bearing age; more common in blacks than whites. Course of disease is often characterized by periods of exacerbation and relative quiescence. May involve virtually any organ system and have a wide range of disease severity. Common features include:

- *Constitutional:* fatigue, fever, malaise, weight loss
- *Cutaneous:* rashes (especially malar "butterfly" rash), photosensitivity, vasculitis, alopecia, oral ulcers
- *Arthritis:* inflammatory, symmetric, nonerosive
- *Hematologic:* anemia (may be hemolytic), neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, venous or arterial thrombosis
- *Cardiopulmonary:* pleuritis, pericarditis, myocarditis, endocarditis. Pts are also at increased risk of myocardial infarction usually due to accelerated atherosclerosis.
- *Nephritis:* classification is primarily histologic (Table 378-2, p. 2127, in HPIM-19)
- *GI:* peritonitis, vasculitis
- *Neurologic:* organic brain syndromes, seizures, psychosis, cerebritis

Drug-Induced Lupus

A clinical and immunologic picture similar to spontaneous SLE may be induced by drugs; in particular: procainamide, hydralazine, isoniazid, chlorpromazine, methyldopa, minocycline, anti-TNF agents. Features are predominantly constitutional, joint, and pleuropericardial; CNS and renal disease are rare. All pts have ANAs; antihistone antibodies may be present, but antibodies to dsDNA and hypocomplementemia are uncommon. Most pts improve following withdrawal of offending drug.

EVALUATION

- History and physical examination
- Presence of ANA is a cardinal feature, but a (+) ANA is not specific for SLE. Laboratory assessment should include: CBC, ESR, ANA and ANA subtypes (antibodies to dsDNA, ssDNA, Sm, anti-Ro/SS-A, anti-La/SS-B, histone), complement levels (C3, C4, CH50), serum immunoglobulins, VDRL, PT, PTT, anticardiolipin antibody, lupus anticoagulant, urinalysis.
- Appropriate radiographic studies
- ECG
- Consideration of renal biopsy if evidence of glomerulonephritis

DIAGNOSIS

Classification criteria used to confirm SLE in studies can provide a basis in individual patients for estimating the probability that a disease is SLE. Four or more published criteria carry a 93% specificity and 92% sensitivity for SLE (Table 378-3, p. 2127, in HPIM-19).

TREATMENT SYSTEMIC LUPUS ERYTHEMATOSUS

Choice of therapy is based on type and severity of disease manifestations. Goals are to control acute, severe flares and to develop maintenance strategies whereby symptoms are suppressed to an acceptable level. Treatment choices depend on (1) whether disease is life threatening or likely to cause organ damage; (2) whether manifestations are reversible; and (3) the best approach to prevent complications of disease and treatment (Fig. 378-2, p. 2128, and Table 378-5, p. 2130, in HPIM-19).

Conservative Therapies for Non-Life-Threatening Disease

- *NSAIDs* (e.g., ibuprofen 400–800 mg three to four times a day). Must consider renal, GI, and cardiovascular complications.
- *Antimalarials* (hydroxychloroquine 400 mg/d): may improve constitutional, cutaneous, articular manifestations. Ophthalmologic evaluation required before and during treatment to rule out ocular toxicity.
- *Belimumab* (10 mg/kg IV at weeks 0, 2, 4 then monthly). B-lymphocyte stimulator (BLyS)-specific inhibitor. Should not be used in severe SLE such as nephritis or CNS disease and limited to pts with mild to moderate active disease.

Treatments for Life-Threatening SLE

- *Systemic glucocorticoids*.
- *Cytotoxic/immunosuppressive agents:* added to glucocorticoids to treat serious SLE.
  1. Cyclophosphamide: administered as IV pulse 500–1000 mg/M^2 IV × 6 months followed by maintenance with mycophenolate mofetil or azathioprine. European studies have found cyclophosphamide 500 mg every 2 weeks for 6 doses may be effective, but it remains unclear whether these data will apply to U.S. populations.
  2. Mycophenolate mofetil: 2–3 g/d; efficacy data limited to nephritis. A higher proportion of African-American pts appear to respond to mycophenolate mofetil compared with cyclophosphamide.
  3. Azathioprine: may be effective but is slower in inducing therapeutic response.

RHEUMATOID ARTHRITIS (RA)

DEFINITION AND PATHOGENESIS

A chronic multisystem disease of unknown etiology characterized by persistent inflammatory synovitis, usually involving peripheral joints symmetrically. Although cartilaginous destruction, bony erosions, and joint deformity are hallmarks, the course of RA can be quite variable. An association with HLA-DR4 has been noted; both genetic and environmental factors may play a role in initiating disease. The propagation of RA is an immunologically mediated event in which joint injury occurs from synovial hyperplasia; lymphocytic infiltration of synovium; and local production of cytokines and chemokines by activated lymphocytes, macrophages, and fibroblasts.

CLINICAL MANIFESTATIONS

RA occurs in 0.5–1.0% of the population; women affected three times more often than men; prevalence increases with age, onset most frequent in fourth and fifth decades.

Articular Manifestations

Typically a symmetric polyarthritis of peripheral joints with pain, tenderness, and swelling of affected joints; morning stiffness is common; proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints frequently involved; joint deformities may develop after persistent inflammation.

Extraarticular Manifestations

Cutaneous: rheumatoid nodules, vasculitis
Pulmonary: nodules, interstitial disease, bronchiolitis obliterans–organizing pneumonia (BOOP), pleural disease, Caplan's syndrome [sero (+) RA associated with pneumoconiosis]
Ocular: keratoconjunctivitis sicca (KCS), episcleritis, scleritis
Hematologic: anemia, Felty's syndrome (splenomegaly and neutropenia)
Cardiac: pericarditis, myocarditis
Neurologic: myelopathies secondary to cervical spine disease, entrapment, vasculitis

EVALUATION

- History and physical examination with careful examination of all joints.
- Rheumatoid factor (RF) is present in >66% of pts; its presence correlates with severe disease, nodules, extra-articular features.
- Antibodies to cyclic citrullinated protein (anti-CCP) have similar sensitivity but higher specificity than RF; may be most useful in early RA; presence most common in pts with aggressive disease with a tendency for developing bone erosions.
- Other laboratory data: CBC, ESR.
- Synovial fluid analysis: useful to rule out crystalline disease, infection.
- Radiographs: juxta-articular osteopenia, joint space narrowing, marginal erosions. CXR should be obtained.

DIAGNOSIS

Not difficult in pts with typical established disease. May be confusing early. Classification criteria were updated in 2010 (Table 380-1, p. 2143, in HPIM-19).

DIFFERENTIAL DIAGNOSIS

Gout, SLE, psoriatic arthritis, infectious arthritis, osteoarthritis, sarcoid.

TREATMENT RHEUMATOID ARTHRITIS

Goals: lessen pain, reduce inflammation, improve/maintain function, prevent long-term joint damage, control of systemic involvement. Increasing trend to treat RA more aggressively earlier in disease course (Table 380-2, HPIM-19, pp. 2146–2147). All RA therapies have individual toxicities, with many requiring pretreatment screening and monitoring.

- Pt education on disease, joint protection.
- Physical and occupational therapy: strengthen periarticular muscles, consider assistive devices.
- Aspirin or NSAIDs.
- Intra-articular glucocorticoids.
- Systemic glucocorticoids.
- Disease-modifying antirheumatic drugs (DMARDs): e.g., methotrexate, hydroxychloroquine, sulfasalazine, leflunomide.
- Biologic therapies.
- TNF-modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab): effective at controlling RA in many pts and can slow the rate of

progression of radiographic joint damage and decrease disability; carry potential for serious infection and individual toxicities.

- Abatacept (CTLA4-Ig): inhibits T-cell activation, can be given with or without methotrexate.
- Rituximab: a chimeric antibody directed to CD20 that depletes mature B cells and is approved for refractory RA.
- Tocilizumab: humanized monoclonal antibody directed against the IL-6 receptor.
- Tofacitinib: oral small molecule inhibitor that primarily inhibits JAK1 and JAK3.
- Anakinra: an IL-1 receptor antagonist approved for RA but rarely used in RA due to only modest clinical efficacy.
- Surgery: may be considered for severe functional impairment due to deformity.

SYSTEMIC SCLEROSIS (SCLERODERMA, SSC)

DEFINITION AND PATHOGENESIS

Systemic sclerosis (SSc) is a multisystem disorder characterized by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs (chiefly GI tract, lungs, heart, and kidney). Pathogenesis unclear; involves immunologic mechanisms leading to vascular endothelial damage and activation of fibroblasts.

CLINICAL MANIFESTATIONS

- *Cutaneous:* edema followed by fibrosis of the skin (chiefly extremities, face, trunk); telangiectasis; calcinosis; Raynaud's phenomenon
- *Arthralgias and/or arthritis*
- *GI:* esophageal hypomotility; intestinal hypofunction, gastric antral vascular ectasia (GAVE)
- *Pulmonary:* interstitial lung disease, pulmonary arterial hypertension, alveolitis
- *Cardiac:* pericarditis, cardiomyopathy, conduction abnormalities
- *Renal:* hypertension; renal crisis/failure

Two distinct subsets can be identified:

1. *Diffuse cutaneous SSc:* rapid development of symmetric skin thickening of proximal and distal extremity, face, and trunk. At high risk for development of visceral disease early in course.
2. *Limited cutaneous SSc:* often have long-standing Raynaud's phenomenon before other features appear; skin involvement limited to fingers (sclerodactyly), extremity distal to elbows, and face; generally associated with better prognosis but can be associated with pulmonary arterial hypertension; a subset of limited SSc has features of *CREST syndrome* (*c*alcinosis, *R*aynaud's, *e*sophageal dysmotility, *sc*lerodactyly, *t*elangiectasias).

EVALUATION

- History and physical examination with particular attention to blood pressure (heralding feature of renal disease).
- Laboratories: ESR, ANA (anticentromere pattern associated with limited SSc), specific antibodies may include antitopoisomerase I (Scl-70), (UA). An increased range of autoantibodies correlating with specific clinical features have become recognized (Table 382-3, HPIM-19, p. 2157).
- Radiographs: CXR, barium swallow if indicated, hand x-rays may show distal tuft resorption and calcinosis.
- Additional studies: ECG, echo, PFT, consider skin biopsy.

TREATMENT SYSTEMIC SCLEROSIS

- Education regarding warm clothing, smoking cessation, antireflux measures.
- Calcium channel blockers (e.g., nifedipine) useful for Raynaud's phenomenon. Other agents with potential benefit include sildenafil, losartan, nitroglycerin paste, fluoxetine, bosentan, digital sympathectomy.
- ACE inhibitors: particularly important for controlling hypertension and limiting progression of renal disease.
- Antacids, H_2 antagonists, omeprazole, and metoclopramide may be useful for esophageal reflux.
- D-Penicillamine: controversial benefit to reduce skin thickening and prevent organ involvement; no advantages to using doses >125 mg every other day.
- Glucocorticoids: no efficacy in slowing progression of SSc; indicated for inflammatory myositis or pericarditis; high doses may be associated with development of renal crisis.
- Cyclophosphamide: improves lung function and survival in pts with alveolitis.
- Epoprostenol or treprostinil (prostacyclin), bosentan (endothelin-1 receptor antagonist), sildenafil (phosphodiesterase type 5 inhibitor): may improve cardiopulmonary hemodynamics in pts with pulmonary hypertension.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

DEFINITION

Syndrome characterized by a combination of clinical features similar to those of SLE, SSc, polymyositis, and RA; unusually high titers of circulating antibodies to a nuclear ribonucleoprotein (RNP) are found. It is controversial whether MCTD is a truly distinct entity or a subset of SLE or SSc.

CLINICAL MANIFESTATIONS

Raynaud's phenomenon, polyarthritis, swollen hands or sclerodactyly, esophageal dysfunction, pulmonary fibrosis, inflammatory myopathy. Renal involvement occurs in about 25%. Laboratory abnormalities include high-titer ANAs, very high titers of antibody to RNP, positive RF in 50% of pts.

EVALUATION

Similar to that for SLE and SSc.

TREATMENT MIXED CONNECTIVE TISSUE DISEASE

Few published data. Treat based on manifestations with similar approach to that used if feature occurred in SLE/SSc/polymyositis/RA.

SJÖGREN'S SYNDROME

DEFINITION

An immunologic disorder characterized by progressive lymphocytic destruction of exocrine glands most frequently resulting in symptomatic eye and mouth dryness; can be associated with extraglandular manifestations; predominantly affects middle-age females; may be primary or secondary when it occurs in association with other

autoimmune diseases. Lymphoma can occur in 6% with glandular MALT being most common.

CLINICAL MANIFESTATIONS

- *Constitutional:* fatigue
- *Sicca symptoms:* KCS and xerostomia
- *Dryness of other surfaces:* nose, vagina, trachea, skin
- *Extraglandular features:* arthralgia/arthritis, Raynaud's, lymphadenopathy, interstitial pneumonitis, vasculitis (usually cutaneous), nephritis, lymphoma

EVALUATION

- History and physical examination: with special attention to oral, ocular, lymphatic examination and presence of other autoimmune disorders.
- Presence of autoantibodies is a hallmark of disease (ANA, RF, anti-Ro/SS-A, anti-La/SS-B).
- Other laboratory tests: ESR; CBC; renal, liver, and thyroid function tests; serum protein electrophoresis (SPEP) (hypergammaglobulinemia or monoclonal gammopathy common); UA.
- Ocular studies: to diagnose and quantitate KCS; Schirmer's test, Rose bengal staining.
- Oral examination: unstimulated salivary flow, dental examination.
- Labial salivary gland biopsy: demonstrates lymphocytic infiltration and destruction of glandular tissue.

DIAGNOSIS

International classification criteria based on clinical and laboratory features have been established (Table 383-5, HPIM-19, p. 2168).

TREATMENT SJÖGREN'S SYNDROME

- Regular follow-up with dentist and ophthalmologist.
- Dry eyes: artificial tears, ophthalmic lubricating ointments, local stimulation with cyclic adenosine monophosphate or cyclosporine drops.
- Xerostomia: frequent sips of water, sugarless candy.
- Pilocarpine or cevimeline: may help sicca manifestations.
- Hydroxychloroquine: may help arthralgias.
- Glucocorticoids: not effective for sicca symptoms but may have role in treatment of extraglandular manifestations.

ANTIPHOSPHOLIPID SYNDROME (APS)

DEFINITION

Autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thromboses and/or pregnancy morbidity in the presence of autoantibodies against phospholipid (PL)-binding plasma proteins. Can occur alone (primary) or in association with another autoimmune disease (secondary).

CLINICAL MANIFESTATIONS

Consist of vascular thrombotic features and pregnancy morbidity (Table 379-2 in HPIM-19, p. 2135). Catastrophic APS (CAPS) is rapidly progressive thromboembolic disease involving three or more organ systems that can be life threatening.

EVALUATION

Laboratory examination of clotting parameters to include PTT, kaolin clotting time, dilute Russell viper venom test, antibodies directed against cardiolipin, β_2 glycoprotein, prothrombin. Antibodies should be measured on two occasions 12 weeks apart.

DIAGNOSIS

Suggested by the presence of at least one clinical and one laboratory feature.

TREATMENT ANTIPHOSPHOLIPID SYNDROME

- After first thrombotic event, warfarin for life to achieve an international normalized ratio (INR) 2.5–3.5.
- Pregnancy morbidity prevented by heparin with aspirin 80 mg daily. IV immunoglobulins (IVIG) may also prevent pregnancy loss. Glucocorticoids are ineffective.
- For CAPS, consider anticoagulation, glucocorticoids, plasma exchange, and IVIG.

For a more detailed discussion, see Hahn BH: Systemic Lupus Erythematosus, Chap. 378, p. 2124; Shah A, St. Clair EW: Rheumatoid Arthritis, Chap. 380, p. 2136; Varga J: Systemic Sclerosis (Scleroderma) and Related Disorders, Chap. 382, p. 2154; Moutsopoulos HM, Tzioufas AG: Sjögren's Syndrome, Chap. 383, p. 2166; Moutsopoulos HM, Vlachoyiannopoulos PG: Antiphospholipid Syndrome, Chap. 379, p. 2134, in HPIM-19.

159 Vasculitis

DEFINITION AND PATHOGENESIS

A clinicopathologic process characterized by inflammation of and damage to blood vessels, compromise of vessel lumen, and resulting ischemia. Clinical manifestations depend on size and location of affected vessel. Most vasculitic syndromes appear to be mediated by immune mechanisms. May be primary or sole manifestation of a disease or secondary to another disease process. Unique vasculitic syndromes can differ greatly with regards to clinical features, disease severity, histology, and treatment.

PRIMARY VASCULITIS SYNDROMES

Granulomatosis with Polyangiitis (Wegener's)

Granulomatous vasculitis of upper and lower respiratory tracts together with glomerulonephritis; upper airway lesions affecting the nose and sinuses can cause purulent or bloody nasal discharge, mucosal ulceration, septal perforation, and cartilaginous destruction (saddlenose deformity). Lung involvement may be asymptomatic or cause cough, hemoptysis, dyspnea; eye involvement may occur; glomerulonephritis can be rapidly progressive and asymptomatic and can lead to renal failure.

Microscopic Polyangiitis

Small-vessel vasculitis that can affect the glomerulus and lungs; medium-sized vessels also may be affected.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Granulomatous vasculitis of multiple organ systems, particularly the lung; characterized by asthma, peripheral eosinophilia, eosinophilic tissue infiltration; glomerulonephritis can occur.

Polyarteritis Nodosa

Medium-sized muscular arteries involved; frequently associated with arteriographic aneurysms; commonly affects renal arteries, liver, GI tract, peripheral nerves, skin, heart; can be associated with hepatitis B and C.

Giant Cell Arteritis

Inflammation of medium- and large-sized arteries; primarily involves temporal artery but systemic and large vessel involvement may occur; symptoms include headache, jaw/tongue claudication, scalp tenderness, fever, musculoskeletal symptoms (*polymyalgia rheumatica*); sudden blindness from involvement of optic vessels is a dreaded complication.

Takayasu Arteritis

Vasculitis of the large arteries with strong predilection for aortic arch and its branches; most common in young women; presents with inflammatory or ischemic symptoms in arms and neck, systemic inflammatory symptoms, aortic regurgitation.

IgA Vasculitis (Henoch-Schönlein)

Characterized by involvement of skin, GI tract, kidneys; more common in children; may recur after initial remission.

Cryoglobulinemic Vasculitis

Majority of cases are associated with hepatitis C where an aberrant immune response leads to formation of cryoglobulin; characterized by cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis.

Idiopathic Cutaneous Vasculitis

Cutaneous vasculitis is defined broadly as inflammation of the blood vessels of the dermis; due to underlying disease in >70% of cases (see "Secondary Vasculitis Syndromes" below) with 30% occurring idiopathically.

Miscellaneous Vasculitic Syndromes

- Kawasaki disease
- Primary central nervous system vasculitis
- Behçet's disease
- Cogan's syndrome
- Polyangiitis overlap syndrome

SECONDARY VASCULITIS SYNDROMES

- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with infection, malignancy, rheumatic disease

EVALUATION (FIG. 159-1)

- Thorough history and physical examination: special reference to ischemic manifestations and systemic inflammatory signs/symptoms.
- Laboratories: important in assessing organ involvement: CBC with differential, ESR, renal function tests, UA. Should also be obtained to rule out other diseases: ANA, rheumatoid factor, anti-GBM, hepatitis B/C serologies, HIV.
- Antineutrophil cytoplasmic autoantibodies (ANCA): associated with granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and some pts with eosinophilic granulomatosis with polyangiitis (Churg-Strauss); presence of ANCA is adjunctive and should not be used in place of biopsy as a means of diagnosis or to guide treatment decisions.
- Radiographs: CXR should be performed even in the absence of symptoms in small-vessel vasculitides.
- Diagnosis: can usually be made only by arteriogram or biopsy of affected organ(s).

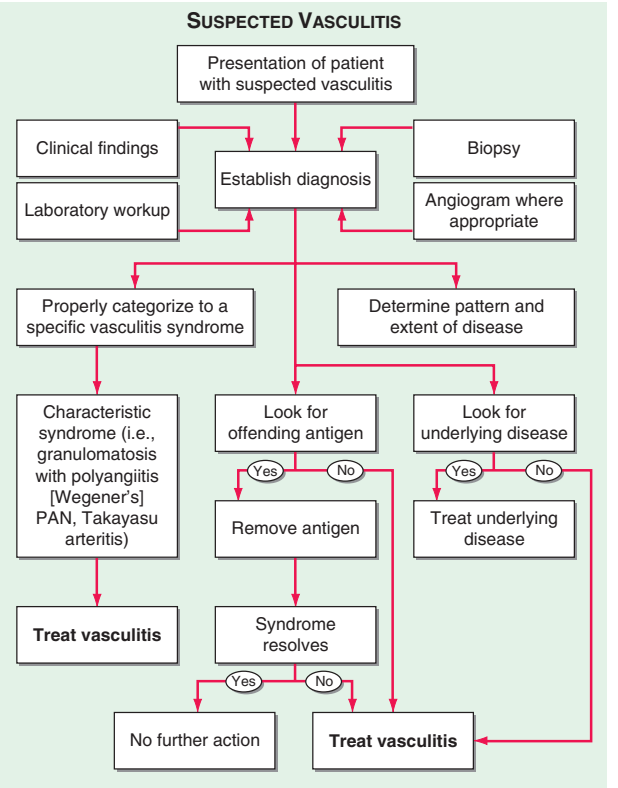


FIGURE 159-1 Algorithm for the approach to a pt with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

TABLE 159-1 CONDITIONS THAT CAN MIMIC VASCULITIS

Infectious diseases
Bacterial endocarditis
Disseminated gonococcal infection
Pulmonary histoplasmosis
Coccidioidomycosis
Syphilis
Lyme disease
Rocky Mountain spotted fever
Whipple's disease
Coagulopathies/thrombotic microangiopathies
Antiphospholipid syndrome
Thrombotic thrombocytopenic purpura
Neoplasms
Atrial myxoma
Lymphoma
Carcinomatosis
Drug toxicity
Cocaine/Levamisole
Amphetamines
Ergot alkaloids
Methysergide
Arsenic
Sarcoidosis
Atheroembolic disease
Anti–glomerular basement membrane antibody disease (Goodpasture's syndrome)
Amyloidosis
Migraine
Collagen vascular disorders
Ehlers-Danlos type IV
Marfan syndrome
Loey-Dietz syndrome
Vasospastic disorders
Reversible cerebral vasoconstrictive syndrome

DIFFERENTIAL DIAGNOSIS

Guided by organ manifestations. In many instances includes infections and neoplasms, which must be ruled out prior to beginning immunosuppressive therapy. Consideration must also be given for diseases that can mimic vasculitis (Table 159-1).

TREATMENT VASCULITIS

Therapy is based on the specific vasculitic syndrome and the severity of its manifestations. Immunosuppressive therapy should be avoided in disease that

rarely results in irreversible organ system dysfunction or that usually does not respond to such agents (e.g., isolated cutaneous vasculitis). Antiviral agents play an important role in treating vasculitis occurring with hepatitis B or C. Glucocorticoids alone may control giant cell arteritis and Takayasu arteritis. Therapy that combines glucocorticoids with another immunosuppressive agent is particularly important in syndromes with life-threatening organ system involvement, especially active glomerulonephritis. Frequently used agents:

- Prednisone 1 (mg/kg)/d initially, then tapered.
- Cyclophosphamide 2 (mg/kg)/d, adjusted to avoid severe leukopenia. Morning administration with a large amount of fluid is important in minimizing bladder toxicity. IV cyclophosphamide (15 mg/kg every 2 weeks for three doses then every 3 weeks thereafter) can also induce remission but may be associated with a higher relapse rate. Treatment should be limited to 3–6 months followed by transition to maintenance therapy with methotrexate or azathioprine.
- Rituximab 375 (mg/m^2)/week for 4 weeks. As effective as cyclophosphamide to induce remission of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis.
- Methotrexate in weekly doses up to 25 mg/week may be used to induce remission in granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis pts who do not have immediately life-threatening disease or cannot tolerate cyclophosphamide. It may also be used for maintaining remission after induction with cyclophosphamide. Cannot be used in renal insufficiency or chronic liver disease.
- Azathioprine 2 (mg/kg)/d. Less effective in treating active disease but useful in maintaining remission after induction with cyclophosphamide.
- Mycophenolate mofetil 1000 mg bid. Less effective than azathioprine to maintain remission but an option in pts who cannot take or who have relapsed with methotrexate and azathioprine.
- Plasmapheresis may have an adjunctive role in rapidly progressive glomerulonephritis.

For a more detailed discussion, see Langford CA, Fauci AS: The Vasculitis Syndromes, Chap. 385, p. 2179; in HPIM-19.

160 Ankylosing Spondylitis

DEFINITION

Ankylosing spondylitis (AS) belongs to the family of *spondyloarthritides* that also includes reactive arthritis (Chap. 162), psoriatic arthritis (Chap. 161), enteropathic arthritis (Chap. 165) juvenile-onset spondyloarthritis, and undifferentiated spondyloarthritis. Classification criteria based on their main clinical features of axial spondyloarthritis (Table 160-1) and peripheral spondyloarthritis (Table 160-2) have been

TABLE 160-1 ASAS CRITERIA FOR CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS (TO BE APPLIED FOR PATIENTS WITH BACK PAIN ≥3 MONTHS AND AGE OF ONSET <45 YEARS)[a]

Sacroiliitis on Imaging Plus ≥1 SpA Feature	or	HLA-B27 Plus ≥ 2 Other SpA Features
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliitis[b] *and/or* • Definite radiographic sacroiliitis according to modified New York criteria[c]		SpA features • Inflammatory back pain[d] • Arthritis[e] • Enthesitis (heel)[f] • Anterior uveitis[g] • Dactylitis[e] • Psoriasis[e] • Crohn's disease or ulcerative colitis[e] • Good response to NSAIDs[h] • Family history of SpA[i] • HLA-B27 • Elevated CRP[j]

[a]Sensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%.
[b]Bone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image.
[c]Bilateral grade ≥2 or unilateral grade 3 or 4.
[d]See text for criteria.
[e]Past or present, diagnosed by a physician.
[f]Past or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia.
[g]Past or present, confirmed by an ophthalmologist.
[h]Substantial relief of back pain at 24–48 h after a full dose of NSAID.
[i]First- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD).
[j]After exclusion of other causes of elevated CRP.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CRP, C-reactive protein; SpA, spondyloarthritis.
Source: From M Rudwaleit et al: *Ann Rheum Dis* 68:777, 2009. Copyright 2009, with permission from BMJ Publishing Group Ltd.

developed that aide in early identification. AS is a chronic and progressive inflammatory disease of the axial skeleton with sacroiliitis (usually bilateral) as its hallmark. Peripheral joints and extra-articular structures may also be affected. Most frequently presents in second or third decade more commonly in men; strong association with histocompatibility antigen HLA-B27.

CLINICAL MANIFESTATIONS

- *Back pain and stiffness:* not relieved by lying down, often present at night forcing pt to leave bed, worse in the morning, improves with activity, insidious onset, duration >3 months (often called symptoms of "inflammatory" back pain).

TABLE 160-2 ASAS CRITERIA FOR PERIPHERAL SPONDYLOARTHRITIS[a]

Arthritis[b]	*or* ***plus***	Enthesitis
One or more of the following: • Uveitis • Psoriasis • Crohn's disease or ulcerative colitis		
OR two or more of the following: • Arthritis • Enthesitis • Dactylitis • Inflammatory back pain ever • Family history for SpA		

[a]Sensitivity 79.5%, specificity 83.3%.
[b]Peripheral arthritis, usually predominantly lower limb and/or asymmetric.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; SpA, spondyloarthritis.
Source: M Rudawaleit et al: *Ann Rheum Dis* 70:25, 2011.

- *Extra-axial arthritis:* hip and shoulders 25–35%, other peripheral joint involvement up to 30%, usually asymmetric.
- *Chest pain:* from involvement of thoracic skeleton and muscular insertions.
- *Extra/juxta-articular pain:* due to "enthesitis": inflammation at insertion of tendons and ligaments into bone; frequently affects greater trochanter, iliac crests, ischial tuberosities, tibial tubercles, heels.
- *Extra-articular findings*—include acute anterior uveitis in up to 40% of pts, aortitis, aortic insufficiency, GI inflammation, cardiac conduction defects, amyloidosis, bilateral upper lobe pulmonary fibrosis.
- *Constitutional symptoms:* fever, fatigue, weight loss may occur.
- *Neurologic complications:* related to spinal fracture/dislocation (can occur with even minor trauma), atlantoaxial subluxation (can lead to spinal cord compression), cauda equina syndrome.

PHYSICAL EXAMINATION

- Tenderness over involved joints
- Diminished chest expansion
- Diminished anterior flexion of lumbar spine (Schober test)

EVALUATION

- ESR and C-reactive protein elevated in majority.
- Mild anemia.
- Rheumatoid factor and ANA negative.
- HLA-B27 may be helpful in pts with inflammatory back symptoms but negative x-rays.
- Radiographs: early may be normal. Sacroiliac joints: usually symmetric; bony erosions with "pseudowidening" followed by fibrosis and ankylosis. Spine: squaring of vertebrae; syndesmophytes; ossification of annulus fibrosis and anterior longitudinal ligament causing "bamboo spine." Sites of enthesitis may ossify and be visible on x-ray. MRI is procedure of choice when plain radiographs do not reveal sacroiliac abnormalities and can show early intra-articular inflammation, cartilage changes, and bone marrow edema.

DIAGNOSIS (TABLE 160-1)

Differential Diagnosis

Osteoarthritis/spondylosis, degenerative disk disease, muscular strain, fibromyalgia; metabolic, infectious, or malignant causes of back pain; diffuse idiopathic skeletal hyperostosis.

TREATMENT ANKYLOSING SPONDYLITIS

- Exercise program to maintain posture and mobility is important.
- NSAIDs first-line treatment, useful in most pts.
- TNF-modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) have been found to improve disease activity and function and reduce bone marrow edema on MRI. Generally used in active disease with failure of at least two NSAIDs.
- Secukinumab, an IL-17A antagonist, has been found to reduce signs and symptoms of active disease.
- Sulfasalazine 2–3 g/d is of modest benefit, primarily for peripheral arthritis.
- Methotrexate, widely used but has not been of proven benefit.
- No documented therapeutic role for systemic glucocorticoids.
- Intra-articular glucocorticoids for persistent enthesitis or peripheral synovitis; ocular glucocorticoids for uveitis with systemic immunosuppression required in some cases; surgery for severely affected or deformed joints.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

161 Psoriatic Arthritis

DEFINITION

Psoriatic arthritis is a chronic inflammatory arthritis that affects 5–42% of persons with psoriasis. Some pts, especially those with spondylitis, will carry the HLA-B27 histocompatibility antigen. Onset of psoriasis usually precedes development of joint disease; approximately 15–20% of pts develop arthritis prior to onset of skin disease. Nail changes are seen in 90% of pts with psoriatic arthritis.

PATTERNS OF JOINT INVOLVEMENT

There are five patterns of joint involvement in psoriatic arthritis.

- Asymmetric oligoarthritis: often involves distal interphalangeal/proximal interphalangeal (DIP/PIP) joints of hands and feet, knees, wrists, ankles; "sausage digits" may be present, reflecting tendon sheath inflammation.
- Symmetric polyarthritis (40%): resembles rheumatoid arthritis except rheumatoid factor is negative, absence of rheumatoid nodules.

- Predominantly DIP joint involvement (15%): high frequency of association with psoriatic nail changes.
- "Arthritis mutilans" (3–5%): aggressive, destructive form of arthritis with severe joint deformities and bony dissolution.
- Spondylitis and/or sacroiliitis: axial involvement is present in 20–40% of pts with psoriatic arthritis; may occur in absence of peripheral arthritis.

EVALUATION

- Negative tests for rheumatoid factor.
- Hypoproliferative anemia, elevated ESR.
- Hyperuricemia may be present.
- HIV infection should be suspected in fulminant disease.
- Inflammatory synovial fluid and biopsy without specific findings.
- Radiographic features include erosion at joint margin, bony ankylosis, tuft resorption of terminal phalanges, "pencil-in-cup" deformity (bone proliferation at base of distal phalanx with tapering of proximal phalanx), axial skeleton with asymmetric sacroiliitis, asymmetric nonmarginal syndesmophytes.

DIAGNOSIS (TABLE 161-1)

TREATMENT PSORIATIC ARTHRITIS

- Coordinated therapy is directed at the skin and joints.
- Pt education, physical and occupational therapy.
- TNF modulatory agents (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) can improve joint disease and delay radiographic progression.

TABLE 161-1 THE CASPAR (CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS) CRITERIA[a]

To meet the CASPAR criteria, a pt must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from any of the following five categories:

1. Evidence of current psoriasis,[b,c] a personal history of psoriasis, or a family history of psoriasis[d]
2. Typical psoriatic nail dystrophy[e] observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis[f] or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation[g] in the hand or foot

[a]Specificity of 99% and sensitivity of 91%.
[b]Current psoriasis is assigned 2 points; all other features are assigned 1 point.
[c]Psoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.
[d]History of psoriasis in a first- or second-degree relative.
[e]Onycholysis, pitting, or hyperkeratosis.
[f]Swelling of an entire digit.
[g]III-defined ossification near joint margins, excluding osteophyte formation.
Source: From Taylor W et al: Classification criteria for psoriatic arthritis. Development of new criteria from a large international study. *Arthritis Rheum*, 54:2665, 2006.

- Ustekinumab (anti-IL-12/23 p40 monoclonal antibody) has efficacy for both skin and joint disease.
- Apremilast (phosphodiesterase 4 inhibitor) benefit skin and joint involvement.
- Secukinumab, an IL-17A antagonist, has been found to improve disease activity and can also be used for moderate to severe plaque psoriasis.
- NSAIDs.
- Intraarticular steroid injections—useful in some settings. Systemic glucocorticoids should rarely be used as may induce rebound flare of skin disease upon tapering.
- Efficacy of gold salts and antimalarials controversial.
- Sulfasalazine 2–3 g/d has clinical efficacy but do not halt joint erosion.
- Methotrexate 15 mg/week had no improvement in synovitis but it improved skin scores and may have symptom-modifying effects.
- Leflunomide may be of benefit for skin and joint disease.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

162 Reactive Arthritis

DEFINITION

Reactive arthritis (ReA) refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. The term has been used primarily to refer to spondyloarthritides following enteric or urogenital infections

PATHOGENESIS

The bacteria identified as being definitive triggers of ReA include enteric organisms *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* species; and genitourinary infection with *Chlamydia trachomatis*; there is also evidence implicating *Clostridium difficile*, certain toxigenic *Escherichia coli*, and possibly other agents.

CLINICAL MANIFESTATIONS

Average age 18–40 years. The male:female ratio following enteric infection is 1:1; however, genitourinary-acquired reactive arthritis is predominantly seen in young males. In a majority of cases, history will elicit symptoms of genitourinary or enteric infection 1–4 weeks prior to onset of other features.

Constitutional: fatigue, malaise, fever, weight loss.

Arthritis: usually acute, asymmetric, oligoarticular, involving predominantly lower extremities; sacroiliitis may occur.

Enthesitis: inflammation at insertion of tendons and ligaments into bone; dactylitis or "sausage digit," plantar fasciitis, and Achilles tendinitis are common.

Ocular features: conjunctivitis, usually minimal; uveitis, keratitis, and optic neuritis rarely present.

Urethritis: discharge intermittent and may be asymptomatic.

Other urogenital manifestations: prostatitis, cervicitis, salpingitis.

Mucocutaneous lesions: painless lesions on glans penis (circinate balanitis) and oral mucosa in approximately a third of pts; *keratoderma blennorrhagica*: cutaneous vesicles that become hyperkeratotic, most common on soles and palms.

Uncommon manifestations: pleuropericarditis, aortic regurgitation, neurologic manifestations, secondary amyloidosis.

Reactive arthritis is associated with and may be the presenting sign and symptom of HIV.

EVALUATION

- Pursuit of triggering infection by culture, serology, or molecular methods as clinically suggested.
- Rheumatoid factor and ANA negative.
- Mild anemia, leukocytosis, elevated ESR may be seen.
- HLA-B27 association was initially overestimated with recent studies showing a prevalence <50%. May be helpful in atypical cases and may have prognostic significance.
- HIV screening should be performed in all pts.
- Synovial fluid analysis—often very inflammatory; negative for crystals or infection.
- Radiographs—erosions may be seen with new periosteal bone formation, ossification of entheses, sacroiliitis (often unilateral).

DIFFERENTIAL DIAGNOSIS

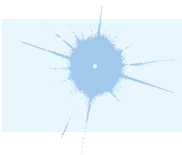
Includes septic arthritis (gram +/–), gonococcal arthritis, crystalline arthritis, psoriatic arthritis.

TREATMENT REACTIVE ARTHRITIS

- Controlled trials have failed to demonstrate any benefit of antibiotics in reactive arthritis. Prompt antibiotic treatment of acute chlamydial urethritis may prevent subsequent reactive arthritis.
- NSAIDs (e.g., indomethacin 25–50 mg PO tid) benefit most pts.
- Intra-articular glucocorticoids.
- Sulfasalazine up to 3 g/d in divided doses may help some pts with persistent arthritis.
- Immunosuppressive agents, such as azathioprine (1–2 [mg/kg]/d) or methotrexate (7.5–15 mg/week) may be considered for debilitating disease refractory to other modalities; contraindicated in HIV disease.
- Anti-TNF agents can be considered in severe chronic cases.
- Uveitis may require therapy with ocular or systemic glucocorticoids.

OUTCOME

Arthritis typically persists for 3–5 months; recurrence of the acute syndrome is common. Chronic joint symptoms persist in 15% with associated disability.



For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169, in HPIM-19.

163 Osteoarthritis

DEFINITION

Osteoarthritis (OA) is a disorder characterized by progressive joint failure in which all structures of the joint have undergone pathologic change. The pathologic sine qua non of OA is hyaline articular cartilage loss accompanied by increasing thickness and sclerosis of the subchondral bone plate, outgrowth of osteophytes at the joint margin, stretching of the articular capsule, and weakness of the muscles bridging the joint. There are numerous pathways that lead to OA, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

EPIDEMIOLOGY

OA is the most common type of arthritis. The prevalence of OA correlates strikingly with age, and it is much more common in women than in men. Joint vulnerability and joint loading are the two major risk factors contributing to OA. These are influenced by factors that include age, female sex, race, genetic factors, nutritional factors, joint trauma, previous damage, malalignment, proprioceptive deficiencies, and obesity.

PATHOGENESIS

The earliest changes of OA may begin in cartilage. The two major components of cartilage are type 2 collagen, which provides tensile strength, and aggrecan, a proteoglycan. OA cartilage is characterized by gradual depletion of aggrecan, unfurling of the collagen matrix, and loss of type 2 collagen, which leads to increased vulnerability.

CLINICAL MANIFESTATIONS

OA can affect almost any joint but usually occurs in weight-bearing and frequently used joints such as the knee, hip, spine, and hands. The hand joints that are typically affected are the distal interphalangeal (DIP), proximal interphalangeal (PIP), or first carpometacarpal (thumb base); metacarpophalangeal joint involvement is rare.

Symptoms

- Use-related pain affecting one or a few joints (rest and nocturnal pain less common)
- Stiffness after rest or in morning may occur but is usually brief (<30 min)
- Loss of joint movement or functional limitation
- Joint instability
- Joint deformity
- Joint crepitation ("crackling")

Physical Examination

- Chronic monarthritis or asymmetric oligo/polyarthritis
- Firm or "bony" swellings of the joint margins, e.g., Heberden's nodes (hand DIP) or Bouchard's nodes (hand PIP)
- Mild synovitis with a cool effusion can occur but is uncommon
- Crepitance—audible creaking or crackling of joint on passive or active movement
- Deformity, e.g., OA of knee may involve medial, lateral, or patellofemoral compartments resulting in varus or valgus deformities
- Restriction of movement, e.g., limitation of internal rotation of hip
- Objective neurologic abnormalities may be seen with spine involvement (may affect intervertebral disks, apophyseal joints, and paraspinal ligaments)

EVALUATION

- Routine lab work usually normal.
- ESR usually normal but may be elevated in pts who have synovitis.
- Rheumatoid factor, ANA studies negative.
- Joint fluid is straw-colored with good viscosity; fluid WBCs <1000/μL; of value in ruling out crystal-induced arthritis, inflammatory arthritis, or infection.
- Radiographs may be normal at first but as disease progresses may show joint space narrowing, subchondral bone sclerosis, subchondral cysts, and osteophytes. Erosions are distinct from those of rheumatoid and psoriatic arthritis as they occur subchondrally along the central portion of the joint surface.

DIAGNOSIS

Usually established on basis of pattern of joint involvement. Radiographic features, normal laboratory tests, and synovial fluid findings can be helpful if signs suggest an inflammatory arthritis.

Differential Diagnosis

Osteonecrosis, Charcot joint, rheumatoid arthritis, psoriatic arthritis, crystal-induced arthritides.

TREATMENT OSTEOARTHRITIS

- Treatment goal—alleviate pain and minimize loss of physical function.
- Nonpharmacotherapy strategies aimed at altering loading across the painful joint—include pt education, weight reduction, appropriate use of cane and other supports, isometric exercises to strengthen muscles around affected joints, bracing/orthotics to correct malalignment.
- Topical capsaicin cream may help relieve hand or knee pain.
- Acetaminophen—commonly used analgesic, caution regarding hepatic toxicity.
- NSAIDs, COX-2 inhibitors—GI, renal, cardiovascular toxicity, must weigh individual risks and benefits.
- Topical NSAIDs—fewer GI and systemic side effects; can cause skin irritation
- Opioid analgesics—may be considered in selected pts whose symptoms are inadequately controlled with other measures and who cannot undergo surgery; habituation is a potential concern.
- Intraarticular glucocorticoids—may provide symptomatic relief but typically short-lived.
- Intraarticular hyaluronan—can be given for symptomatic knee and hip OA, but it is controversial whether it has efficacy beyond placebo.
- Glucosamine and chondroitin—large scale trials have failed to show efficacy for pain relief; recent guidelines recommend against use.
- Systemic glucocorticoids have no place in the treatment of OA.
- Arthroscopic debridement and lavage—randomized trials have shown no greater effect on pain relief or disability compared to sham procedure or no treatment.
- Joint replacement surgery may be considered in pts with advanced OA who have intractable pain and loss of function in whom aggressive medical management has failed.

For a more detailed discussion, see Felson DT: Osteoarthritis, Chap. 394, p. 2226, in HPIM-19.

164 Gout, Pseudogout, and Related Diseases

GOUT

DEFINITION

Gout is a metabolic disease most often affecting middle-aged to elderly men and postmenopausal women. Hyperuricemia is the biologic hallmark of gout. When present, plasma and extracellular fluids become supersaturated with uric acid, which, under the right conditions, may crystallize and result in a spectrum of clinical manifestations that may occur singly or in combination.

PATHOGENESIS

Uric acid is the end product of purine nucleotide degradation; its production is closely linked to pathways of purine metabolism, with the intracellular concentration of 5-phosphoribosyl-1-pyrophosphate (PRPP) being the major determinant of the rate of uric acid biosynthesis. Uric acid is excreted primarily by the kidney through mechanisms of glomerular filtration, tubular secretion, and reabsorption. Hyperuricemia may thus arise in a wide range of settings that cause overproduction or reduced excretion of uric acid or a combination of the two.

ACUTE GOUTY ARTHRITIS

Monosodium urate (MSU) crystals present in the joint are phagocytosed by leukocytes; release of inflammatory mediators and lysosomal enzymes leads to recruitment of additional phagocytes into the joint and to synovial inflammation.

CLINICAL MANIFESTATIONS

Acute arthritis: most frequent early clinical manifestation of gout. Usually initially affects one joint, but may be polyarticular in later episodes. The first metatarsophalangeal joint (*podagra)* is often involved. Acute gout frequently begins at night with dramatic pain, swelling, warmth, and tenderness. Attack will generally subside spontaneously after 3–10 days. Although some pts may have a single attack, most pts have recurrent episodes with intervals of varying length with no symptoms between attacks. Acute gout may be precipitated by dietary excess, trauma, surgery, excessive ethanol ingestion, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

Chronic arthritis: a proportion of gout pts may have a chronic nonsymmetric synovitis; may rarely be the only manifestation. Can also present with periarticular *tophi* (aggregates of MSU crystals surrounded by a giant cell inflammatory reaction). Occurs in the setting of long-standing gout.

Extraarticular tophi: often occur in olecranon bursa, helix and anthelix of ears, ulnar surface of forearm, Achilles tendon.

Tenosynovitis

Urate nephropathy: deposition of MSU crystals in renal interstitium and pyramids. Can cause chronic renal insufficiency.

Acute uric acid nephropathy: reversible cause of acute renal failure due to precipitation of urate in the tubules; pts receiving cytotoxic treatment for neoplastic disease are at risk.

Uric acid nephrolithiasis: responsible for 10% of renal stones in the United States.

DIAGNOSIS

- Synovial fluid analysis: should be performed to confirm gout even when clinical appearance is strongly suggestive; joint aspiration and demonstration of both intracellular and extracellular needle-shaped negatively birefringent MSU crystals by polarizing microscopy. Gram stain and culture should be performed on all fluid to rule out infection. MSU crystals can also be demonstrated in chronically involved joints or tophaceous deposits.
- Serum uric acid: normal levels do not rule out gout.
- Urine uric acid: excretion of >800 mg/d on regular diet in the absence of drugs suggests overproduction.
- Screening for risk factors or sequelae: urinalysis; serum creatinine, liver function tests, glucose and lipids; complete blood counts.
- If overproduction is suspected, measurement of erythrocyte hypoxanthine guanine phosphoribosyl transferase (HGPRT) and PRPP levels may be indicated.
- Joint x-rays: may demonstrate cystic changes, erosions with sclerotic margins in advanced chronic arthritis.
- If renal stones suspected, abdominal flat plate (stones often radiolucent), possibly IVP.
- Chemical analysis of renal stones.

Differential Diagnosis

Septic arthritis, reactive arthritis, calcium pyrophosphate dihydrate (CPPD) deposition disease, rheumatoid arthritis.

TREATMENT GOUT

ASYMPTOMATIC HYPERURICEMIA

As only ~5% of hyperuricemic pts develop gout, treatment of asymptomatic hyperuricemia is not indicated. Exceptions are pts about to receive cytotoxic therapy for neoplasms.

ACUTE GOUTY ARTHRITIS

Treatment is given for symptomatic relief only since attacks are self-limited and will resolve spontaneously. Toxicity of therapy must be considered in each pt.

- Analgesia
- NSAIDs: Treatment of choice when not contraindicated.
- Colchicine: generally only effective within first 24 h of attack; overdose has potentially life-threatening side effects; use is contraindicated in pts with renal insufficiency, cytopenias, LFTs >2 × normal, sepsis. PO—0.6 mg every 8 h with tapering or 1.2 mg followed by 0.6 mg in 1 h with subsequent day dosing depending on response.
- Intraarticular glucocorticoids: septic arthritis must be ruled out prior to injection.
- Systemic glucocorticoids: brief taper may be considered in pts with a polyarticular gouty attack for whom other modalities are contraindicated and where articular or systemic infection has been ruled out.
- Anakinra and other inhibitors of interleukin-1β have been studied, but are not widely used in clinical practice.

URIC ACID–LOWERING AGENTS

Indications for initiating uric acid–lowering therapy include recurrent frequent acute gouty arthritis, polyarticular gouty arthritis, tophaceous gout, renal stones, prophylaxis during cytotoxic therapy. Should not start during an acute attack. Initiation of such therapy can precipitate an acute flare; in pts without contraindications consider concomitant PO colchicine 0.6 mg qd until uric acid <5.0 mg/dL, then discontinue.

1. *Xanthine oxidase inhibitors* (allopurinol, febuxostat): Decrease uric acid synthesis. Allopurinol must be dose-reduced in renal insufficiency. Both have side effects and drug interactions.
2. *Uricosuric drugs* (probenecid, sulfinpyrazone): Increases uric acid excretion by inhibiting its tubular reabsorption; ineffective in renal insufficiency; should not be used in these settings: age >60, renal stones, tophi, increased urinary uric acid excretion, prophylaxis during cytotoxic therapy.
3. *Pegloticase*: Recombinant uricase that lowers uric acid by oxidizing urate to allantoin. Risk of severe infusion reactions. Should be used only in selected pts with chronic tophaceous gout refractory to conventional therapy.

CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE (PSEUDOGOUT)

DEFINITION AND PATHOGENESIS

CPPD disease is characterized by acute and chronic inflammatory joint disease, usually affecting older individuals. The knee and other large joints are most commonly affected. Calcium deposits in articular cartilage (*chondrocalcinosis*) may be seen radiographically; these are not always associated with symptoms.

CPPD is most often idiopathic but can be associated with other conditions (Table 164-1).

Crystals are thought not to form in synovial fluid but are probably shed from articular cartilage into joint space, where they are phagocytosed by neutrophils and incite an inflammatory response.

CLINICAL MANIFESTATIONS

- *Acute CPPD arthritis ("pseudogout"):* knee is most frequently involved, but polyarticular in two-thirds of cases; involved joint is erythematous, swollen, warm, and painful. Most pts have evidence of chondrocalcinosis.
- *Chronic arthropathy:* progressive degenerative changes in multiple joints; can resemble osteoarthritis (OA). Joint distribution may suggest CPPD with common sites including knee, wrist, metacarpophalangeal (MCP), hips, and shoulders.
- *Symmetric proliferative synovitis:* seen in familial forms with early onset; clinically similar to RA.

TABLE 164-1 CONDITIONS ASSOCIATED WITH CPPD DEPOSITION DISEASE

Aging
Disease-associated
Primary hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Chronic gout
Postmeniscectomy
Gitelman's syndrome
Epiphyseal dysplasias

- *Intervertebral disk and ligament calcification*
- *Spinal stenosis*

DIAGNOSIS

- Synovial fluid analysis—demonstration of CPPD crystals that appear as short blunt rods, rhomboids, and cuboids with weak positive birefringence by polarizing microscopy.
- Radiographs may demonstrate chondrocalcinosis and degenerative changes (joint space narrowing, subchondral sclerosis/cysts).
- Secondary causes of CPPD deposition disease should be considered in pts <50 years old.

Differential Diagnosis

OA, RA, gout, septic arthritis.

TREATMENT PSEUDOGOUT

- NSAIDs—when not contraindicated.
- Intraarticular injection of glucocorticoids.
- Colchicine (variably effective).

CALCIUM APATITE DEPOSITION DISEASE

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation can occur in a wide range of clinical settings (Table 164-2). Apatite is an important factor in *Milwaukee shoulder*, a destructive arthropathy of the elderly that occurs in the shoulders and knees. Apatite crystals are small; clumps may stain purplish on Wright's stain and bright red with alizarin red S. Definitive identification requires electron microscopy or x-ray diffraction studies. Radiographic appearance resembles CPPD disease. *Treatment*: NSAIDs, repeated aspiration, and rest of affected joint.

TABLE 164-2 CONDITIONS ASSOCIATED WITH APATITE DEPOSITION DISEASE

Aging
Osteoarthritis
Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder)
Destructive arthropathy
Tendinitis, bursitis
Tumoral calcinosis (sporadic cases)
Disease-associated
Hyperparathyroidism
Milk-alkali syndrome
Renal failure/long-term dialysis
Connective tissue diseases (e.g., systemic sclerosis, idiopathic myositis, SLE)
Heterotopic calcification following neurologic catastrophes (e.g., stroke, spinal cord injury)
Heredity
Bursitis, arthritis
Tumoral calcinosis
Fibrodysplasia ossificans progressiva

CALCIUM OXALATE DEPOSITION DISEASE

CaOx crystals may be deposited in joints in primary oxalosis (rare) or secondary oxalosis (a complication of end-stage renal disease). Clinical syndrome similar to gout and CPPD disease. *Treatment*: marginally effective.



For a more detailed discussion, see Schumacher HR, Chen LX: Gout and Other Crystal-Associated Arthropathies, Chap. 395, p. 2233 and Burns CM, Wortmann RL: Disorders of Purine and Pyrimidine Metabolism, Chap. 431e, in HPIM-19.

165 Other Musculoskeletal Disorders

ENTEROPATHIC ARTHRITIS

Both peripheral and axial arthritis may be associated with the inflammatory bowel diseases (IBD) of ulcerative colitis or Crohn's disease. The arthritis can occur after or before the onset of intestinal symptoms. Peripheral arthritis is episodic and asymmetric; it most frequently affects knee and ankle. Attacks usually subside within several weeks and characteristically resolve completely without residual joint damage. Enthesitis (inflammation at insertion of tendons and ligaments into bone) can occur with manifestations of "sausage digit," Achilles tendinitis, and plantar fasciitis. Axial involvement can manifest as spondylitis and/or sacroiliitis (often symmetric). Laboratory findings are nonspecific; rheumatoid factor (RF) absent; HLA-B27 is positive in 70% with IBD and axial disease but <15% with IBD and peripheral arthritis; radiographs of peripheral joints usually normal; axial involvement is often indistinguishable from ankylosing spondylitis.

TREATMENT ENTEROPATHIC ARTHRITIS

Directed at underlying IBD; treatment of Crohn's disease with anti-TNF agents has improved arthritis; NSAIDs may alleviate joint symptoms but can precipitate flares of IBD; sulfasalazine may benefit peripheral arthritis.

WHIPPLE'S DISEASE

Characterized by arthritis in up to 75% of pts that usually precedes appearance of other symptoms. Usually oligo- or polyarticular, symmetric, transient but may become chronic. Joint manifestations respond to antibiotic therapy.

NEUROPATHIC JOINT DISEASE

Also known as *Charcot's joint*, this is a severe destructive arthropathy that occurs in joints deprived of pain and position sense; may occur in diabetes mellitus, tabes dorsalis, syringomyelia, amyloidosis, spinal cord or peripheral nerve injury. Distribution depends on the underlying joint disease. Joint effusions are usually noninflammatory

but can be hemorrhagic. Radiographs can reveal either bone resorption or new bone formation with bone dislocation and fragmentation.

TREATMENT NEUROPATHIC JOINT DISEASE

Stabilization of joint; surgical fusion may improve function.

RELAPSING POLYCHONDRITIS

An idiopathic disorder characterized by recurrent inflammation of cartilaginous structures. Cardinal manifestations include ear and nose involvement with floppy ear and saddlenose deformities, inflammation and collapse of tracheal and bronchial cartilaginous rings, and asymmetric episodic nondeforming polyarthritis. Other features can include scleritis, conjunctivitis, iritis, keratitis, aortic regurgitation, glomerulonephritis, and other features of systemic vasculitis. Onset is frequently abrupt, with the appearance of 1–2 sites of cartilaginous inflammation. Diagnosis is made clinically and may be confirmed by biopsy of affected cartilage.

TREATMENT RELAPSING POLYCHONDRITIS

Glucocorticoids (prednisone 40–60 mg/d with subsequent taper) may suppress acute features and reduce the severity/frequency of recurrences. Cytotoxic agents should be reserved for unresponsive disease or for pts who require high glucocorticoid doses. When airway obstruction is severe, tracheostomy is required.

HYPERTROPHIC OSTEOARTHROPATHY

Syndrome consisting of periosteal new bone formation, digital clubbing, and arthritis. Most commonly seen in association with lung carcinoma but, also occurs with selected chronic lung or liver disease; congenital heart, lung, or liver disease in children; and idiopathic and familial forms. Symptoms include burning and aching pain most pronounced in distal extremities. Radiographs show periosteal thickening with new bone formation of distal ends of long bones.

TREATMENT HYPERTROPHIC OSTEOARTHROPATHY

Identify and treat associated disorder; aspirin, NSAIDs, other analgesics, vagotomy, or percutaneous nerve block may help to relieve symptoms.

FIBROMYALGIA

A common disorder characterized by chronic widespread musculoskeletal pain, aching, stiffness, paresthesia, disturbed sleep, and easy fatigability along with multiple tender points. More common in women than in men. Diagnosis is made clinically; evaluation reveals soft tissue tender points but no objective joint abnormalities by examination, laboratory, or radiograph.

TREATMENT FIBROMYALGIA

Pregabalin, duloxetine, and milnacipran have shown benefit for fibromyalgia. Tricyclics for sleep disorder, local measures (heat, massage), physical conditioning, and cognitive-behavioral strategies to improve sleep hygiene.

POLYMYALGIA RHEUMATICA (PMR)

Clinical syndrome characterized by aching and morning stiffness in the shoulder girdle, hip girdle, or neck for >1 month, elevated ESR, and rapid response to low-dose prednisone (10–20 mg qd). Rarely occurs before age 50; more common in women. PMR can occur in association with giant cell arteritis, which requires treatment with higher doses of prednisone. Evaluation should include a careful history to elicit symptoms suggestive of giant cell arteritis (Chap. 159); ESR; laboratory test results to rule out other processes usually include RF, ANA, CBC, CPK, serum protein electrophoresis; and renal, hepatic, and thyroid function tests.

TREATMENT PMR

Pts rapidly improve on prednisone, 10–20 mg qd, but may require treatment over months to years.

OSTEONECROSIS (AVASCULAR NECROSIS)

Caused by death of cellular elements of bone, believed to be due to impairment in blood supply. Frequent associations include glucocorticoid treatment, connective tissue disease, trauma, sickle cell disease, embolization, alcohol use, and HIV disease. Commonly involved sites include femoral and humeral heads, femoral condyles, and proximal tibia. Hip disease is bilateral in >50% of cases. Clinical presentation is usually the abrupt onset of articular pain. Early changes are not visible on plain radiograph and are best seen by MRI; later stages demonstrate bone collapse ("crescent sign"), flattening of articular surface with joint space loss. Osteonecrosis of the jaw is a rare occurrence associated with cancer treatments (including radiation), infection, glucocorticoids, or bone antiresorptive therapies.

TREATMENT OSTEONECROSIS

Limited weight-bearing of unclear benefit; NSAIDs for symptoms. Surgical procedures to enhance blood flow may be considered in early-stage disease but are of controversial efficacy; joint replacement may be necessary in late-stage disease for pain unresponsive to other measures.

PERIARTICULAR DISORDERS

BURSITIS

Inflammation of the thin-walled bursal sac surrounding tendons and muscles over bony prominences. The subacromial and greater trochanteric bursae are most commonly involved.

TREATMENT BURSITIS

Prevention of aggravating conditions, rest, NSAIDs, and local glucocorticoid injections.

TENDINITIS

May involve virtually any tendon but frequently affects tendons of the rotator cuff around shoulder, especially the supraspinatus. Pain is dull and aching but becomes acute and sharp when tendon is squeezed below acromion.

TREATMENT **TENDINITIS**

NSAIDs, glucocorticoid injection, and physical therapy may be beneficial. The rotator cuff tendons or biceps tendon may rupture acutely, frequently requiring surgical repair.

CALCIFIC TENDINITIS

Results from deposition of calcium salts (primarily hydroxyapatite) in tendon, usually supraspinatus. The resulting pain may be sudden and severe.

TREATMENT **CALCIFIC TENDINITIS**

Most are self-limited and respond to physical therapy, NSAIDs. Refractory disease treated with ultrasound-guided needle aspiration and lavage or surgery.

ADHESIVE CAPSULITIS ("FROZEN SHOULDER")

Results from conditions that enforce prolonged immobility of shoulder joint. Shoulder is painful and tender to palpation, and both active and passive range of motion is restricted.

TREATMENT **ADHESIVE CAPSULITIS**

Spontaneous improvement may occur; physical therapy is the foundation; NSAIDs, local injections of glucocorticoids may be helpful.

For a more detailed discussion, see Taurog JD, Carter JD: The Spondyloarthritides, Chap. 384, p. 2169; Crofford LJ: Fibromyalgia, Chap. 396, p. 2238; Langford CA, Mandell BF: Arthritis Associated with Systemic Disease, and Other Arthritides, Chap. 397, p. 2240; Langford CA: Periarticular Disorders of the Extremities, Chap. 398, p. 2247; Langford CA: Relapsing Polychondritis, Chap. 389, p. 2202, in HPIM-19.

166 Sarcoidosis

DEFINITION

An inflammatory multisystem disease characterized by the presence of noncaseating granulomas of unknown etiology.

PATHOPHYSIOLOGY

The cause of sarcoid is unknown, and current evidence suggests that the triggering of an inflammatory response by an unidentified antigen in a genetically susceptible host is

involved. The granuloma is the pathologic hallmark of sarcoidosis. The initial inflammatory response is an influx of CD4+ (helper) T cells and an accumulation of activated monocytes. This leads to an increased release of cytokines and the formation of a granuloma. The granuloma may resolve or lead to chronic disease, including fibrosis.

CLINICAL MANIFESTATIONS

Up to one-third of sarcoidosis patients are asymptomatic with 20–30% of pulmonary sarcoidosis being detected by CXR in asymptomatic individuals. Sarcoid manifests symptomatically in organs where it affects function or where it is readily observed. *Löfgren's syndrome* consists of hilar adenopathy, erythema nodosum, often with uveitis and acute arthritis presenting in one or both ankles spreading to involve other joints.

Disease manifestations of sarcoid include:

- *Lung:* >90% of pts with sarcoidosis will have lung involvement. Features include hilar adenopathy, infiltrates, interstitial pneumonitis, and fibrosis; airways may be involved and cause obstruction to airflow; pulmonary hypertension from direct vascular involvement or lung fibrosis.
- *Lymph nodes:* intrathoracic nodes enlarged in 75–90% of pts. Extrathoracic lymph nodes affected in up to 20%.
- *Skin:* >33% will have skin involvement; lesions include erythema nodosum, maculopapular lesions, subcutaneous nodules, and *lupus pernio* (indurated blue-purple shiny lesions around nasal bridge, eyes, cheeks).
- *Eye:* uveitis 30% in the United States (higher in other countries); may progress to blindness.
- *Bone marrow and spleen*—lymphopenia, anemia 20%, splenomegaly 5–10%.
- *Liver:* involved on biopsy in >50%; 20–30% abnormal liver function studies.
- *Kidney*—parenchymal disease <5%, nephrolithiasis, acute renal failure due to hypercalcemia 1–2%.
- *Nervous system:* occurs in 5–10%; cranial/peripheral neuropathy, chronic meningitis, pituitary involvement, space-occupying lesions, seizures.
- *Heart:* disturbances of rhythm and/or contractility, pericarditis.
- *Musculoskeletal:* involvement of bone or muscle occurs in 10%, bone lesions consist of cysts in areas of expanded bone or lattice-like changes; joint involvement includes acute arthropathy often of the ankles and chronic mono- or oligoarthritis of knee, ankle, proximal interphalangeal (PIP) joints.
- *Constitutional symptoms*—fever, weight loss, anorexia, fatigue.
- *Other organ systems*—hypercalcemia 10%, endocrine/reproductive, exocrine glands, GI, upper respiratory tract.

EVALUATION

- History and physical examination.
- CBC, Ca^{2+}, LFTs, ACE, tuberculosis screening.
- CXR and/or chest CT, ECG, PFTs.
- Biopsy of lung or other affected organ.
- Positron emission tomography (PET) has increasingly replaced gallium-67 scanning to identify areas of granulomatous disease. Both can be used to identify potential areas for biopsy.
- MRI can assess extrapulmonary sarcoidosis.

DIAGNOSIS

Made on basis of clinical, radiographic, and histologic findings. Biopsy of lung or other affected organs is helpful in supporting the diagnosis and ruling out other diseases. Pulmonary involvement can be approached by bronchoscopy with transbronchial lung biopsy. Differential diagnosis includes neoplasms, infections including HIV, and other granulomatous processes.

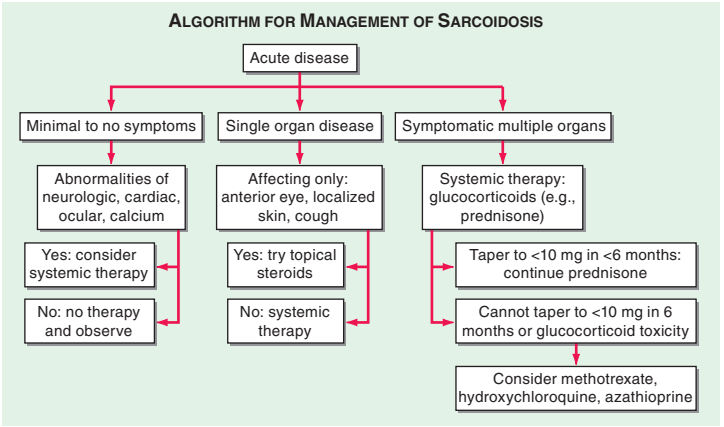


FIGURE 166-1 The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In pts with mild symptoms, no therapy may be needed unless specified manifestations are noted.

TREATMENT SARCOIDOSIS

As sarcoidosis may remit spontaneously, treatment is based largely on the level of symptoms and extent of organ involvement (Figs. 166-1 and 166-2). When systemic therapy is indicated, glucocorticoids are the mainstay of therapy. Other immunomodulatory agents have been used in refractory or severe cases or when prednisone cannot be tapered.

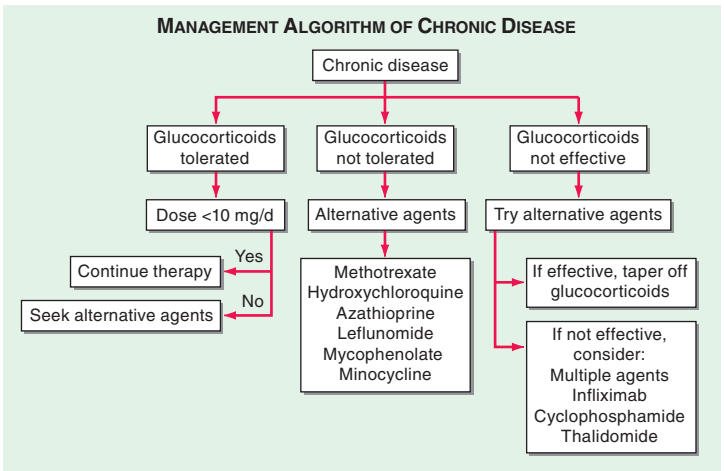


FIGURE 166-2 Approach to chronic disease is based on whether glucocorticoid therapy is tolerated.

OUTCOME

Sarcoidosis is usually a self-limited, non-life-threatening disease. Remission occurs in >50% within 2–5 years of diagnosis with 20–50% developing chronic disease Death directly due to disease occurs in 5% of cases usually related to lung, cardiac, neurologic, or liver involvement.

For a more detailed discussion, see Baughman RP, Lower EE: Sarcoidosis, Chap. 390, p. 2205, in HPIM-19.

167 Amyloidosis

DEFINITION

Amyloidosis is a term for a group of protein folding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in organs and tissues. Clinical manifestations depend on anatomic distribution and intensity of amyloid protein deposition; they range from local deposition with little significance to involvement of virtually any organ system with severe pathophysiologic consequences.

CLASSIFICATION

Amyloid diseases are defined by the biochemical nature of the protein in the fibril deposits and are classified according to whether they are systemic or localized, acquired or inherited, and their clinical patterns. The accepted nomenclature is *AX* where *A* indicates amyloidosis and *X* is the protein in the fibril (Table 137-1, p. 720, in HPIM-19).

- AL (immunoglobulin light chains): *primary amyloidosis*; most common form of systemic amyloidosis; arises from a clonal B-cell disorder, usually multiple myeloma.
- AA (serum amyloid A): *secondary amyloidosis*; can occur in association with almost any chronic inflammatory state (e.g., RA, SLE, periodic fever syndromes such as familial Mediterranean fever [FMF], Crohn's disease) or chronic infections.
- AF (familial amyloidoses): number of different types that are dominantly transmitted in association with a mutation that enhances protein misfolding and fibril formation; most commonly due to transthyretin.
- $A\beta_2M$: composed of β_2 microglobulin; occurs in end-stage renal disease of long duration.
- Localized or organ-limited amyloidoses: most common form is Aβ found in Alzheimer's disease derived from abnormal proteolytic processing of the amyloid precursor protein.

CLINICAL MANIFESTATIONS

Clinical features are varied and depend entirely on biochemical nature of the fibril protein. Frequent sites of involvement:

- *Kidney:* seen with AA and AL; proteinuria, nephrosis, azotemia.
- *Liver:* occurs in AA, AL, and AF; hepatomegaly.

- *Skin:* characteristic of AL but can be seen in AA; raised waxy papules.
- *Heart:* common in AL and AF; CHF, cardiomegaly, arrhythmias.
- *GI:* common in all types; GI obstruction or ulceration, hemorrhage, protein loss, diarrhea, macroglossia, disordered esophageal motility.
- *Joints:* usually AL, frequently with myeloma; periarticular amyloid deposits, "shoulder pad sign": firm amyloid deposits in soft tissue around the shoulder, symmetric arthritis of shoulders, wrists, knees, hands.
- *Nervous system:* prominent in AF; peripheral neuropathy, postural hypotension, dementia. Carpal tunnel syndrome may occur in AL and $A\beta_2M$.
- *Respiratory:* lower airways can be affected in AL; localized amyloid can cause obstruction along upper airways.

DIAGNOSIS

Diagnosis relies on the identification of fibrillar deposits in tissues and typing of the amyloid (Fig. 167-1). Congo red staining of abdominal fat will demonstrate amyloid deposits in >80% of pts with systemic amyloid.

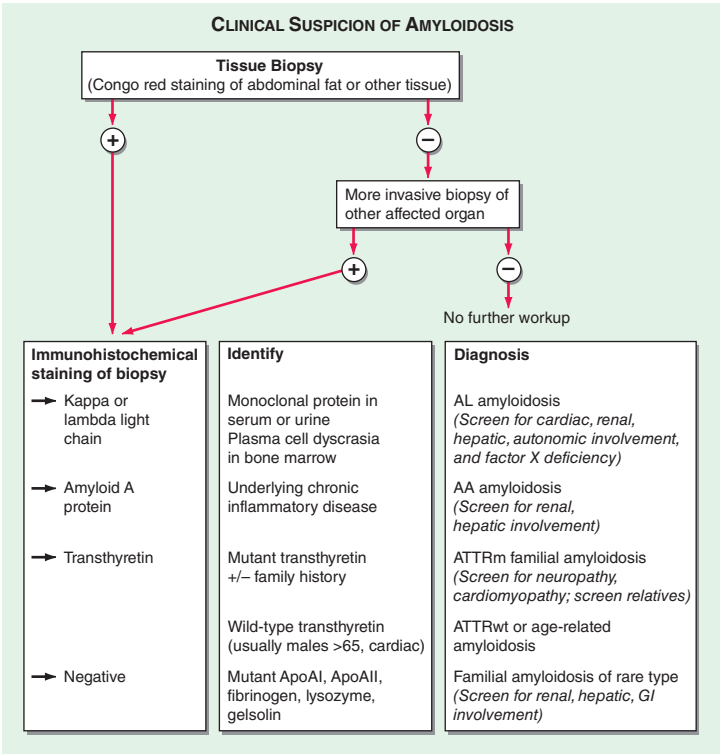


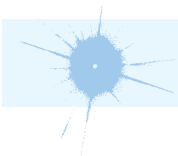
FIGURE 167-1 Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII.

PROGNOSIS

Outcome is variable and depends on type of amyloidosis and organ involvement. Average survival of AL amyloid without treatment is ~1–2 years; cardiac involvement is the leading cause of death with a median survival of ~6 months without treatment.

TREATMENT AMYLOIDOSIS

For AL, current therapies target the clonal bone-marrow plasma cells using approaches used for multiple myeloma. High-dose IV melphalan followed by autologous stem-cell transplantation produces complete hematologic responses in ~40% but only 50% are eligible for such aggressive treatment, and peritransplant mortality is higher than for other hematologic diseases because of impaired organ function. Treatment of AA is directed toward controlling the underlying inflammatory condition. Colchicine (1.2–1.8 mg/d) is the standard treatment for FMF but has not been helpful for AA of other causes. TNF inhibitors and interleukin-1 antagonists can be effective in syndromes related to cytokine elevation. Eprodisate designed to disrupt fibril formation is being studied. In certain forms of AF, genetic counseling is important and liver transplantation is a successful form of therapy.



For a more detailed discussion, see Seldin DC, Berk JL: Amyloidosis, Chap. 137, p. 719, in HPIM-19.

This page intentionally left blank

168 Disorders of the Anterior Pituitary and Hypothalamus

The anterior pituitary is often referred to as the "master gland" because, together with the hypothalamus, it orchestrates the complex regulatory functions of multiple other glands (Fig. 168-1). The anterior pituitary produces six major hormones: (1) prolactin (PRL), (2) growth hormone (GH), (3) adrenocorticotropin hormone (ACTH), (4) luteinizing hormone (LH), (5) follicle-stimulating hormone (FSH), and (6) thyroid-stimulating hormone (TSH). Pituitary hormones are secreted in a pulsatile manner, reflecting intermittent stimulation by specific hypothalamic-releasing factors. Each of these pituitary hormones elicits specific responses in peripheral target glands. The hormonal products of these peripheral glands, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function. Disorders of the pituitary include neoplasms or other lesions (granulomas, hemorrhage) that lead to mass effects and clinical syndromes due to excess or deficiency of one or more pituitary hormones.

PITUITARY TUMORS

Pituitary adenomas are benign monoclonal tumors that arise from one of the five anterior pituitary cell types and may cause clinical effects from either overproduction of a pituitary hormone or compressive/destructive effects on surrounding structures, including the hypothalamus, pituitary, optic chiasm, and cavernous sinus. About one-third of all adenomas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. Among hormonally functioning neoplasms, tumors secreting PRL is the most common (~50%); they have a greater prevalence in women than in men. GH- and ACTH-secreting tumors each account for about 10–15% of functioning pituitary tumors. Adenomas are classified as microadenomas (<10 mm) or macroadenomas (≥10 mm). Pituitary adenomas (especially PRL- and GH-producing tumors) may be part of genetic familial syndromes such as MEN 1, Carney syndrome, or mutant aryl hydrocarbon receptor inhibitor protein (AIP) syndrome. Other entities that can present as a sellar mass include craniopharyngiomas, Rathke's cleft cysts, sella chordomas, meningiomas, pituitary metastases, gliomas, and granulomatous disease (e.g., histiocytosis X, sarcoidosis).

Clinical Features

Symptoms from mass effects include headache; visual loss through compression of the optic chiasm superiorly (classically a bitemporal hemianopia); and diplopia, ptosis, ophthalmoplegia, and decreased facial sensation from cranial nerve compression laterally. Pituitary stalk compression from the tumor may also result in mild hyperprolactinemia. Symptoms of hypopituitarism or hormonal excess may be present as well (see below).

Pituitary apoplexy, typically resulting from hemorrhage into a preexisting adenoma or post-partum as Sheehan's syndrome, is an endocrine emergency that typically presents with features that include severe headache, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness. It may result in hypotension, severe hypoglycemia, CNS hemorrhage, and death. Pts with no evident visual loss or impaired consciousness can usually

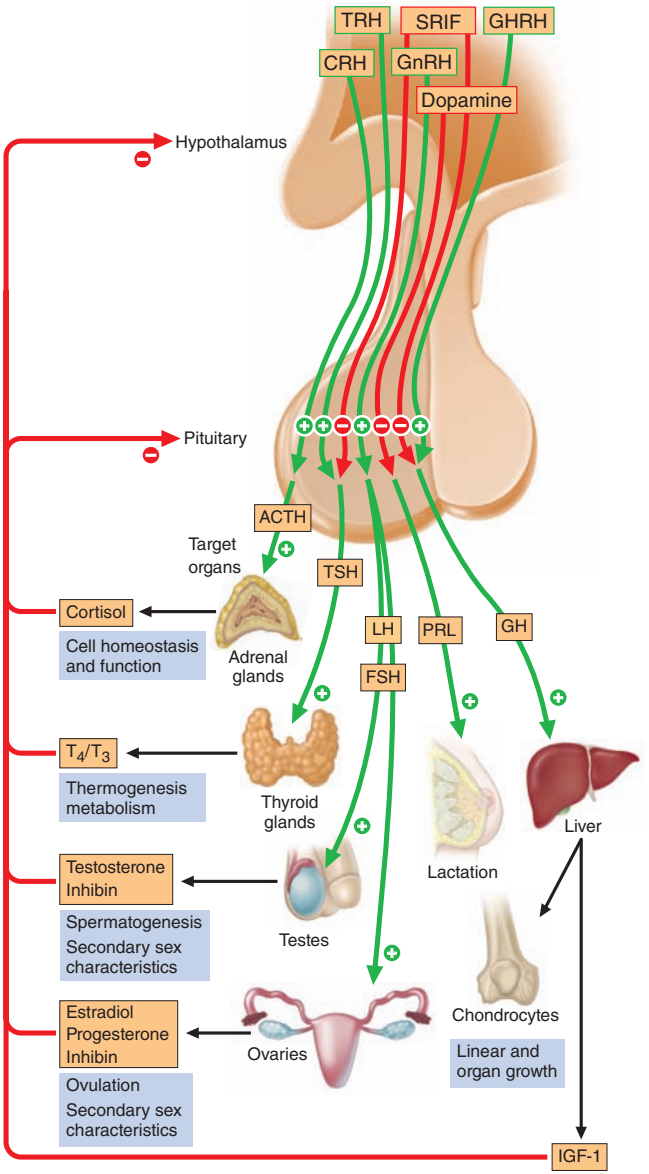


FIGURE 168-1 Diagram of pituitary axes. Hypothalamic hormones regulate anterior pituitary tropic hormones that, in turn, determine target gland secretion. Peripheral hormones feedback to regulate hypothalamic and pituitary hormones. ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; PRL, prolactin; SRIF, somatostatin, somatotropin release–inhibiting factor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

be observed and managed conservatively with high-dose glucocorticoids; surgical decompression should be considered when visual or neurologic symptoms/signs are present.

Diagnosis

Sagittal and coronal T1-weighted MRI images with specific pituitary cuts should be obtained before and after administration of gadolinium. In pts with lesions close to the optic chiasm, visual field assessment that uses perimetry techniques should be performed. In pituitary apoplexy, CT or MRI of the pituitary may reveal signs of sellar hemorrhage, with deviation of the pituitary stalk and compression of pituitary tissue.

TREATMENT PITUITARY TUMORS

Pituitary surgery is indicated for mass lesions that impinge on surrounding structures or to correct hormonal hypersecretion, except in the case of prolactinoma, where medical treatment is usually effective (see below). Transsphenoidal surgery, rather than transfrontal resection, is the desired surgical approach for most pts. The goal is selective resection of the pituitary mass lesion without damage to the normal pituitary tissue, to decrease the likelihood of hypopituitarism. Transient or permanent diabetes insipidus, hypopituitarism, CSF rhinorrhea, visual loss, and oculomotor palsy may occur postoperatively. Tumor invasion outside of the sella is rarely amenable to surgical cure, but debulking procedures may relieve tumor mass effects and reduce hormonal hypersecretion. Radiation may be used as an adjunct to surgery, but efficacy is delayed and >50% of pts develop hormonal deficiencies within 10 years, usually due to hypothalamic damage. GH- and TSH-secreting tumors may also be amenable to medical therapy; in PRL-secreting tumors, medical therapy is the initial treatment of choice.

PITUITARY HORMONE HYPERSECRETION SYNDROMES

HYPERPROLACTINEMIA

Prolactin is unique among the pituitary hormones in that the predominant central control mechanism is inhibitory, reflecting dopamine-mediated suppression of PRL release. Prolactin acts to induce and maintain lactation and decrease reproductive function and drive (via suppression of gonadotropin-releasing hormone [GnRH], gonadotropins, and gonadal steroidogenesis).

Etiology

Physiologic elevation of PRL occurs in pregnancy and lactation. Otherwise, PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >100 μg/L. Less pronounced hyperprolactinemia is commonly caused by medications (risperidone, chlorpromazine, perphenazine, haloperidol, metoclopramide, opiates, H_2 antagonists, amitriptyline, selective serotonin reuptake inhibitors [SSRIs], verapamil, estrogens), pituitary stalk damage (tumors, lymphocytic hypophysitis, granulomas, trauma, irradiation), primary hypothyroidism, or renal failure. Nipple stimulation may also cause acute PRL increases.

Clinical Features

In women, amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia. In men, symptoms of hypogonadism (Chap. 174) or mass effects are the usual presenting symptoms, and galactorrhea is rare.

Diagnosis

Fasting, morning PRL levels should be measured; when clinical suspicion is high, measurement of levels on several different occasions may be required. If

hyperprolactinemia is present, nonneoplastic causes should be excluded (e.g., pregnancy test, hypothyroidism, medications).

TREATMENT HYPERPROLACTINEMIA

If the pt is taking a medication that is known to cause hyperprolactinemia, the drug should be withdrawn, if possible. A pituitary MRI should be performed if the underlying cause of PRL elevation is unknown. Resection of hypothalamic or sellar mass lesions can reverse hyperprolactinemia due to stalk compression. Medical therapy with a dopamine agonist is indicated in microprolactinomas for control of symptomatic galactorrhea, for restoration of gonadal function, or when fertility is desired. Alternatively, estrogen replacement may be indicated if fertility is not desired, but tumor size should be carefully monitored. Dopamine agonist therapy for macroprolactinomas generally results in both adenoma shrinkage and reduction of PRL levels. Cabergoline (initial dose 0.5 mg a week, usual dose 0.5–1 mg twice a week) and bromocriptine (initial dose 0.625–1.25 mg qhs, usual dose 2.5 PO three times a day) are the two most frequently used dopamine agonists. Cabergoline is the more effective and better-tolerated drug. These medications should initially be taken at bedtime with food, followed by gradual dose increases, to reduce the side effects of nausea and postural hypotension. Other side effects include constipation, nasal stuffiness, dry mouth, nightmares, insomnia, or vertigo; decreasing the dose usually alleviates these symptoms. Dopamine agonists may also precipitate or worsen underlying psychiatric conditions. Cardiac echocardiography is prudent before starting cabergoline therapy as there has been concern about an association with valvular heart disease. In pts with microadenomas successfully treated (normal PRL, full tumors shrinkage), therapy may be withdrawn after 2 years, followed by careful monitoring for tumor recurrence. Spontaneous remission of microadenomas, presumably caused by infarction, occurs in some pts. Surgical debulking may be required for macroprolactinomas that do not adequately respond to medical therapy.

Women with microprolactinomas who become pregnant should discontinue dopaminergic therapy, as the risk for significant tumor growth during pregnancy is low. In those with macroprolactinomas, visual field testing should be performed at each trimester. A pituitary MRI should be performed if severe headache and/or visual defects occur.

ACROMEGALY

Etiology

GH hypersecretion is primarily the result of pituitary somatotrope adenomas, mostly sporadic, but also in conjunction with MEN 1, Carney syndrome, McCune-Albright syndrome, and familial AIP mutations. Extrapituitary causes of acromegaly (ectopic growth hormone–releasing hormone [GHRH] production) are very rare.

Clinical Features

The peak occurrence of acromegaly is at age 40–45. In children, GH hypersecretion prior to long bone epiphyseal closure results in gigantism. The presentation of acromegaly in adults is usually indolent, and diagnosis is typically delayed by up to a decade. Pts may note a change in facial features, widened teeth spacing, deepening of the voice, snoring, increased shoe or glove size, ring tightening, hyperhidrosis, oily skin, arthropathy, and carpal tunnel syndrome. Frontal bossing, mandibular enlargement with prognathism, macroglossia, an enlarged thyroid, skin tags, thick heel pads, and hypertension may be present on examination. Associated conditions include cardiomyopathy, left ventricular hypertrophy, diastolic dysfunction, sleep

apnea, glucose intolerance, diabetes mellitus, colon polyps, and colonic malignancy. Overall mortality is increased approximately threefold.

Diagnosis

Insulin-like growth factor type I (IGF-I) levels are a useful screening measure, with elevation suggesting acromegaly. Due to the pulsatility of GH, measurement of a single random GH level is not useful for screening. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <0.4 μg/L within 1–2 h of a 75-g oral glucose load. MRI of the pituitary usually reveals a macroadenoma.

TREATMENT ACROMEGALY

The primary treatment modality for acromegaly is transsphenoidal surgery. GH levels are not normalized by surgery alone in many pts with macroadenomas; in those, somatostatin analogues provide adjunctive medical therapy that suppresses GH secretion with modest to no effect on tumor size. Octreotide (50 μg SC three times a day) is used for initial therapy to determine response. Once a positive response and tolerance of side effects (nausea, abdominal discomfort, diarrhea, flatulence) are established, pts are changed to long-acting depot formulations (octreotide LAR 20–30 mg IM every 2–4 weeks or lanreotide autogel 90–120 mg IM once a month). Dopamine agonists (bromocriptine, cabergoline) can be used as adjunctive therapy but are generally not very effective. The GH receptor antagonist pegvisomant (10–30 mg SC daily) can be added in pts who do not respond to somatostatin analogues. Pegvisomant is highly effective in lowering IGF-I levels but does not lower GH levels or decrease tumor size. Pituitary irradiation may also be required as adjuvant therapy but has a slow therapeutic onset and a high rate of late hypopituitarism.

CUSHING'S DISEASE (SEE CHAP. 171)

NONFUNCTIONING AND GONADOTROPIN-PRODUCING ADENOMAS

These tumors are the most common type of pituitary neoplasm and usually present with symptoms of one or more hormonal deficiencies or mass effect. They typically produce small amounts of intact gonadotropins (usually FSH) as well as uncombined α-subunit and LHβ and FSHβ subunits. Surgery is indicated for mass effects or hypopituitarism; asymptomatic small adenomas may be followed with regular MRI and visual field testing. Diagnosis is based on immunohistochemical analysis of resected tumor tissue. Medical therapy is usually ineffective in shrinking these tumors.

TSH-SECRETING ADENOMAS

TSH-producing adenomas are rare but often large and locally invasive when they occur. Pts present with goiter and hyperthyroidism, and/or sella mass effects. Diagnosis is based on elevated serum free T_4 levels in the setting of inappropriately normal or high TSH secretion and MRI evidence of a pituitary adenoma. Surgery is indicated and is usually followed by somatostatin analogue therapy to treat residual tumor. Somatostatin analogue therapy (see above) leads to normalization of TSH and euthyroidism in most and tumor shrinkage in 50–75% of pts. If necessary, thyroid ablation or antithyroid drugs can be used to reduce thyroid hormone levels.

HYPOPITUITARISM

Etiology

A variety of disorders may cause deficiencies of one or more pituitary hormones. These disorders may be genetic, congenital, traumatic (pituitary surgery, cranial

irradiation, head injury), neoplastic (large pituitary adenoma, parasellar mass, craniopharyngioma, metastases, meningioma), infiltrative (hemochromatosis, lymphocytic hypophysitis, sarcoidosis, histiocytosis X), vascular (pituitary apoplexy, postpartum necrosis, sickle cell disease), or infectious (tuberculous, fungal, parasitic). The most common cause of hypopituitarism is neoplastic in origin (macroadenomatous destruction, or following hypophysectomy or radiation therapy). Pituitary hormone failure due to compression, destruction, or radiation therapy typically follows a sequential pattern: GH>FSH>LH>TSH>ACTH. Genetic causes of hypopituitarism may affect several hormones (e.g., pituitary dysplasia, PROP-1 and PIT-1 mutations) or be restricted to single pituitary hormones or axes (e.g., isolated GH deficiency, Kallmann syndrome, isolated ACTH deficiency). Hypopituitarism following cranial irradiation develops over 5–15 years. Varying degrees of partial to complete hormone deficiencies occur during evolution of pituitary destruction.

Clinical Features

Each hormone deficiency is associated with specific findings:

- *GH:* growth disorders in children; increased intraabdominal fat, reduced lean body mass, hyperlipidemia, reduced bone mineral density, decreased stamina, and social isolation in adults
- *FSH/LH:* menstrual disorders and infertility in women (Chap. 175); hypogonadism in men (Chap. 174)
- *ACTH:* features of hypocortisolism (Chap. 171) without mineralocorticoid deficiency
- *TSH:* growth retardation in children; features of hypothyroidism in children and adults (Chap. 170)
- *PRL:* failure to lactate postpartum

Diagnosis

Biochemical diagnosis of pituitary insufficiency is made by demonstrating low or inappropriately normal levels of pituitary hormones in the setting of low target hormone levels. Initial testing should include an 8 A.M. cortisol level, TSH and free T_4, IGF-I, testosterone in men, assessment of menstrual cycles in women, and PRL level. Provocative tests are required for definitive diagnosis of GH and ACTH deficiency. Adult GH deficiency is diagnosed by demonstrating a subnormal GH response to a standard provocative test (insulin tolerance test, L-arginine + GHRH). Acute ACTH deficiency may be diagnosed by a subnormal response in an insulin tolerance test, metyrapone test, or corticotropin-releasing hormone (CRH) stimulation test. Standard ACTH (cosyntropin) stimulation tests may be normal in acute ACTH deficiency; with adrenal atrophy, the cortisol response to cosyntropin is blunted.

TREATMENT HYPOPITUITARISM

Hormonal replacement should aim to mimic physiologic hormone production. Effective dose schedules are outlined in Table 168-1. Doses should be individualized, particularly for GH, glucocorticoids, and L-thyroxine. GH therapy, particularly when excessive, may be associated with fluid retention, joint pain, and carpal tunnel syndrome. Glucocorticoid replacement should always precede L-thyroxine therapy to avoid precipitation of adrenal crisis. Pts requiring glucocorticoid replacement should wear a medical alert bracelet and should be instructed to take additional doses during stressful events such as acute illness, dental procedures, trauma, and acute hospitalization.

TABLE 168-1 HORMONE REPLACEMENT THERAPY FOR ADULT HYPOPITUITARISM[a]

Trophic Hormone Deficit	Hormone Replacement
ACTH	Hydrocortisone (10–20 mg A.M.; 5–10 mg P.M.)
	Cortisone acetate (25 mg A.M.; 12.5 mg P.M.)
	Prednisone (5 mg A.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males
	Testosterone enanthate (200 mg IM every 2 weeks)
	Testosterone gel (5–10 g/d applied to skin)
	Females
	Conjugated estrogen (0.625–1.25 mg qd for 25 days)
	Estradiol skin patch (0.025–0.1 mg, every week)
	Progesterone (5–10 mg qd) on days 16–25
	For fertility: Menopausal or biosynthetic gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.1–1.25 mg SC qd)
	Children: Somatotropin (0.02–0.05 [mg/kg per day])
Vasopressin	Intranasal desmopressin (5–20 μg twice daily)
	Oral desmopressin (300–600 μg qd)

[a]All doses shown should be individualized for specific pts and should be reassessed during stress, surgery, or pregnancy. Male and female fertility requirements should be managed as discussed in Chaps. 174 and 175.

Abbreviations: ACTH, adrenocorticotropin hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

For a more detailed discussion, see Melmed S, Jameson JL: Anterior Pituitary: Physiology of Pituitary Hormones, Chap 401e; Hypopituitarism, Chap 402, p. 2255; Anterior Pituitary Tumor Syndromes, Chap 403, p. 2261, in HPIM-19.

169 Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone

The neurohypophysis, or posterior pituitary gland, produces two hormones: (1) arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and (2) oxytocin. AVP acts on the renal tubules to induce water retention, leading to concentration of the urine. Oxytocin stimulates postpartum milk letdown in response to suckling. Clinical syndromes may result from deficiency or excess of AVP.

DIABETES INSIPIDUS

Etiology

Diabetes insipidus (DI) results from insufficient AVP production by the hypothalamus or from impaired AVP action in the kidney. AVP deficiency is characterized by production of large amounts of dilute urine. In *central DI*, insufficient AVP is released in response to physiologic stimuli. Causes include acquired (head trauma; neoplastic or inflammatory conditions affecting the hypothalamus/posterior pituitary), congenital, and genetic disorders, but almost half of cases are idiopathic. In *gestational DI*, increased metabolism of plasma AVP by an aminopeptidase (vasopressinase) produced by the placenta leads to a relative deficiency of AVP during pregnancy. *Primary polydipsia* results in secondary insufficiency of AVP due to physiologic inhibition of AVP secretion by excessive fluid intake. *Nephrogenic DI* is caused by AVP resistance at the level of the kidney; it can be genetic or acquired from drug exposure (lithium, demeclocycline, amphotericin B), metabolic conditions (hypercalcemia, hypokalemia), or renal damage.

Clinical Features

Symptoms include polyuria, excessive thirst, and polydipsia, with a 24-h urine output of >50 mL/kg per day and a urine osmolality that is less than that of serum (<300 mosmol/kg; specific gravity <1.010). DI can be partial or complete; in the latter case the urine is maximally diluted (<100 mosmol/kg) and the daily urine output can reach 10–20 L. Clinical or laboratory signs of dehydration, including hypernatremia, occur only if the pt simultaneously has a thirst defect (not uncommon in pts with CNS disease) or does not have access to water. Other etiologies of hypernatremia are described in Chap. 1.

Diagnosis

DI must be differentiated from other etiologies of polyuria (Chap. 46). Unless an inappropriately dilute urine is present in the setting of serum hyperosmolality, a fluid deprivation test is used to make the diagnosis of DI. This test should be started in the morning with careful supervision to avoid dehydration. Body weight, plasma osmolality, serum sodium, and urine volume and osmolality should be measured hourly. The test should be stopped when body weight decreases by 5% or plasma osmolality/sodium exceeds the upper limit of normal. If the urine osmolality is <300 mosmol/kg with serum hyperosmolality, desmopressin (0.03 μg/kg SC) should be administered with repeat measurement of urine osmolality 1–2 h later. An increase of >50% indicates severe pituitary DI, whereas a smaller or absent response suggests nephrogenic DI. Measurement of AVP levels before and after fluid deprivation may be helfpul to distinguish central and nephrogenic DI. Occasionally, hypertonic saline infusion may be required if fluid deprivation does not achieve the requisite level of hypertonic dehydration, but this should be administered with caution.

TREATMENT DIABETES INSIPIDUS

Pituitary DI can be treated with desmopressin (DDAVP) subcutaneously (1–2 μg once or twice per day), via nasal spray (10–20 μg two or three times a day), or orally (100–400 μg two or three times a day), with recommendations to drink to thirst. Symptoms of nephrogenic DI may be ameliorated by treatment with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet, or with prostaglandin synthesis inhibitors (e.g., indomethacin).

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

Etiology

Excessive or inappropriate production of AVP predisposes to hyponatremia, reflecting water retention. The evaluation of hyponatremia is described in Chap. 1. Etiologies of SIADH include neoplasms, lung infections, CNS disorders, and drugs (Table 169-1).

Clinical Features

If hyponatremia develops gradually, it may be asymptomatic until it reaches a severe stage. However, if it develops acutely, symptoms of water intoxication may include mild headache, confusion, anorexia, nausea, vomiting, coma, and convulsions. Laboratory findings include low BUN, creatinine, uric acid, and albumin; serum Na <130 meq/L and plasma osmolality <270 mosmol/kg; urine is not maximally diluted and frequently hypertonic to plasma, and urinary Na^+ is usually >20 mmol/L.

TABLE 169-1 CAUSES OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

Neoplasms	Neurologic
Carcinomas	Guillain-Barré syndrome
Lung	Multiple sclerosis
Duodenum	Delirium tremens
Pancreas	Amyotrophic lateral sclerosis
Ovary	Hydrocephalus
Bladder, ureter	Psychosis
Other neoplasms	Peripheral neuropathy
Thymoma	Congenital malformations
Mesothelioma	Agenesis corpus callosum
Bronchial adenoma	Cleft lip/palate
Carcinoid	Other midline defects
Gangliocytoma	Metabolic
Ewing's sarcoma	Acute intermittent porphyria
Head trauma	Pulmonary
Infections	Asthma
Pneumonia, bacterial or viral	Pneumothorax
Abscess, lung or brain	Positive-pressure respiration
Cavitation (aspergillosis)	Drugs
Tuberculosis, lung or brain	Vasopressin or desmopressin
Meningitis, bacterial or viral	Chlorpropamide
Encephalitis	Oxytocin, high dose
AIDS	Vincristine
Vascular	Carbamazepine
Cerebrovascular occlusions, hemorrhage	Nicotine
Cavernous sinus thrombosis	Phenothiazines
Genetic	Cyclophosphamide
X-linked recessive	Tricyclic antidepressants
(V_2 receptor gene)	Monoamine oxidase inhibitors
	Serotonin reuptake inhibitors

TREATMENT SIADH

Fluid intake should be restricted to 500 mL less than urinary output. In pts with severe symptoms or signs, hypertonic (3%) saline can be infused at ≤0.05 mL/kg body weight IV per minute, with hourly sodium levels measured until Na increases by 12 meq/L or to 130 meq/L, whichever occurs first. However, if the hyponatremia has been present for >24–48 h and is corrected too rapidly, saline infusion has the potential to produce central pontine myelinolysis, a serious, potentially fatal neurologic complication caused by osmotic fluid shifts. Vasopressin antagonists (conivaptan, tolvaptan) are now available, but experience with these agents in SIADH treatment is limited. Oral vaptan (tolvaptan), a selective V_2 antagonist increases urinary water excretion by blocking the antidiuretic effect of AVP. It should be initiated in the hospital (typically 15 mg PO qd) to evaluate the clinical response and avoid excessive diuresis. Other options include demeclocycline, 150–300 mg PO tid or qid, or fludrocortisone, 0.05–0.2 mg PO bid. The effect of the demeclocycline manifests in 7–14 days and is due to induction of a reversible form of nephrogenic DI. The effect of fludrocortisone also requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements and may induce hypertension.

For a more detailed discussion, see Robertson GL: Disorders of the Neurohypophysis, Chap. 404, p. 2274, in HPIM-19.

170 Thyroid Gland Disorders

Disorders of the thyroid gland result primarily from autoimmune processes that stimulate the overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and underproduction of thyroid hormones (*hypothyroidism*). *Neoplastic processes* in the thyroid gland can lead to benign nodules or thyroid cancer.

Thyroidal production of the hormones thyroxine (T_4) and triiodothyronine (T_3) is controlled via a classic endocrine feedback loop (see Fig. 168-1). Some T_3 is secreted by the thyroid, but most is produced by deiodination of T_4 in peripheral tissues. Both T_4 and T_3 are bound to carrier proteins (thyroid-binding globulin [TBG], transthyretin [binds T_4], and albumin) in the circulation. Increased levels of total T_4 and T_3 with normal free levels are seen in states of increased carrier proteins (pregnancy, estrogens, cirrhosis, hepatitis, and inherited disorders). Conversely, decreased total T_4 and T_3 levels with normal free levels are seen in severe systemic illness, chronic liver disease, and nephrosis.

HYPOTHYROIDISM

Etiology

Deficient thyroid hormone production can be due to thyroid failure (primary hypothyroidism) or, less commonly, pituitary or hypothalamic disease (secondary

TABLE 170-1 CAUSES OF HYPOTHYROIDISM

Primary
Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon α and other cytokines, aminoglutethimide, sunitinib
Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
Iodine deficiency
Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis
Overexpression of type 3 deiodinase in infantile hemangioma
Transient
Silent thyroiditis, including postpartum thyroiditis
Subacute thyroiditis
Withdrawal of thyroxine treatment in individuals with an intact thyroid
After ^{131}I treatment or subtotal thyroidectomy for Graves' disease
Secondary
Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
Isolated TSH deficiency or inactivity
Bexarotene treatment
Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Abbreviations: TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

hypothyroidism) (Table 170-1). Congenital hypothyroidism is present in 1 of 4000 newborns; the importance of its recognition and prompt treatment for child development has led to the adoption of neonatal screening programs. Transient hypothyroidism may occur in silent or subacute thyroiditis. *Subclinical* (or *mild*) *hypothyroidism* is a state of normal free thyroid hormone levels and mild elevation of thyroid-stimulating hormone (TSH); despite the name, some pts may have minor symptoms. With higher TSH levels and low free T_4 levels, symptoms become more readily apparent in *clinical* (or *overt*) *hypothyroidism*. In areas of iodine sufficiency, autoimmune disease and iatrogenic causes are the most common etiologies of hypothyroidism. The peak age of occurrence is around 60 years, and prevalence increases with age.

Clinical Features

Symptoms of hypothyroidism include lethargy, dry hair and skin, cold intolerance, hair loss, difficulty concentrating, poor memory, constipation, mild weight gain with poor appetite, dyspnea, hoarse voice, muscle cramping, and menorrhagia. Cardinal features on examination include bradycardia, mild diastolic hypertension, prolongation of the relaxation phase of deep tendon reflexes, and cool peripheral extremities. Goiter may be palpated, or the thyroid may be atrophic and nonpalpable. Carpal tunnel syndrome may be present. Cardiomegaly may be present due to pericardial effusion. The most extreme presentation is a dull, expressionless face, sparse hair, periorbital puffiness, large tongue, and pale, doughy, cool skin. The condition may

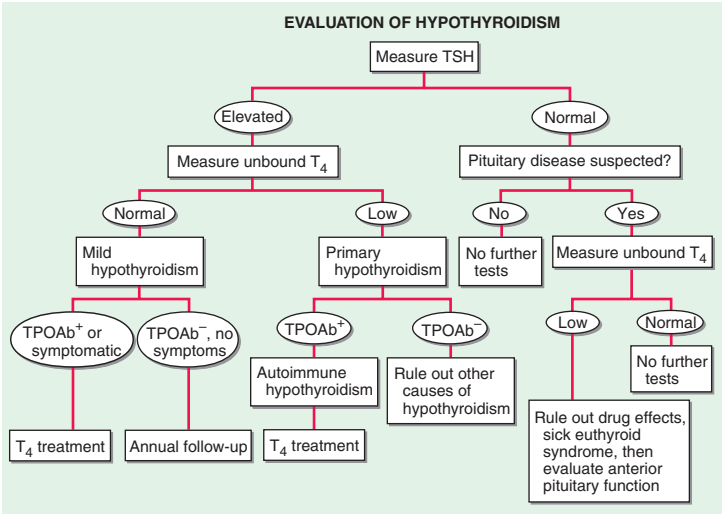


FIGURE 170-1 Evaluation of hypothyroidism. $TPOAb^+$, thyroid peroxidase antibodies present; $TPOAb^-$, thyroid peroxidase antibodies not present; TSH, thyroid-stimulating hormone.

progress into a hypothermic, stuporous state (*myxedema coma*) with respiratory depression. Factors that predispose to myxedema coma include cold exposure, trauma, infection, and administration of narcotics. In mild hypothyroidism, the classic findings of overt hypothyroidism may not be present, and the clinical picture may be dominated by fatigue and ill-defined symptoms.

Diagnosis

Decreased serum free T_4 is common to all varieties of hypothyroidism. An elevated serum TSH is a sensitive marker of primary hypothyroidism but is not found in secondary hypothyroidism. A summary of the investigations used to determine the existence and cause of hypothyroidism is provided in Fig. 170-1. Thyroid peroxidase (TPO) antibodies are increased in >90% of pts with autoimmune-mediated hypothyroidism. Elevated cholesterol, increased creatine phosphokinase, and anemia may be present; bradycardia, low-amplitude QRS complexes, and flattened or inverted T waves may be present on ECG.

TREATMENT HYPOTHYROIDISM

Adult pts <60 years without evidence of heart disease may be started on 50–100 μg of levothyroxine (T_4) daily. In the elderly or in pts with known coronary artery disease, the starting dose of levothyroxine is 12.5–25 μg/d. The dose should be adjusted in 12.5- to 25-μg increments every 6–8 weeks on the basis of TSH levels, until a normal TSH level is achieved. The average daily replacement dose is 1.6 μg/kg per day, but dosing should be individualized and guided by TSH measurement. In *secondary* hypothyroidism, TSH levels cannot be used, and therapy needs to be guided by free T_4 measurement. Women on levothyroxine replacement should have a TSH level checked as soon as pregnancy is diagnosed, as the replacement dose typically increases by 30–50% during pregnancy. Failure to recognize and treat maternal hypothyroidism may

adversely affect fetal neural development. Therapy for myxedema coma should include levothyroxine (500 μg) as a single IV bolus followed by daily treatment with levothyroxine (50–100 μg/d), along with hydrocortisone (50 mg every 6 h) for impaired adrenal reserve, ventilatory support, space blankets, and treatment of precipitating factors.

THYROTOXICOSIS

Etiology

Causes of thyroid hormone excess include primary hyperthyroidism (Graves' disease, toxic multinodular goiter [MNG], toxic adenoma, iodine excess); thyroid destruction (subacute thyroiditis, silent thyroiditis, amiodarone, radiation); extrathyroidal sources of thyroid hormone (thyrotoxicosis factitia, struma ovarii, functioning follicular carcinoma); and secondary hyperthyroidism (TSH-secreting pituitary adenoma, thyroid hormone resistance syndrome, human chorionic gonadotropin [hCG]-secreting tumors, gestational thyrotoxicosis). Graves' disease, caused by activating TSH-receptor antibodies, is the most common cause of thyrotoxicosis and accounts for 60–80% of cases. Its prevalence in women is 10-fold higher than in men; its peak occurrence is at age 20–50 years.

Clinical Features

Symptoms include nervousness, irritability, heat intolerance, excessive sweating, palpitations, fatigue and weakness, weight loss with increased appetite, frequent bowel movements, and oligomenorrhea. Pts are anxious, restless, and fidgety. Skin is warm and moist, and fingernails may separate from the nail bed (Plummer's nails). Eyelid retraction and lid lag may be present. Cardiovascular findings include tachycardia, systolic hypertension, systolic murmur, and atrial fibrillation. A fine tremor, hyperreflexia, and proximal muscle weakness also may be present. Long-standing thyrotoxicosis may lead to osteopenia. In the elderly, the classic signs of thyrotoxicosis may not be apparent, the main manifestations being weight loss and fatigue ("apathetic thyrotoxicosis").

In Graves' disease, the thyroid is usually diffusely enlarged to two to three times its normal size, and a bruit or thrill may be present. Infiltrative ophthalmopathy (with variable degrees of proptosis, periorbital swelling, and ophthalmoplegia) and dermopathy (pretibial myxedema) also may be found; these are extrathyroidal manifestations of the autoimmune process. In subacute thyroiditis, the thyroid is exquisitely tender and enlarged with referred pain to the jaw or ear, and sometimes accompanied by fever and preceded by an upper respiratory tract infection. Solitary or multiple nodules may be present in toxic adenoma or toxic MNG.

Thyrotoxic crisis, or thyroid storm, is rare, presents as a life-threatening exacerbation of hyperthyroidism, and can be accompanied by fever, delirium, seizures, arrhythmias, coma, vomiting, diarrhea, and jaundice.

Diagnosis

Investigations used to determine the existence and causes of thyrotoxicosis are summarized in Fig. 170-2. Serum TSH is a sensitive marker of thyrotoxicosis caused by Graves' disease, autonomous thyroid nodules, thyroiditis, and exogenous levothyroxine treatment. Associated laboratory abnormalities include elevation of bilirubin, liver enzymes, and ferritin. Thyroid radioiodine uptake may be required to distinguish the various etiologies: high uptake in Graves' disease and nodular disease versus low uptake in thyroid destruction, iodine excess, and extrathyroidal sources of thyroid hormone. (***Note:*** Radioiodine is the nuclide required for quantitative thyroid uptake, whereas technetium is sufficient for imaging purposes.) The ESR is elevated in subacute thyroiditis.

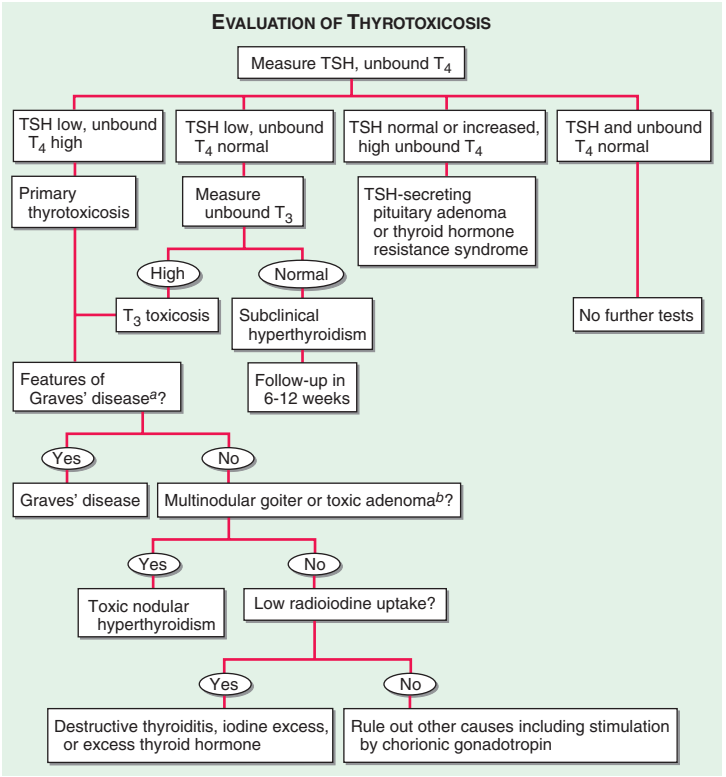


FIGURE 170-2 Evaluation of thyrotoxicosis. [a]Diffuse goiter, positive TPO antibodies, ophthalmopathy, dermopathy; [b]can be confirmed by radionuclide scan. TSH, thyroid-stimulating hormone.

TREATMENT THYROTOXICOSIS

Graves' disease may be treated with antithyroid drugs or radioiodine; subtotal thyroidectomy is rarely indicated. The main antithyroid drugs are methimazole or carbimazole (10–20 mg two to three times a day initially, titrated to 2.5–10 mg/d) and propylthiouracil (PTU) (100–200 mg every 8 h initially, titrated to 50 mg once or twice a day). Methimazole is preferred in most pts because of easier dosing. Thyroid function tests should be checked 3–4 weeks after initiation of treatment, with adjustments to maintain a normal free T_4 level. Since TSH recovery from suppression is delayed, serum TSH levels should not be used for dose adjustment in the first few months. The common side effects are rash, urticaria, fever, and arthralgia (1–5% of pts). Uncommon but major side effects include hepatitis, an SLE-like syndrome, and, rarely, agranulocytosis (<1%). All pts should be given written instructions regarding the symptoms of possible agranulocytosis (sore throat, fever, mouth ulcers) and the need to stop treatment pending a complete blood count to confirm that agranulocytosis is not present. Propranolol (20–40 mg every 6 h) or longer-acting beta blockers such as atenolol (50 mg/d) may be useful at the start of treatment to control adrenergic symptoms until euthyroidism is reached. Anticoagulation with warfarin

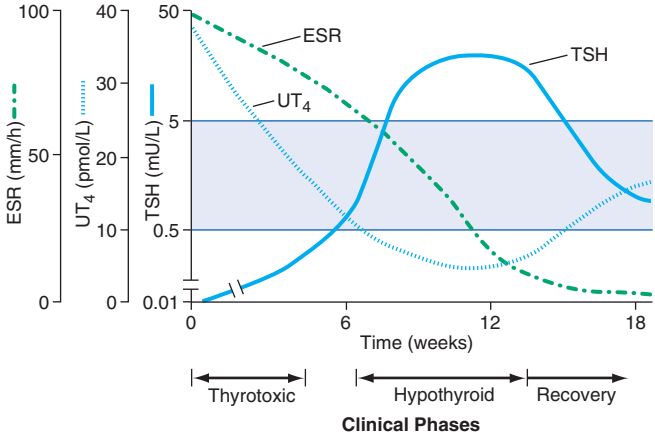


FIGURE 170-3 Clinical course of subacute thyroiditis. The release of thyroid hormones is initially associated with a thyrotoxic phase and suppressed TSH levels. A hypothyroid phase then ensues, with T_4 and TSH levels that are initially low but gradually increase. During the recovery phase, increased TSH levels combined with resolution of thyroid follicular injury leads to normalization of thyroid function, often several months after the beginning of the illness. ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; UT_4, unbound T_4.

should be considered in pts with atrial fibrillation. Radioiodine can also be used as initial treatment or in pts who do not undergo remission after a 1- to 2-year trial of antithyroid drugs. Antecedent treatment with antithyroid drugs should be considered in elderly pts and those with cardiac problems, with cessation of antithyroid drugs 3–5 days prior to radioiodine administration. Radioiodine treatment is contraindicated in pregnancy; instead, symptoms should be controlled with the lowest effective dose of PTU. (Methimazole is not recommended in pregnancy because of reports of fetal agenesis cutis.) Corneal drying may be relieved with artificial tears and taping the eyelids shut during sleep. Progressive exophthalmos with chemosis, ophthalmoplegia, or vision loss is treated with large doses of prednisone (40–80 mg/d) and ophthalmologic referral; orbital decompression may be required.

In thyroid storm, large doses of PTU (600-mg loading dose) should be administered orally, per nasogastric tube, or per rectum, followed 1 h later by five drops saturated solution of KI (SSKI) q6h. PTU (200–300 mg every 6 h) should be continued, along with propranolol (40–60 mg PO q4h or 2 mg IV every 4 h) and dexamethasone (2 mg every 6 h). Any underlying precipitating cause should be identified and treated.

Radioiodine is the treatment of choice for toxic nodules. Subacute thyroiditis in its thyrotoxic phase should be treated with NSAIDs and beta blockade to control symptoms, with monitoring of the TSH and free T_4 levels every 4 weeks. Antithyroid drugs are not effective in thyroiditis. The clinical course of subacute thyroiditis is summarized in Fig. 170-3. Transient levothyroxine replacement (50–100 μg/d) may be required if the hypothyroid phase is prolonged. Silent thyroiditis (or postpartum thyroiditis if within 3–6 months of delivery) should be treated with beta blockade during the thyrotoxic phase and levothyroxine in the hypothyroid phase, with withdrawal after 6–9 months to assess recovery.

SICK EUTHYROID SYNDROME

Any acute, severe illness can cause abnormalities of circulating thyroid hormone levels or TSH, even in the absence of underlying thyroid disease. Therefore, the routine testing of thyroid function should be avoided in acutely ill pts unless a thyroid disorder is strongly suspected. The most common pattern in sick euthyroid syndrome is a decrease in total and free T_3 levels, with normal levels of TSH and T_4. This is considered an adaptive response to a catabolic state. More ill pts may additionally have a fall in total T_4 levels, with normal free T_4 levels. TSH levels may range from <0.1 to >20 mU/L, with normalization after recovery from illness. The pathogenesis of this condition is not fully understood but may involve altered binding of T_4 to TBG and effects of high glucocorticoid and cytokine levels. Unless there is historic or unequivocal clinical evidence of hypothyroidism, thyroid hormone should not be administered and thyroid function tests should be repeated after recovery.

AMIODARONE

Amiodarone is a type III antiarrhythmic agent that has some structural similarity to thyroid hormone and has a high iodine content. Amiodarone treatment leads to substantial iodine overload and is associated with (1) acute, transient suppression of thyroid function, (2) hypothyroidism, or (3) thyrotoxicosis. These effects are only partially attributable to iodine overload. Hypothyroidism can occur in pts with preexisting thyroid disease, with an inability to escape from the suppressive effect of excess iodine. Pts with hypothyroidism can be easily managed with levothyroxine replacement therapy, without a need to stop amiodarone. There are two major forms of amiodarone-induced thyrotoxicosis (AIT). Type 1 AIT is associated with an underlying thyroid abnormality (preclinical Graves' disease or nodular goiter). Thyroid hormone synthesis becomes excessive as a result of increased iodine exposure. Type 2 AIT occurs in pts with no intrinsic thyroid abnormalities and is the result of destructive thyroiditis. Differentiation between type 1 and type 2 AIT may be difficult as the high iodine load interferes with thyroid scans. The drug should be stopped, if possible, although this is often difficult to achieve without compromising the arrhythmia management. Amiodarone has a long biologic half-life, and its effects persist for weeks following discontinuation. Therapy of type 1 AIT consists of high-dose antithyroid drugs, but efficacy may be limited. In type 2 AIT, sodium ipodate (500 mg/d) or sodium tyropanoate (500 mg, 1–2 doses/d) can be used to rapidly lower thyroid hormone levels. Potassium perchlorate (200 mg every 6 h) can be used to deplete the thyroid of iodine, but long-term use carries a risk of agranulocytosis. Glucocorticoids in high doses are partially effective. Lithium can be used to block thyroid hormone release. In some cases, subacute thyroidectomy may be necessary to control thyrotoxicosis.

NONTOXIC GOITER

Goiter refers to an enlarged thyroid gland (>20–25 g), which can be diffuse or nodular. Goiter is more common in women than men. Biosynthetic defects, iodine deficiency, autoimmune disease, dietary goitrogens (cabbage, cassava root), and nodular diseases can lead to goiter. Worldwide, iodine deficiency is the most common etiology of goiter. Nontoxic MNG is common in both iodine-deficient and iodine-replete populations, with a prevalence of up to 12%. The etiology, other than iodine deficiency, is usually not known and may be multifactorial. If thyroid function is preserved, most goiters are asymptomatic. Substernal goiter may obstruct the thoracic inlet and should be evaluated with respiratory flow measurements and CT or MRI in pts with obstructive signs or symptoms (difficulty swallowing, tracheal compression, or plethora). Thyroid function tests should be performed in all pts with goiter to exclude thyrotoxicosis or hypothyroidism. Ultrasound is not generally

indicated in the evaluation of diffuse goiter, unless a nodule is palpable on physical examination.

Iodine or thyroid hormone replacement induces variable regression of goiter in iodine deficiency. Thyroid hormone replacement is rarely effective in significantly shrinking a nontoxic goiter that is not due to iodine deficiency or a biosynthetic defect. Radioiodine reduces goiter size by about 50% in the majority of pts. Surgery is rarely indicated for diffuse goiter but may be required to alleviate compression in pts with nontoxic MNG.

TOXIC MULTINODULAR GOITER AND TOXIC ADENOMA

TOXIC MULTINODULAR GOITER (MNG)

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. The pt is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis; this may be prevented by prior administration of an antithyroid drug. The TSH level is low. T_4 may be normal or minimally increased; T_3 is often elevated to a greater degree than T_4. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake; 24-h uptake of radioiodine may not be increased. Cold nodules in a MNG should be evaluated in the same way as solitary nodules (see below). Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function and improve clinical features of thyrotoxicosis but do not induce remission. A trial of radioiodine should be considered before subjecting pts, many of whom are elderly, to surgery. Subtotal thyroidectomy provides definitive treatment of goiter and thyrotoxicosis. Pts should be rendered euthyroid with antithyroid drugs before surgical intervention.

TOXIC ADENOMA

A solitary, autonomously functioning thyroid nodule is referred to as *toxic adenoma*. Most cases are cause by somatic activating mutations of the TSH receptor. Thyrotoxicosis is typically mild. A thyroid scan provides a definitive diagnostic test, demonstrating focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland, as activity of the normal thyroid is suppressed. Radioiodine ablation with relatively large doses (e.g., 10–29.9 mCi ^{131}I) is usually the treatment of choice.

THYROID NEOPLASMS

Etiology

Thyroid neoplasms may be benign (adenomas) or malignant (carcinomas). Carcinomas of the follicular epithelium include papillary, follicular, and anaplastic thyroid cancer. Thyroid cancer incidence is ~12/100,000 per year and increases with age. Papillary thyroid cancer is the most common type of thyroid cancer (70–90%). It tends to be multifocal and to invade locally. Follicular thyroid cancer is difficult to diagnose via fine-needle aspiration (FNA) because the distinction between benign and malignant follicular neoplasms rests largely on evidence of invasion into vessels, nerves, or adjacent structures. It tends to spread hematogenously, leading to bone, lung, and CNS metastases. Anaplastic carcinoma is rare, highly malignant, and rapidly fatal. Thyroid lymphoma may arise in the background of Hashimoto's thyroiditis and occurs in the setting of a rapidly expanding thyroid mass. Medullary thyroid carcinoma arises from parafollicular (C) cells producing calcitonin and may occur sporadically or as a familial disorder, sometimes in association with multiple endocrine neoplasia type 2.

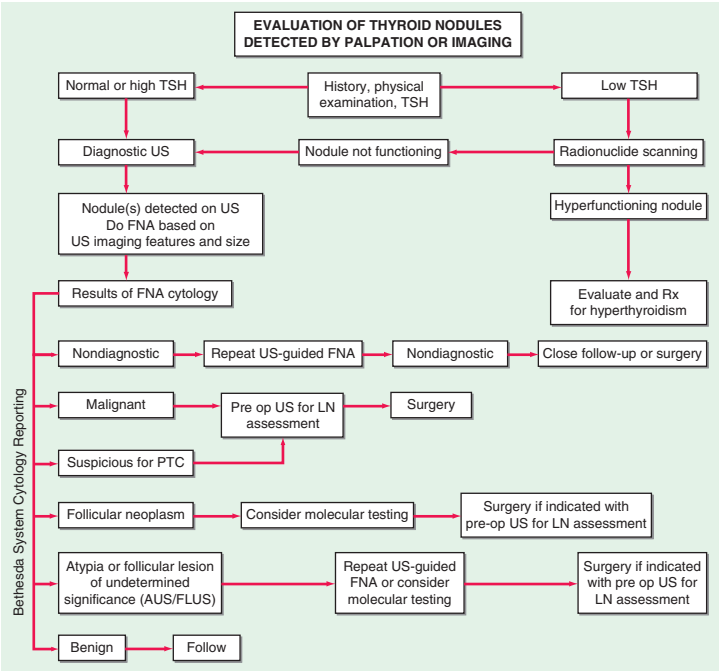


FIGURE 170-4 Approach to the patient with a thyroid nodule. FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone; US, ultrasound.

Clinical Features

Features suggesting carcinoma include recent or rapid growth of a nodule or mass, history of neck irradiation, lymph node involvement, hoarseness, and fixation to surrounding tissues. Glandular enlargement may result in compression and displacement of the trachea or esophagus and obstructive symptoms. Age <20 or >45, male sex, and larger nodule size are associated with a worse prognosis.

Diagnosis

An approach to the evaluation of a solitary nodule is outlined in Fig. 170-4.

TREATMENT THYROID NEOPLASMS

Benign nodules should be monitored via serial examination. TSH suppression with levothyroxine results in decreased nodule size in about 30% of pts. Suppressive therapy should not exceed 6–12 months if unsuccessful.

Follicular adenomas cannot be distinguished from follicular carcinomas on the basis of cytologic analysis of FNA specimens. The extent of surgical resection (lobectomy vs. near-total thyroidectomy) should be discussed prior to surgery.

Near-total thyroidectomy is required for papillary and follicular carcinoma and should be performed by a surgeon who is highly experienced in the procedure. If risk factors and pathologic features indicate the need for radioiodine treatment, the pt should be treated for several weeks postoperatively with liothyronine

(T_3, 25 μg two to three times a day), followed by withdrawal for an additional 2 weeks, in preparation for postsurgical radioablation of remnant tissue. A therapeutic dose of ^{131}I is administered when the TSH level is >25 IU/L. Alternatively, recombinant TSH (0.9 mg) is administered as two daily consecutive injections followed by ^{131}I 24 h after the second injection. This appears to be equally effective as thyroid hormone withdrawal for radioablation therapy. Subsequent levothyroxine suppression of TSH to a low, but detectable, level (0.1–0.5 IU/L) should be attempted in pts with a low risk of recurrence, and to a completely suppressed level in those with a high risk of recurrence. In the latter case, free T_4 should be monitored to avoid overtreatment. Follow-up scans and serum thyroglobulin levels (acting as a tumor marker in an athyreotic pt) should be performed at regular intervals after either thyroid hormone withdrawal or administration of recombinant human TSH.

The management of medullary thyroid carcinoma is surgical, as these tumors do not take up radioiodine. Testing for *RET* mutations should be performed to assess for the presence of MEN 2, and the family should be screened if testing is positive. Following surgery, serum calcitonin provides a marker of residual or recurrent disease.

For a more detailed discussion, see Jameson JL, Mandel SJ, Weetman AP: Disorders of the Thyroid Gland, Chap. 405, p. 2283, in HPIM-19.

171 Adrenal Gland Disorders

The adrenal cortex produces three major classes of steroids: (1) glucocorticoids, (2) mineralocorticoids, and (3) adrenal androgens. Clinical syndromes may result from deficiency or excess of these hormones. The adrenal medulla produces catecholamines, with excess being caused by a pheochromocytoma (Chap. 117).

HYPERFUNCTION OF THE ADRENAL GLAND

CUSHING'S SYNDROME

Etiology

The most common cause of Cushing's syndrome is iatrogenic, due to administration of glucocorticoids for therapeutic reasons. Endogenous Cushing's syndrome results from production of excess cortisol (and other steroid hormones) by the adrenal cortex. The major cause is bilateral adrenal hyperplasia secondary to hypersecretion of adrenocorticotropic hormone (ACTH) by the pituitary (Cushing's disease) or from ectopic sources such as small cell carcinoma of the lung; carcinoids of the bronchus, thymus, gut and ovary, medullary carcinoma of the thyroid; or pheochromocytoma. Adenomas or carcinoma of the adrenal gland account for about 15–20% of endogenous Cushing's syndrome cases. There is a female preponderance in endogenous Cushing's syndrome except for the ectopic ACTH syndrome.

Clinical Features

Some common manifestations (central obesity, hypertension, osteoporosis, psychological disturbances, acne, hirsutism, amenorrhea, and diabetes mellitus) are relatively nonspecific. More specific findings include easy bruising, purple striae, proximal myopathy, fat deposition in the face and nuchal areas (moon facies and buffalo hump), and rarely virilization. Thin, fragile skin and plethoric moon facies also may be found. Hypokalemia and metabolic alkalosis are prominent, particularly with ectopic production of ACTH.

Diagnosis

The diagnosis of Cushing's syndrome requires demonstration of increased cortisol production and abnormal cortisol suppression in response to dexamethasone. For initial screening, measurement of 24-h urinary free cortisol, the 1-mg overnight dexamethasone test [8:00 A.M. plasma cortisol <1.8 μg/dL (50 nmol/L)], or late-night salivary cortisol measurement is appropriate. Repeat testing or performance of more than one screening test may be required. Definitive diagnosis is established in equivocal cases by inadequate suppression of urinary cortisol [<10 μg/d (25 nmol/d)] or plasma cortisol [<5 μg/dL (140 nmol/L)] after 0.5 mg dexamethasone every 6 h for 48 h. Once the diagnosis of Cushing's syndrome is established, further biochemical testing is required to localize the source. This evaluation is best performed by an experienced endocrinologist. Low levels of plasma ACTH levels suggest an adrenal adenoma or carcinoma; inappropriately normal or high plasma ACTH levels suggest a pituitary or ectopic source. In 95% of ACTH-producing pituitary microadenomas, cortisol production is suppressed by high-dose dexamethasone (2 mg every 6 h for 48 h). MRI of the pituitary should be obtained but may not reveal a microadenoma because these tumors are typically very small. Furthermore, because up to 10% of ectopic sources of ACTH may also suppress after high-dose dexamethasone testing, inferior petrosal sinus sampling may be required to distinguish pituitary from peripheral sources of ACTH. Testing with corticotropin-releasing hormone (CRH) also may be helpful in determining the source of ACTH. Imaging of the chest and abdomen is required to localize the source of ectopic ACTH production; small bronchial carcinoids may escape detection by conventional CT. Pts with chronic alcoholism, depression, or obesity may have false-positive results in testing for Cushing's syndrome—a condition named pseudo-Cushing's syndrome. Similarly, pts with acute illness may have abnormal laboratory test results, since major stress alters the normal regulation of ACTH secretion. The management of Cushing's syndrome is summarized in Fig. 171-1.

TREATMENT CUSHING'S SYNDROME

Uncontrolled hypercorticism carries a poor prognosis, and treatment of Cushing's syndrome is therefore necessary. Transsphenoidal surgery for pituitary ACTH-secreting microadenomas is curative in 70–80% when performed by a highly experienced surgeon, but long-term follow-up is required because these tumors may recur. Radiation therapy may be used when a surgical cure is not achieved (Chap. 168). Therapy of adrenal adenoma or carcinoma requires surgical excision; stress doses of glucocorticoids must be given pre- and postoperatively. Metastatic and unresectable adrenal carcinomas are treated with mitotane in doses gradually increased to 6 g/d in three or four divided doses. On occasion, debulking of lung carcinoma or resection of carcinoid tumors can result in remission of ectopic Cushing's syndrome. If the source of ACTH cannot be resected, medical management with ketoconazole (600–1200 mg/d), metyrapone (2–3 g/d), or mitotane (2–3 mg/d) may relieve manifestations of cortisol excess. In some cases, bilateral total adrenalectomy is required to control hypercorticism. Pts with unresectable pituitary adenomas who have had bilateral adrenalectomy are at risk for Nelson's syndrome (aggressive pituitary adenoma enlargement).

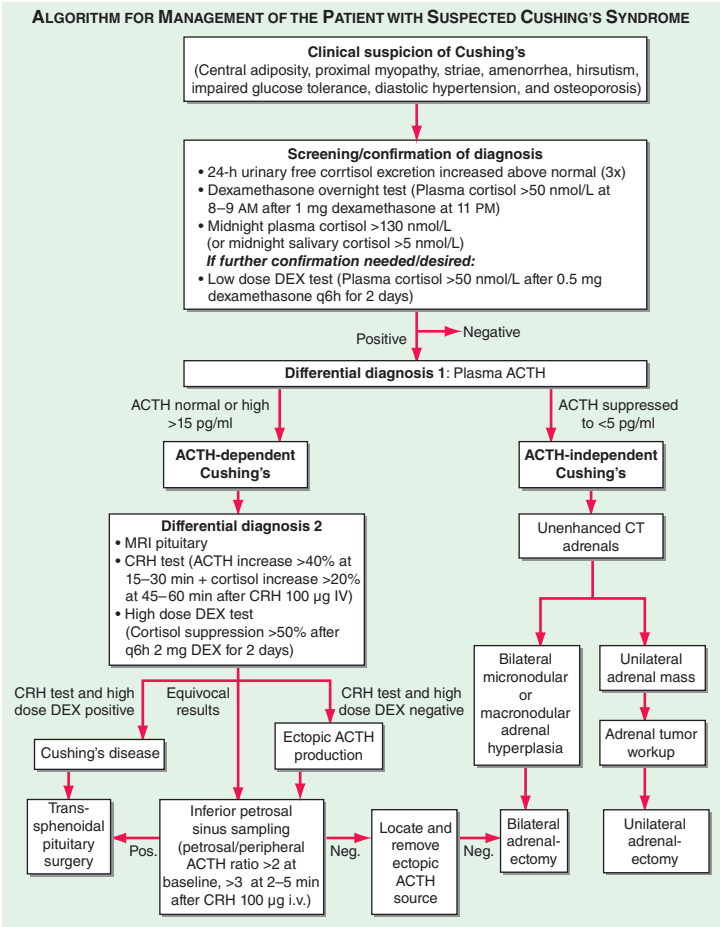


FIGURE 171-1 Management of the patient with suspected Cushing's syndrome. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DEX, dexamethasone.

HYPERALDOSTERONISM

Etiology

Aldosteronism is caused by hypersecretion of the adrenal mineralocorticoid aldosterone. *Primary hyperaldosteronism* refers to an adrenal cause and can be due to either an adrenal adenoma or bilateral adrenal hyperplasia. Rare causes include glucocorticoid-remediable hyperaldosteronism, some forms of congenital adrenal hyperplasia, and other disorders of true or apparent mineralocorticoid excess (see Table 406-3, HPIM-19). The term *secondary hyperaldosteronism* is used when an extraadrenal stimulus for renin secretion is present, as in renal artery stenosis, decompensated liver cirrhosis, or diuretic therapy.

Clinical Features

Most pts with primary hyperaldosteronism have difficult to control hypertension (especially diastolic) and hypokalemia. Headaches are common. Edema is characteristically absent, unless congestive heart failure or renal disease is present. Hypokalemia, caused by urinary potassium losses, may cause muscle weakness, fatigue, and polyuria, although potassium levels may be normal in mild primary hyperaldosteronism. Metabolic alkalosis is a typical feature.

Diagnosis

The diagnosis is suggested by treatment-resistant hypertension that is associated with persistent hypokalemia in a nonedematous pt who is not receiving potassium-wasting diuretics. In pts receiving potassium-wasting diuretics, the diuretic should be discontinued and potassium supplements should be administered for 1–2 weeks. If hypokalemia persists after supplementation, screening using a serum aldosterone and plasma renin activity should be performed. Ideally, antihypertensives should be stopped before testing, but that is often impractical. Aldosterone receptor antagonists, beta-adrenergic blockers, ACE inhibitors, and angiotensin receptor blockers interfere with testing and should be substituted with other antihypertensives if possible. A ratio of serum aldosterone (in ng/dL) to plasma renin activity (in ng/mL per hour) >30 and an absolute level of aldosterone >15 ng/dL suggest primary aldosteronism. Failure to suppress plasma aldosterone (to <5 ng/dL after 500 mL/h of normal saline × 4 h) or urinary aldosterone after saline or sodium loading (to <10 μg/d on day 3 of 200 mmol/d oral NaCl + fludrocortisone 0.2 mg twice daily × 3 days) confirms primary hyperaldosteronism. Caution should be used with sodium loading in a hypertensive pt. Localization should then be undertaken with a high-resolution CT scan of the adrenal glands. If the CT scan is negative, bilateral adrenal vein sampling may be required to diagnose a unilateral aldosterone-producing adenoma. Secondary hyperaldosteronism is associated with elevated plasma renin activity.

TREATMENT HYPERALDOSTERONISM

Surgery can be curative in pts with adrenal adenoma but is not effective for adrenal hyperplasia, which is managed with sodium restriction and spironolactone (25–100 mg twice daily) or eplerenone (25–50 mg twice daily). The sodium channel blocker amiloride (5–10 mg twice a day) also can be used. Secondary hyperaldosteronism is treated with salt restriction and correction of the underlying cause.

SYNDROMES OF ADRENAL ANDROGEN EXCESS

See Chap. 175 for discussion of hirsutism and virilization.

HYPOFUNCTION OF THE ADRENAL GLAND

Primary adrenal insufficiency is due to failure of the adrenal gland, whereas *secondary adrenal insufficiency* is due to failure of ACTH production or release.

ADDISON'S DISEASE

Etiology

Addison's disease occurs when >90% of adrenal tissue is destroyed. The most common cause is autoimmune destruction (alone, or as part of type I or type II polyglandular autoimmune syndromes). Tuberculosis used to be the leading etiology. Other granulomatous diseases (histoplasmosis, coccidioidomycosis, cryptococcosis, sarcoidosis), bilateral adrenalectomy, bilateral tumor metastases, bilateral hemorrhage, CMV, HIV, amyloidosis, and congenital diseases (some types of congenital

adrenal hypoplasia, adrenal hypoplasia congenita, and adrenoleukodystrophy) are additional etiologies.

Clinical Features

Manifestations include fatigue, weakness, anorexia, nausea and vomiting, weight loss, abdominal pain, cutaneous and mucosal pigmentation, salt craving, hypotension (especially orthostatic), and, occasionally, hypoglycemia. Routine laboratory parameters may be normal, but typically serum Na is reduced and serum K increased. Extracellular fluid depletion accentuates hypotension. In secondary adrenal insufficiency, pigmentation is diminished and serum potassium is not elevated. Serum Na tends to be low because of hemodilution stemming from excess vasopressin secreted in the setting of cortisol deficiency.

Diagnosis

The best screening test is the cortisol response 60 min after 250 μg ACTH (cosyntropin) IV or IM. Cortisol levels should exceed 18 μg/dL 30–60 min after the ACTH. If the response is abnormal, then primary and secondary deficiency may be distinguished by measurement of aldosterone from the same blood samples. In secondary, but not primary, adrenal insufficiency, the aldosterone increment from baseline will be normal (≥5 ng/dL). Furthermore, in primary adrenal insufficiency, plasma ACTH is elevated, whereas in secondary adrenal insufficiency, plasma ACTH values are low or inappropriately normal. Pts with recent onset or partial pituitary insufficiency may have a normal response to the rapid ACTH stimulation test. In these pts, alternative testing (metyrapone test or insulin tolerance testing) can be used for diagnosis.

TREATMENT ADDISON'S DISEASE

Hydrocortisone, at 15–25 mg/d divided into $^{2}/_{3}$ in the morning and $^{1}/_{3}$ in the afternoon, is the mainstay of glucocorticoid replacement. Some pts benefit from doses administered three times daily, and other glucocorticoids may be given at equivalent doses. Mineralocorticoid supplementation is usually needed for primary adrenal insufficiency, with administration of 0.05–0.1 mg fludrocortisone PO qd and maintenance of adequate Na intake. Doses should be titrated to normalize Na and K levels and to maintain normal blood pressure without postural changes. Measurement of plasma renin levels may also be useful in titrating the dose. Mineralocorticoid replacement is not needed in pts with secondary adrenal insufficiency. All pts with adrenal insufficiency should be instructed in the parenteral self-administration of steroids and should be registered with a medical alert system. During periods of intercurrent illness, the dose of hydrocortisone should be doubled. During adrenal crisis, high-dose hydrocortisone (10 mg/h continuous IV or 100-mg bolus IV three times a day) should be administered along with normal saline. Thereafter, if the pt is improving and is afebrile, the dose can be tapered by 20–30% daily to usual replacement doses.

HYPOALDOSTERONISM

Isolated aldosterone deficiency accompanied by normal cortisol production occurs with hyporeninism, as an inherited aldosterone synthase deficiency, postoperatively following removal of aldosterone-secreting adenomas (transient), and during protracted heparin therapy. Hyporeninemic hypoaldosteronism is seen most commonly in adults with diabetes mellitus and mild renal failure; it is characterized by mild to moderate hyperkalemia. This is usually a benign condition that can be managed by observation. If needed, oral fludrocortisone (0.05–0.15 mg/d PO) restores electrolyte balance if salt intake is adequate. In pts with hypertension, mild renal insufficiency,

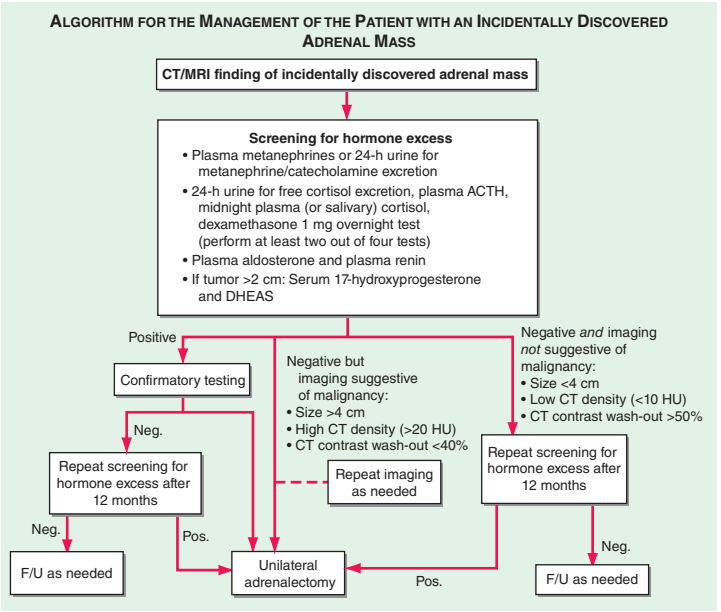


FIGURE 171-2 Management of the patient with an incidentally discovered adrenal mass. F/U, follow-up.

or congestive heart failure, an alternative approach is to reduce salt intake and to administer furosemide.

INCIDENTAL ADRENAL MASSES

Adrenal masses are common findings on abdominal CT or MRI scans (1–7% prevalence with increasing age). The majority (70–80%) of such "incidentalomas" are clinically nonfunctional, and the probability of an adrenal carcinoma is low (<0.01%). Genetic syndromes such as MEN 1, MEN 2, Carney syndrome, and McCune-Albright syndrome are all associated with adrenal masses. The first step in evaluation is to determine the functional status by measurement of plasma free metanephrines to screen for pheochromocytoma (Fig. 171-2). In a pt with a known extraadrenal malignancy, there is a 30–50% chance that the incidentaloma is a metastasis. Additional hormonal evaluation should include 24-h urine for urinary free cortisol or overnight 1-mg dexamethasone suppression testing, plasma renin activity/aldosterone ratio in hypertensives, DHEAS in women with signs of androgen excess, and estradiol in males with feminization. Fine-needle aspiration is rarely indicated and absolutely contraindicated if a pheochromocytoma is suspected. Adrenocortical cancer is suggested by large size (>4–6 cm), irregular margins, tumor inhomogeneity, soft tissue calcifications, and high unenhanced CT attenuation values (>10 HU).

For a more detailed discussion, see Arlt W: Disorders of the Adrenal Cortex, Chap. 406, p. 2309, in HPIM-19.

172 Obesity

Obesity is a state of excess adipose tissue mass. Obesity should not be defined by body weight alone, as muscular individuals may be overweight by arbitrary standards without having increased adiposity. The most widely used method to classify weight status and risk of disease is the *body mass index* (BMI), which is equal to weight/height^2 in kg/m^2 (Table 172-1). At a similar BMI, women have more body fat than men. Furthermore, regional fat distribution may influence the risks associated with obesity. Central (primarily visceral) obesity (high ratio of the circumference of the waist to the circumference of the hips [waist-to-hip ratio], >0.9 in women and 1.0 in men) is independently associated with a higher risk for metabolic syndrome, diabetes mellitus, hyperandrogenism in women, and cardiovascular disease. The prevalence of obesity has increased dramatically over the past 3 decades. In the United States, about 34% of adults age >20 are obese (BMI >30), and another 34% are overweight (BMI 25–30). Most alarming is a similar trend among children, where about 16% of adolescents are obese. This has led to an epidemic of type 2 diabetes in children, a condition almost never seen until recently. These trends to increased obesity are not limited to Western societies but are occurring worldwide.

ETIOLOGY

Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Excess accumulation of body fat is the consequence of environmental and genetic factors; social factors and economic conditions also represent important influences. The recent increase in obesity can be attributed to a combination of excess caloric intake and decreasing physical activity. Poorly understood reasons for increased food assimilation due to dietary composition have also been postulated, as have sleep deprivation and an unfavorable gut flora. The susceptibility to obesity is polygenic in nature, and 30–50% of the variability in total fat stores is believed to be genetically determined. Among monogenic causes, mutations in the melanocortin receptor 4 are most common and account for ~1% of obesity in the general population and ~6% in severe, early-onset obesity. Syndromic obesity forms include Prader-Willi syndrome and Laurence-Moon-Biedl syndrome. Other monogenetic or syndromic causes are extremely rare. Secondary causes of obesity include hypothalamic injury, hypothyroidism, Cushing's syndrome, and hypogonadism. Drug-induced weight gain is also common in those who use

TABLE 172-1 CLASSIFICATION OF WEIGHT STATUS AND RISK OF DISEASE

	BMI (kg/m^2)	Obesity Class	Risk of Disease
Underweight	<18.5		
Healthy weight	18.5–24.9		
Overweight	25.0–29.9		Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

Source: Adapted from National Institutes of Health, National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. U.S. Department of Health and Human Services, Public Health Service, 1998.

antidiabetes agents (insulin, sulfonylureas, thiazolidinediones), glucocorticoids, psychotropic agents, mood stabilizers (lithium), antidepressants (tricyclics, monoamine oxidase inhibitors, paroxetine, mirtazapine), or antiepileptic drugs (valproate, gabapentin, carbamazepine). Insulin-secreting tumors can cause overeating and weight gain.

CLINICAL FEATURES

Obesity has major adverse effects on health. Increased mortality from obesity is primarily due to cardiovascular disease, hypertension, gall bladder disease, diabetes mellitus, and several types of cancer, such as cancer of the esophagus, colon, rectum, pancreas, liver, and prostate, and gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries in women. Sleep apnea in severely obese individuals poses serious health risks. Obesity is also associated with an increased incidence of steatohepatitis, gastroesophageal reflux, osteoarthritis, gout, back pain, skin infections, and depression. Hypogonadism in men and infertility in both sexes are prevalent in obesity; in women this may be associated with hyperandrogenism (polycystic ovarian syndrome).

TREATMENT OBESITY

Obesity is a chronic medical condition that requires ongoing treatment and lifestyle modifications. Treatment is important because of the associated health risks, but is made difficult by a limited repertoire of effective therapeutic options. Weight regain after weight loss is common with all forms of therapy. The urgency and selection of treatment modalities should be based on BMI and a risk assessment.

Diet, exercise, and behavior therapy are recommended for all pts with a BMI ≥25 kg/m^2. Behavior modification including group counseling, diet diaries, and changes in eating patterns should be initiated. Food-related behaviors should be monitored carefully (avoid cafeteria-style settings, eat small and frequent meals, eat breakfast). A deficit of 7500 kcal will produce a weight loss of approximately 1 kg. Therefore, eating 100 kcal/d less for a year should cause a 5-kg weight loss, and a deficit of 1000 kcal/d should cause a loss of ~1 kg per week. Physical activity should be increased to a minimum of 150 min of moderate intensity physical activity per week.

Pharmacotherapy may be added to a lifestyle program for pts with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with concomitant obesity-related diseases. Orlistat (120 mg po tid), an inhibitor of intestinal lipase, causes modest weight loss (9–10% at 12 months with lifestyle measures) due to drug-induced fat malabsorption. Lorcaserin and phentermine/topiramate are anorexiants that were recently FDA-approved. Response to medications should be assessed after 3 months. Metformin, exenatide, and liraglutide tend to decrease body weight in pts with obesity and type 2 diabetes mellitus, but they are not indicated for pts without diabetes.

Bariatric surgery should be considered for pts with severe obesity (BMI ≥40 kg/m^2) or moderate obesity (BMI ≥35 kg/m^2) associated with a serious medical condition, with repeated failures of other therapeutic approaches, at eligible weight for >3 years, capable of tolerating surgery, and without addictions or major psychopathology. Weight-loss surgeries are either restrictive (limiting the amount of food the stomach can hold and slowing gastric emptying), such as laparoscopic adjustable silicone gastric banding, or restrictive-malabsorptive, such as Roux-en-Y gastric bypass (Fig. 172-1). These procedures generally produce a 30–35% weight loss that is maintained in about 40% of pts at 4 years. In many patients, there is significant improvement in co-morbid conditions including type 2 diabetes mellitus, hypertension, sleep apnea, hyperlipidemia, and cardiovascular

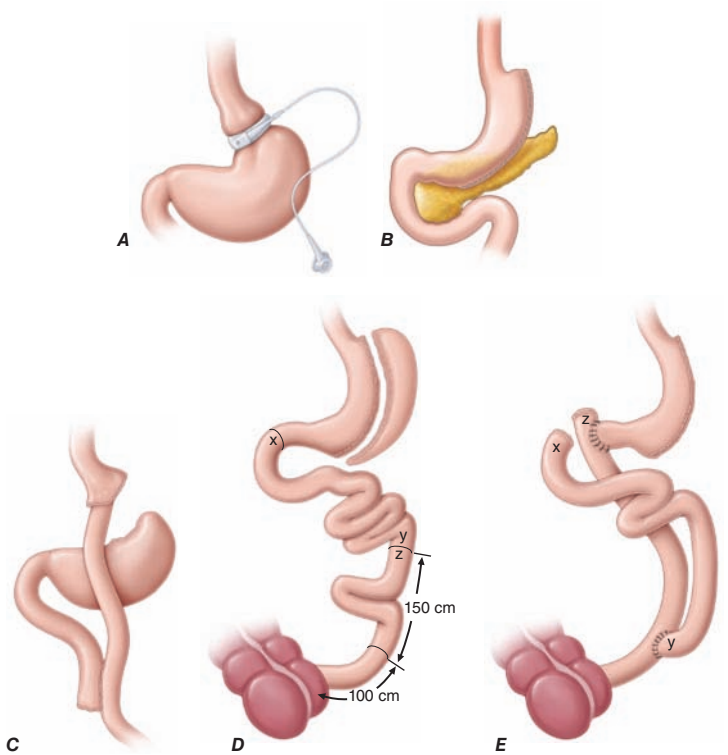


FIGURE 172-1 Bariatric surgical procedures. Examples of operative interventions used for surgical manipulation of the gastrointestinal tract. ***A.*** Laparoscopic adjustable gastric banding. ***B.*** Laparoscopic sleeve gastrectomy. ***C.*** The Roux-en-Y gastric bypass. ***D.*** Biliopancreatic diversion with duodenal switch. ***E.*** Biliopancreatic diversion. *(From ML Kendrick, GF Dakin: Mayo Clin Proc 815:518, 2006; with permission.)*

events. The metabolic benefits appear to be the combined result of weight loss and physiologic responses of gut hormones and adipose tissue metabolism. Complications include stomal stenosis, marginal ulcers, and dumping syndrome. Procedures with a malabsorptive component require lifelong supplementation of micronutrients (iron, folate, calcium, vitamins B_{12} and D) and are associated with a risk of islet cell hyperplasia and hypoglycemia.



For a more detailed discussion, see Flier JS, Maratos-Flier E: Biology of Obesity, Chap. 415e, and Kushner RF: Evaluation and Management of Obesity, Chap. 416, p. 2392, in HPIM-19.

173 Diabetes Mellitus

ETIOLOGY AND PREVALENCE

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common feature of hyperglycemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycemia. Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis, whereas type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and excessive hepatic glucose production. Other specific types include DM caused by genetic defects (maturity-onset diabetes of the young [MODY] and other rare monogenic disorders), diseases of the exocrine pancreas (chronic pancreatitis, cystic fibrosis, hemochromatosis), endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, protease inhibitors), and pregnancy (gestational DM). The phenotype of these monogenetic and secondary types of DM typically resembles type 2 DM; its severity depends on the degree of beta cell dysfunction and prevailing insulin resistance. Type 1 DM usually results from autoimmune destruction of pancreatic beta cells; it is also known as juvenile-onset diabetes because its peak incidence is in children and adolescents.

The prevalence of DM is increasing rapidly; type 2 DM frequency in particular is rising in parallel with the epidemic of obesity (Chap. 172). Between 1985 and 2013, the worldwide prevalence of DM has risen more than 10-fold, from 30 million to 382 million cases. In the United States, DM prevalence at greater than 8% of the population, increasing with age. A significant portion of persons with DM are undiagnosed.

DM is attended by serious morbidity and significant mortality; it is the fifth leading cause of death worldwide.

DIAGNOSIS

Criteria for the diagnosis of DM include one of the following:

- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL)
- Symptoms of diabetes plus a random blood glucose concentration ≥11.1 mmol/L (≥200 mg/dL)
- 2-h plasma glucose ≥11.1 mmol/L (≥200 mg/dL) during a 75-g oral glucose tolerance test.
- Hemoglobin A_{1c} >6.5%

These criteria should be confirmed by repeat testing on a different day, unless unequivocal hyperglycemia is present.

Two intermediate categories also have been designated:

- Impaired fasting glucose (IFG) for a fasting plasma glucose level of 5.6–6.9 mmol/L (100–125 mg/dL)
- Impaired glucose tolerance (IGT) for plasma glucose levels of 7.8–11.1 mmol/L (140–199 mg/dL) 2 h after a 75-g oral glucose load

Individuals with IFG or IGT do not have DM, but are at substantial risk for developing type 2 DM and cardiovascular disease in the future.

Screening with a fasting plasma glucose level is recommended every 3 years for individuals over the age of 45, as well as for younger individuals who are

TABLE 173-1 CRITERIA FOR TESTING FOR PRE-DIABETES AND DIABETES IN ASYMPTOMATIC INDIVIDUALS[a]

Risk Factors
• First-degree relative with diabetes
• Physical inactivity
• Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
• Previously identified IFG, IGT, or a hemoglobin A_{1C} of 5.7–6.4%
• History of GDM or delivery of baby >4 kg (>9 lb)
• Hypertension (blood pressure ≥140/90 mmHg)
• HDL cholesterol level ≤0.90 mmol/L (35 mg/dL) and/or a triglyceride level ≥2.82 mmol/L (250 mg/dL)
• Polycystic ovary syndrome or acanthosis nigricans
• History of vascular disease

[a]Testing should be considered in all adults at age 45 and adults <45 years with BMI ≥25 kg/m^2 and one or more of the following risk factors for diabetes.

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Source: Adapted from American Diabetes Association: *Diabetes Care 37*(Suppl 1): S14, 2014.

overweight (body mass index ≥25 kg/m^2) and have one or more additional risk factors (Table 173-1).

The *metabolic syndrome (*also known as *insulin resistance syndrome* or *syndrome X)* is a term used to describe a commonly found constellation of metabolic derangements that includes insulin resistance (with or without diabetes), hypertension, dyslipidemia, central or visceral obesity, and endothelial dysfunction and is associated with accelerated cardiovascular disease (Chap. 118).

CLINICAL FEATURES

Common presenting symptoms of DM include polyuria, polydipsia, weight loss, fatigue, weakness, blurred vision, frequent superficial infections, and poor wound healing. In early type 2 DM, symptoms may be more subtle and consist of fatigue, poor wound healing, and paresthesias. The lack of symptoms is the main reason for the delayed diagnosis of type 2 DM. Many pts are diagnosed based on screening or during blood tests taken for other reasons. A complete medical history should be obtained with special emphasis on weight, exercise, smoking, ethanol use, family history of DM, and risk factors for cardiovascular disease. In a pt with established DM, assessment of prior diabetes care, HbA_{1c} levels, self-monitoring blood glucose results, frequency of hypoglycemia, and pt's knowledge about DM should be obtained. Special attention should be given on physical examination to retinal examination, bp, foot examination (including vibratory sensation and monofilament testing), peripheral pulses, and insulin injection sites. Acute complications of DM that may be seen on presentation include diabetic ketoacidosis (DKA) (type 1 DM) and hyperglycemic hyperosmolar state (type 2 DM) (Chap. 23).

The chronic complications of DM are listed below:

- *Ophthalmologic:* nonproliferative or proliferative diabetic retinopathy, macular edema, rubeosis of iris, glaucoma, cataracts

- *Renal:* proteinuria, end-stage renal disease (ESRD), type IV renal tubular acidosis
- *Neurologic:* distal symmetric polyneuropathy, polyradiculopathy, mononeuropathy, autonomic neuropathy
- *Gastrointestinal:* gastroparesis, diarrhea, constipation
- *Genitourinary:* cystopathy, erectile dysfunction, female sexual dysfunction, vaginal candidiasis
- *Cardiovascular:* coronary artery disease, congestive heart failure, peripheral vascular disease, stroke
- *Lower extremity:* foot deformity (hammer toe, claw toe, Charcot foot), ulceration, amputation
- *Dermatologic:* Infections (folliculitis, furunculosis, cellulitis), necrobiosis, poor healing, ulcers, gangrene
- *Dental:* Periodontal disease

TREATMENT DIABETES MELLITUS

Optimal treatment of DM requires more than plasma glucose management. Comprehensive diabetes care should also detect and manage DM-specific complications and modify risk factors for DM-associated diseases. The pt with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose. In general, the target HbA_{1c} level should be <7.0%, although individual considerations (age, ability to implement a complex treatment regimen, and presence of other medical conditions) should also be taken into account. Intensive therapy reduces long-term complications but is associated with more frequent and more severe hypoglycemic episodes. Goal preprandial capillary plasma glucose levels should be 3.9–7.2 mmol/L (70–130 mg/dL) and postprandial levels should be <10.0 mmol/L (<180 mg/dL) 1–2 h after a meal.

In general, pts with type 1 DM require 0.5–1.0 U/kg per day of insulin divided into multiple doses. Combinations of insulin preparations with different times of onset and duration of action should be used (**Table 173-2**). Preferred regimens include injection of glargine at bedtime with preprandial lispro, glulisine, or insulin aspart or continuous SC insulin using an infusion device. Pramlintide, an injectable amylin analogue, can be used as adjunct therapy to control postprandial glucose excursions.

Pts with type 2 DM may be managed with diet and exercise alone or in conjunction with oral glucose-lowering agents, insulin, or a combination of oral agents and insulin. The classes of oral glucose-lowering agents and dosing regimens are listed in **Table 173-3**. In addition, exenatide and liraglutide are injectable glucagon-like peptide 1 (GLP-1, an incretin) analogues that may be used in combination with metformin or sulfonylureas. A reasonable treatment algorithm for initial therapy proposes metformin as initial therapy because of its efficacy (1–2% decrease in HbA_{1c}), known side-effect profile, and relatively low cost (**Fig. 173-1**). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, improves the lipid profile slightly, lowers cancer risk, and does not cause hypoglycemia when used as monotherapy, although it is contraindicated in renal insufficiency, congestive heart failure, any form of acidosis, liver disease, or severe hypoxia, and should be temporarily discontinued in pts who are seriously ill or receiving radiographic contrast material. Metformin therapy can be followed by addition of a second oral agent (insulin secretagogue, DPP-IV inhibitor, thiazolidinedione, α-glucosidase inhibitor, or SLGT2 inhibitor). Combinations of two oral agents may be used with additive effects, with stepwise addition of bedtime insulin or a third oral agent if adequate control is not achieved. As endogenous insulin production falls, multiple injections of long-acting and short-acting insulin may be required, as in type

TABLE 173-2 PROPERTIES OF INSULIN PREPARATIONS[a]

Preparation	Time of Action		
	Onset, h	Peak, h	Effective Duration, h
Short-acting			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro	<0.25	0.5–1.5	2–4
Regular	0.5–1.0	2–3	3–6
Long-acting			
Detemir	1–4	—[b]	12-24[c]
Glargine	2–4	—[b]	20–24
NPH	2–4	4–10	10–16
Insulin combinations[d]			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual[e]	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual[e]	15–18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual[e]	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual[e]	10–16

[a]Insulin preparations available in the United States; others are available in the United Kingdom and Europe.
[b]Glargine and detemir have minimal peak activity.
[c]Duration is dose-dependent (shorter at lower doses).
[d]Other insulin combinations are available
[e]Dual: two peaks—one at 2–3 h and the second one several hours later.
Source: Adapted from FR Kaufman: *Medical Management of Type 1 Diabetes, 6th edition*. Alexandria, VA: American Diabetes Association, 2012.

1 DM. Individuals who require >1 U/kg per day of long-acting insulin should be considered for combination therapy with an insulin-sensitizing agent such as metformin or a thiazolidinedione. Insulin-requiring type 2 DM pts may also benefit from addition of pramlintide.

Bariatric surgery should be considered in selected pts (Chap. 172).

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 173-4). A routine urinalysis may be performed as an initial screen for diabetic nephropathy. If it is positive for protein, quantification of protein on a 24-h urine collection should be performed. If the urinalysis is negative for protein, a spot collection for microalbuminuria should be performed (present if 30–300 μg/mg creatinine on two of three tests within a 3- to 6-month period). A resting ECG should be performed in adults, with more extensive cardiac testing for high-risk pts. Therapeutic goals to prevent complications of DM include management of proteinuria with ACE inhibitor or angiotensin receptor blocker therapy, bp control (<130/80 mmHg if no proteinuria, <125/75 if proteinuria), and dyslipidemia management (LDL <2.6 mmol/L [<100 mg/dL], HDL >1.1 mmol/L [>40 mg/dL] in men and >1.38 mmol/L [50 mg/dL] in women, triglycerides <1.7 mmol/L [<150 mg/dL]). In addition, any diabetic pt >40 years should take a statin, regardless of the LDL cholesterol, and in those with existing cardiovascular disease, the LDL target should be <1.8 mmol/L (70 mg/dL).

TABLE 173-3 AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%)[b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis	Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women) (see text), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action	Alogliptin, Anagliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia		Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor–induced angioedema
Insulin secretagogues: Sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease

Insulin secretagogues: Nonsulfonylureas[c,***]	↑ Insulin secretion	Nateglinide, repaglinide, mitiglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium-glucose co-transporter 2 inhibitors[***]	↑ Urinary glucose excretion	Canagliflozin, dapagliflozin, empagliflozin	0.5–1.0	Insulin secretion and action independent	Urinary and vaginal infections, dehydration, exacerbate tendency to hyperkalemia	Limited clinical experience; moderate renal insufficiency
Thiazolidinediones[c,***]	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists[c,d,***]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists[c,***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Exenatide, liraglutide, dulaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid
Insulin[c,d,****]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table 418-4 in HPIM-19	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	

(*Continued*)

TABLE 173-3 AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE 2 DIABETES (*CONTINUED*)

	Mechanism of Action	Examples[a]	HbA_{1c} Reduction (%)[b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Medical nutrition therapy and physical activity[c,*]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

[a]Examples are approved for use in at least one country, but may not be available in the United States or all countries. Examples may not include all agents in the class.
[b]HbA*1c* reduction (absolute) depends partly on starting HbA_{1c}.
[c]Used for treatment of type 2 diabetes.
[d]Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent: *low, **moderate, ***high, ****variable.
Note: Some agents used to treat type 2 DM are not included in table (see text).
Abbreviations: CV, cardiovascular; HbA_{1c}, hemoglobin A_{1c}.

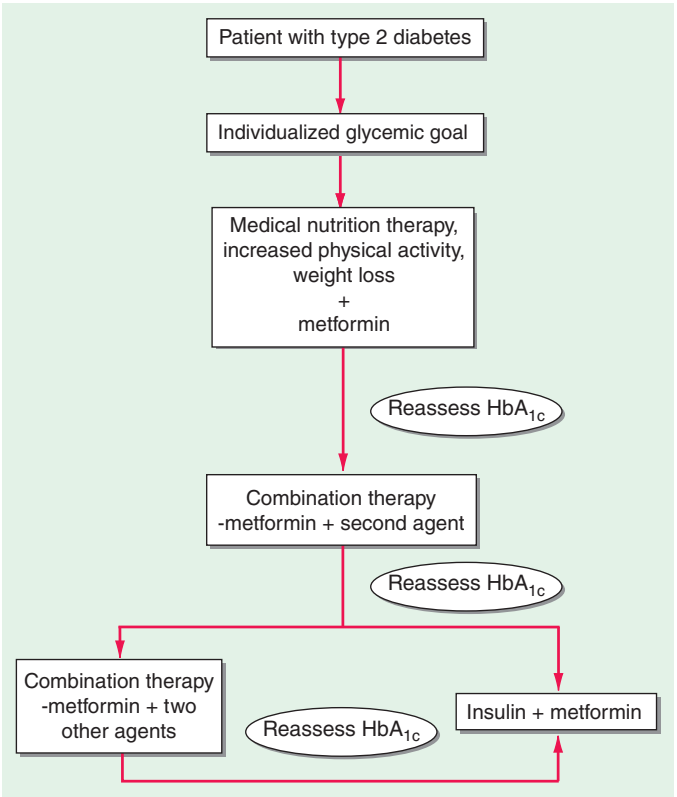


FIGURE 173-1 Glycemic management of type 2 diabetes. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SLGT2 inhibitors, and insulin. HbA_{1c}, hemoglobin HbA_{1c}.

MANAGEMENT OF THE HOSPITALIZED PATIENT

The goals of diabetes management during hospitalization are near-normal glycemic control, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. Pts with type 1 DM undergoing general anesthesia and surgery, or with serious illness, should receive continuous insulin, either through an IV insulin infusion or by SC administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient to prevent the onset of diabetic ketoacidosis. Oral hypoglycemic agents should be discontinued in pts with type 2 DM at the time of hospitalization. Either regular insulin infusion (0.05–0.15 U/kg per hour) or a reduced dose (by 30–50%) of long-acting insulin and short-acting insulin (held, or reduced by 30–50%), with infusion of a solution of 5% dextrose, should be administered when pts are NPO for a procedure. A regimen of long- and short-acting SC insulin should be used in type 2 pts who are eating. The glycemic goal for hospitalized pts with DM should be a preprandial glucose of <7.8 mmol/L (<140 mg/dL) and <10 mmol/L (<180 mg/dL) at post-meal times. For critically ill pts,

TABLE 173-4 GUIDELINES FOR ONGOING, COMPREHENSIVE MEDICAL CARE FOR PATIENTS WITH DIABETES

- Optimal and individualized glycemic control
- Self-monitoring of blood glucose (individualized frequency)
- HbA_{1c} testing (2–4 times/year)
- Patient education in diabetes management (annual); diabetes-self management education and support
- Medical nutrition therapy and education (annual)
- Eye examination (annual or biannual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual)
- Blood pressure measurement (quarterly)
- Lipid profile and serum creatinine (estimate GFR) (annual)
- Influenza/pneumococcal/hepatitis B immunizations
- Consider antiplatelet therapy

Abbreviations: HbA_{1c}, hemoglobin A_{1c}.

glucose levels of 7.8–10.0 mmol/L (140–180 mg/dL) are recommended. Those with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored after the procedure.

For a more detailed discussion, see Powers AC: Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology Chap. 417, p. 2399; Powers AC: Diabetes Mellitus: Management and Therapies, Chap. 418, p. 2407; and Powers AC: Diabetes Mellitus: Complications Chap. 419, p. 2422, in HPIM-19.

174 Disorders of the Male Reproductive System

The testes produce sperm and testosterone. Inadequate production of sperm can occur in isolation or in the presence of androgen deficiency, which impairs spermatogenesis secondarily.

ANDROGEN DEFICIENCY

Etiology

Androgen deficiency can be due to either testicular failure (*primary hypogonadism*) or hypothalamic-pituitary defects (*secondary hypogonadism*).

Primary hypogonadism is diagnosed when testosterone levels are low and gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are high. Klinefelter's syndrome is the most common cause (~1 in 1000 male births) and is due to the presence of one or more extra X chromosomes, usually a 47,XXY karyotype. Other genetic causes of testicular development, androgen biosynthesis, or androgen action are uncommon. Acquired primary testicular failure usually results from viral orchitis but may be due to trauma, testicular torsion, cryptorchidism, radiation damage, or systemic diseases such as amyloidosis, Hodgkin's disease, sickle cell disease, or granulomatous diseases. Testicular failure can occur as a part of polyglandular autoimmune failure syndrome. Malnutrition, AIDS, renal failure, liver cirrhosis, myotonic dystrophy, paraplegia, and toxins such as alcohol, marijuana, heroin, methadone, lead, and antineoplastic and chemotherapeutic agents also can cause testicular failure. Testosterone synthesis may be blocked by ketoconazole, and testosterone action may be blocked at the androgen receptor level by spironolactone or cimetidine.

Secondary hypogonadism is diagnosed when levels of both testosterone and gonadotropins are low (*hypogonadotropic hypogonadism*). Kallmann syndrome is due to maldevelopment of neurons producing gonadotropin-releasing hormone (GnRH) and is characterized by GnRH deficiency, low levels of LH and FSH, and anosmia. Several other types of GnRH deficiency or gonadotropin deficiency present without anosmia. Acquired causes of isolated hypogonadotropic hypogonadism include critical illness, excessive stress, obesity, Cushing's syndrome, opioid and marijuana use, hemochromatosis, and hyperprolactinemia (due to pituitary adenomas or drugs such as phenothiazines). Destruction of the pituitary gland by tumors, infection, trauma, or metastatic disease causes hypogonadism in conjunction with deficiency of other pituitary hormones (see Chap. 168). Normal aging is associated with a progressive decline of testosterone production, which is due to downregulation of the entire hypothalamo-pituitary-testicular axis.

Clinical Features

The history should focus on developmental stages such as puberty and growth spurts, as well as androgen-dependent events such as early morning erections, frequency and intensity of sexual thoughts, and frequency of masturbation or intercourse. The physical examination should focus on secondary sex characteristics such as hair growth on the face, axilla, chest, and pubic regions; gynecomastia; testicular volume; prostate; and height and body proportions. Eunuchoidal proportions are defined as an arm span >2 cm greater than height and suggest that androgen deficiency occurred prior to epiphyseal fusion. Normal testicular size ranges from 3.5 to 5.5 cm in length, which corresponds to a volume of 12–25 mL. The presence of varicocele should be sought by palpation of the testicular veins with the pt standing. Pts with Klinefelter's syndrome have small (1–2 mL), firm testes.

A morning total testosterone level <10.4 nmol/L (<300 ng/dL), in association with symptoms, suggests testosterone deficiency. A level of >12.1 nmol/L (>350 ng/dL) makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 6.9 and 12.1 nmol/L (200 and 350 ng/dL), the total testosterone level should be repeated and a free testosterone level should be measured by a reliable method. In older men and in pts with other clinical states that are associated with alterations in sex hormone–binding globulin levels, a direct measurement of free testosterone by equilibrium dialysis can be useful to confirm testosterone deficiency. When androgen deficiency has been found, LH should be measured to classify the pt as having primary (high LH) or secondary (low or inappropriately normal LH) hypogonadism. In men with primary hypogonadism of unknown cause, a karyotype should be performed to exclude Klinefelter's syndrome. Measurement of a prolactin level and MRI of the hypothalamic-pituitary region should be considered in men with secondary hypogonadism. Gynecomastia in the absence of androgen deficiency should be further evaluated (Fig. 174-1).

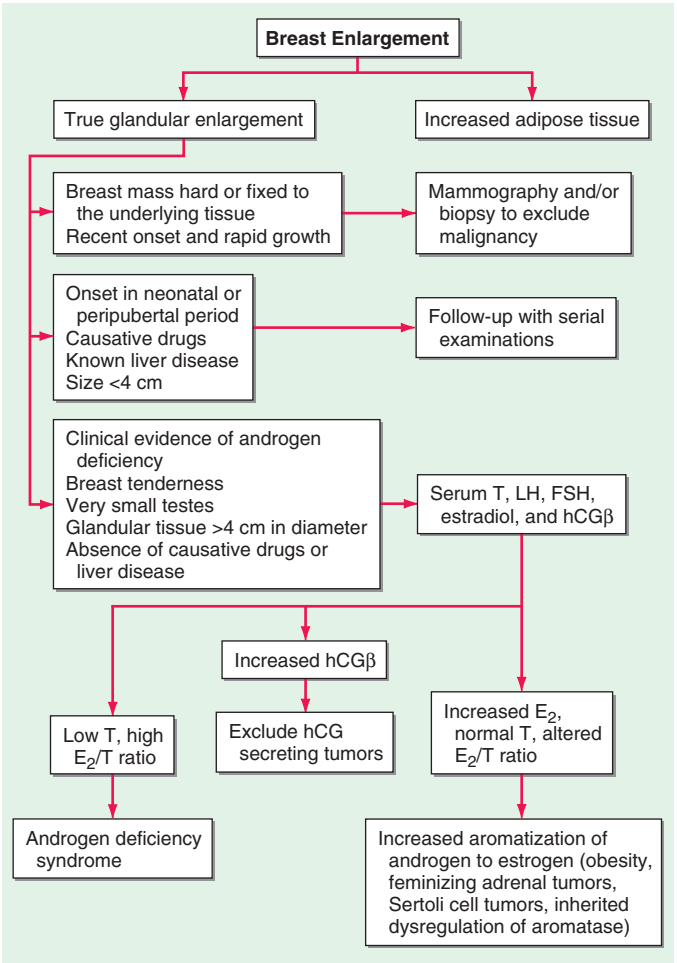


FIGURE 174-1 Evaluation of gynecomastia. E2, 17β-estradiol; FSH, follicle-stimulating hormone; hCGβ, human chorionic gonadotropin β; LH, luteinizing hormone; T, testosterone.

TREATMENT ANDROGEN DEFICIENCY

Treatment of hypogonadal men with androgens restores normal male secondary sexual characteristics (beard, body hair, external genitalia), male sexual drive, and masculine somatic development (hemoglobin, muscle mass), but not fertility. Administration of gradually increasing doses of testosterone is recommended for disorders in which hypogonadism occurred prior to puberty. Testosterone levels in the normal range may be achieved through daily application of transdermal testosterone patches (5–10 mg/d) or gel (50–100 mg/d), parenteral administration of a long-acting testosterone ester (e.g., 100–200 mg testosterone enanthate at 1- to 3-week intervals) or buccal testosterone tablets (30 mg/d). Hct should

be monitored initially during testosterone therapy and the dose lowered if Hct is >54%. Prostate cancer, severe symptoms of lower urinary tract obstruction, baseline Hct >50%, severe sleep apnea, and class IV congestive heart failure are contraindications for androgen replacement. Gonadotropin therapy for secondary hypogonadism should be reserved for fertility induction.

MALE INFERTILITY

Etiology

Male infertility plays a role in 25% of infertile couples (couples who fail to conceive after 1 year of unprotected intercourse). Known causes of male infertility include primary hypogonadism (30–40%), disorders of sperm transport (10–20%), and secondary hypogonadism (2%), with an unknown etiology in up to half of men with suspected male factor infertility. Impaired spermatogenesis occurs with testosterone deficiency but may also be present without testosterone deficiency. Y chromosome microdeletions and substitutions, viral orchitis, tuberculosis, STDs, radiation, chemotherapeutic agents, and environmental toxins have all been associated with isolated impaired spermatogenesis. Prolonged elevations of testicular temperature, as in varicocele, in cryptorchidism, or after an acute febrile illness, may impair spermatogenesis. Ejaculatory obstruction can be a congenital (cystic fibrosis, in utero diethylstilbestrol exposure, or idiopathic) or acquired (vasectomy, accidental ligation of the vas deferens, or obstruction of the epididymis). Androgen abuse by male athletes can lead to testicular atrophy and a low sperm count.

Clinical Features

Evidence of hypogonadism may or may not be present. Testicular size and consistency may be abnormal, and a varicocele may be apparent on palpation. When the seminiferous tubules are damaged prior to puberty, the testes are small (usually <12 mL) and firm, whereas postpubertal damage causes the testes to be soft (the capsule, once enlarged, does not contract to its previous size). The key diagnostic test is a *semen analysis*. Sperm counts of <13 million/mL, motility of <32%, and <9% normal morphology are associated with subfertility. Testosterone levels should be measured if the sperm count is low on repeated exam or if there is clinical evidence of hypogonadism.

TREATMENT MALE INFERTILITY

Men with primary hypogonadism occasionally respond to androgen therapy if there is minimal damage to the seminiferous tubules, whereas those with secondary hypogonadism require gonadotropin therapy to achieve fertility. Fertility occurs in about half of men with varicocele who undergo surgical repair. In vitro fertilization is an option for men with mild to moderate defects in sperm quality; intracytoplasmic sperm injection (ICSI) has been a major advance for men with severe defects in sperm quality.

ERECTILE DYSFUNCTION

Etiology

Erectile dysfunction (ED) is the failure to achieve erection, ejaculation, or both. It affects 10–25% of middle-aged and elderly men. ED may result from three basic mechanisms: (1) failure to initiate (psychogenic, endocrinologic, or neurogenic); (2) failure to fill (arteriogenic); or (3) failure to store adequate blood volume within the lacunar network (venoocclusive dysfunction). Diabetic, atherosclerotic, and drug-related causes account for >80% of cases of ED in older men. The most

common organic cause of ED is vasculogenic; 35–75% of men with diabetes have ED due to a combination of vascular and neurologic complications. Psychogenic causes of ED include performance anxiety, depression, relationship conflict, sexual inhibition, history of sexual abuse in childhood, and fear of pregnancy or sexually transmitted disease. Among the antihypertensive agents, the thiazide diuretics and beta blockers have been implicated most frequently. Estrogens, GnRH agonists and antagonists, H_2 antagonists, and spironolactone suppress gonadotropin production or block androgen action. Antidepressant and antipsychotic agents—particularly neuroleptics, tricyclics, and selective serotonin reuptake inhibitors—are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties. Recreational drugs, including ethanol, cocaine, and marijuana, also may cause ED. Any disorder that affects the sacral spinal cord or the sensory nerves or autonomic fibers innervating the penis may lead to ED.

Clinical Features

Men with sexual dysfunction may complain of loss of libido, inability to initiate or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve orgasm, but frequently are embarrassed to bring up the subject unless specifically asked by the physician. Initial questions should focus on the onset of symptoms, the presence and duration of partial erections, the progression of ED, and ejaculation. Psychosocial history, libido, relationship issues, sexual orientation and sexual practices should be part of the clinical assessment. A history of nocturnal or early morning erections is useful for distinguishing physiologic from psychogenic ED. Relevant risk factors should be identified, such as diabetes mellitus, coronary artery disease, lipid disorders, hypertension, peripheral vascular disease, smoking, alcoholism, and endocrine or neurologic disorders. The pt's surgical history should be explored, with an emphasis on bowel, bladder, prostate, or vascular procedures. Evaluation includes a detailed general as well as genital physical examination. Penile abnormalities (Peyronie's disease), testicular size, and gynecomastia should be noted. Peripheral pulses should be palpated, and bruits should be sought. Neurologic examination should assess anal sphincter tone, perineal sensation, and bulbocavernosus reflex. Serum testosterone and prolactin should be measured. Penile arteriography, electromyography, or penile Doppler ultrasound is occasionally performed.

TREATMENT ERECTILE DYSFUNCTION

Correction of the underlying disorders or discontinuation of responsible medications should be attempted as an initial step. Oral inhibitors of phosphodiesterase-5 (sildenafil, tadalafil, and vardenafil) enhance erections after sexual stimulation, with an onset of approximately 60–120 min. They are contraindicated in men receiving any form of nitrate therapy and should be avoided in those with congestive heart failure. Vacuum constriction devices or injection of alprostadil into the urethra or corpora cavernosa may also be effective. The insertion of a penile prosthesis is reserved for pts with refractory ED.



For a more detailed discussion, see Bhasin S, Jameson JL: Disorders of the Testes and Male Reproductive System, Chap. 411, p. 2357; Hall JE: The Female Reproductive System, Infertility, and Contraception, Chap. 412, p. 2375; and McVary KT: Sexual Dysfunction, Chap. 67, p. 324, in HPIM-19.

175 Disorders of the Female Reproductive System

The pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), stimulate ovarian follicular development and result in ovulation at about day 14 of the 28-day menstrual cycle.

AMENORRHEA

Etiology

Amenorrhea refers to the absence of menstrual periods. It is classified as *primary*, if menstrual bleeding has never occurred by age 15 in the absence of hormonal treatment, or *secondary*, if menstrual periods are absent for >3 months in a woman with previous periodic menses. Pregnancy should be excluded in women of childbearing age with amenorrhea, even when history and physical examination are not suggestive. *Oligomenorrhea* is defined as a cycle length of >35 days or <10 menses per year. Both the frequency and amount of bleeding are irregular in oligomenorrhea. Frequent or heavy irregular bleeding is termed *dysfunctional uterine bleeding* if anatomic uterine lesions or a bleeding diathesis has been excluded.

The causes of primary and secondary amenorrhea overlap, and it is generally more useful to classify disorders of menstrual function into disorders of the uterus and outflow tract and disorders of ovulation (Fig. 175-1).

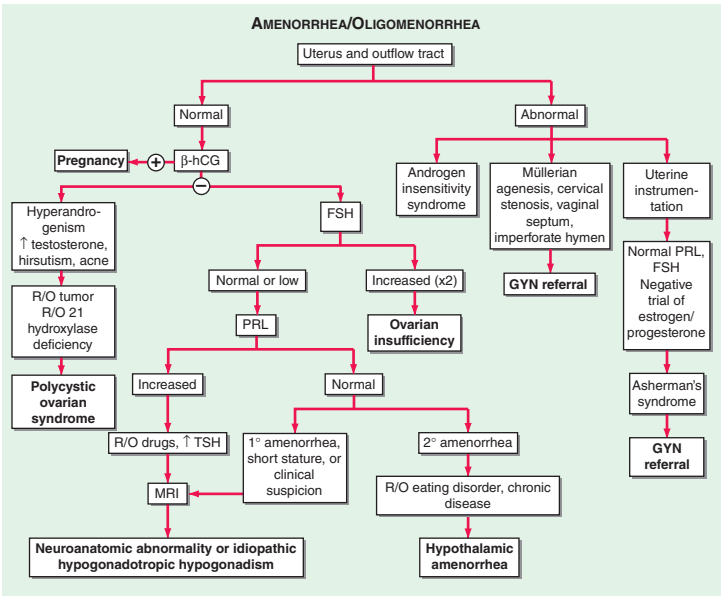


FIGURE 175-1 Algorithm for evaluation of amenorrhea. β-hCG, beta-human chorionic gonadotropin; FSH, follicle-stimulating hormone; GYN, gynecologist; PRL, prolactin; R/O, rule out; TSH, thyroid-stimulating hormone.

Anatomic defects of the outflow tract that prevent vaginal bleeding include absence of vagina or uterus, imperforate hymen, transverse vaginal septae, and cervical stenosis.

Women with amenorrhea and low FSH and LH levels have hypogonadotropic hypogonadism due to disease of either the hypothalamus or the pituitary. Hypothalamic causes include congenital idiopathic hypogonadotropic hypogonadism, hypothalamic lesions (craniopharyngiomas and other tumors, tuberculosis, sarcoidosis, metastatic tumors), hypothalamic trauma or irradiation, vigorous exercise, eating disorders, stress, and chronic debilitating diseases (end-stage renal disease, malignancy, malabsorption). The most common form of hypothalamic amenorrhea is functional, reversible gonadotropin-releasing hormone (GnRH) deficiency due to psychological or physical stress, including excess exercise and anorexia nervosa. Disorders of the pituitary include rare developmental defects, pituitary adenomas, granulomas, postradiation hypopituitarism, and Sheehan's syndrome. They can lead to amenorrhea by two mechanisms: direct interference with gonadotropin production, or inhibition of GnRH secretion via excess prolactin production (Chap. 168).

Women with amenorrhea and high FSH levels have ovarian failure, which may be due to Turner's syndrome, pure gonadal dysgenesis, premature ovarian failure, the resistant-ovary syndrome, and chemotherapy or radiation therapy for malignancy. The diagnosis of premature ovarian failure is applied to women who cease menstruating before age 40.

Polycystic ovarian syndrome (PCOS) is characterized by the presence of clinical or biochemical hyperandrogenism (hirsutism, acne, male pattern baldness) in association with amenorrhea or oligomenorrhea. The metabolic syndrome and infertility are often present; these features are worsened with coexistent obesity. Additional disorders with a similar presentation include excess androgen production from adrenal or ovarian tumors and adult-onset congenital adrenal hyperplasia. Hyperthyroidism may be associated with oligo- or amenorrhea; hypothyroidism more typically with metrorrhagia.

Diagnosis

The initial evaluation involves careful physical examination including assessment of hyperandrogenism, serum or urine human chorionic gonadotropin (hCG), and serum FSH levels (Fig. 175-1). Anatomic defects are usually diagnosed by physical examination, though hysterosalpingography or direct visual examination by hysteroscopy may be required. A karyotype should be performed when gonadal dysgenesis is suspected. The diagnosis of PCOS is based on the coexistence of chronic anovulation and androgen excess, after ruling out other etiologies for these features. The evaluation of pituitary function and hyperprolactinemia is described in Chap. 168. In the absence of a known etiology for hypogonadotropic hypogonadism, MRI of the pituitary-hypothalamic region should be performed when gonadotropins are low or inappropriately normal.

TREATMENT AMENORRHEA

Disorders of the outflow tract are managed surgically. Decreased estrogen production, whether from ovarian failure or hypothalamic/pituitary disease, should be treated with cyclic estrogens, either in the form of oral contraceptives or conjugated estrogens (0.625–1.25 mg/d PO) and medroxyprogesterone acetate (2.5 mg/d PO or 5–10 mg during the last 5 days of the month). PCOS may be treated with medications to induce periodic withdrawal menses (medroxyprogesterone acetate 5–10 mg or progesterone 200 mg daily for 10–14 days of each month, or oral contraceptive agents) and weight reduction, along with treatment of hirsutism and, if desired, ovulation induction (see below). Individuals with PCOS may benefit from insulin-sensitizing drugs, such as metformin, and should be screened for diabetes mellitus.

PELVIC PAIN

Etiology

Pelvic pain may be associated with normal or abnormal menstrual cycles and may originate in the pelvis or be referred from another region of the body. A high index of suspicion must be entertained for extrapelvic disorders that refer to the pelvis, such as appendicitis, diverticulitis, cholecystitis, intestinal obstruction, and urinary tract infections. A thorough history including the type, location, radiation, and status with respect to increasing or decreasing severity can help to identify the cause of acute pelvic pain. Associations with vaginal bleeding, sexual activity, defecation, urination, movement, or eating should be sought. Determination of whether the pain is acute versus chronic, constant versus spasmodic, and cyclic versus noncyclic will direct further investigation (Table 175-1).

Acute Pelvic Pain

Pelvic inflammatory disease most commonly presents with bilateral lower abdominal pain. Unilateral pain suggests adnexal pathology from rupture, bleeding, or torsion of ovarian cysts, or, less commonly, neoplasms of the ovary, fallopian tubes, or paraovarian areas. Ectopic pregnancy is associated with right- or left-sided lower abdominal pain, vaginal bleeding, and menstrual cycle abnormalities, with clinical signs appearing 6–8 weeks after the last normal menstrual period. Orthostatic signs and fever may be present. Uterine pathology includes endometritis and degenerating leiomyomas.

Chronic Pelvic Pain

Many women experience lower abdominal discomfort with ovulation (*mittelschmerz*), characterized as a dull, aching pain at midcycle that lasts minutes to hours. In addition, ovulatory women may experience somatic symptoms during the few days prior to menses, including edema, breast engorgement, and abdominal bloating or discomfort. A symptom complex of cyclic irritability, depression, and lethargy is known as *premenstrual syndrome* (PMS). Severe or incapacitating cramping with ovulatory menses in the absence of demonstrable disorders of the pelvis is termed *primary dysmenorrhea*. *Secondary dysmenorrhea* is caused by underlying pelvic pathology such as endometriosis, adenomyosis, or cervical stenosis.

Diagnosis

Evaluation includes a history, pelvic examination, hCG measurement, tests for chlamydial and gonococcal infections, and pelvic ultrasound. Laparoscopy or laparotomy is indicated in some cases of pelvic pain of undetermined cause.

TABLE 175-1 CAUSES OF PELVIC PAIN

	Acute	Chronic
Cyclic pelvic pain		Premenstrual symptoms
		Mittelschmerz
		Dysmenorrhea
		Endometriosis
Noncyclic pelvic pain	Pelvic inflammatory disease	Pelvic congestion syndrome
	Ruptured or hemorrhagic ovarian cyst or ovarian torsion	Adhesions and retroversion of the uterus
	Ectopic pregnancy	Pelvic malignancy
	Endometritis	Vulvodynia
	Acute growth or degeneration of uterine myoma	Chronic pelvic inflammatory disease
		History of sexual abuse

TREATMENT PELVIC PAIN

Primary dysmenorrhea is best treated with NSAIDs or oral contraceptive agents. Secondary dysmenorrhea not responding to NSAIDs suggests pelvic pathology, such as endometriosis. Infections should be treated with the appropriate antibiotics. Symptoms from PMS may improve with selective serotonin reuptake inhibitor (SSRI) therapy. The majority of unruptured ectopic pregnancies are treated with methotrexate, which has 85–95% success rate. Surgery may be required for structural abnormalities.

HIRSUTISM

Etiology

Hirsutism, defined as excessive male-pattern hair growth, affects ~10% of women. It may be familial or caused by PCOS, ovarian or adrenal neoplasms, congenital adrenal hyperplasia, Cushing's syndrome, pregnancy, and drugs (androgens, oral contraceptives containing androgenic progestins). Other drugs, such as minoxidil, phenytoin, diazoxide, and cyclosporine, can cause excessive growth of non-androgen-dependent vellus hair, leading to hypertrichosis.

Clinical Features

An objective clinical assessment of hair distribution and quantity is central to the evaluation. A commonly used method to grade hair growth is the Ferriman-Gallwey score (see Fig. 68-1, p. 333, in HPIM-19). Associated manifestations of androgen excess include acne and male-pattern balding (androgenic alopecia). *Virilization*, on the other hand, refers to the state in which androgen levels are sufficiently high to cause deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido. Historic elements include menstrual history and the age of onset, rate of progression, and distribution of hair growth. Sudden development of hirsutism, rapid progression, and virilization suggests an ovarian or adrenal neoplasm.

Diagnosis

An approach to testing for androgen excess is depicted in Fig. 175-2. PCOS is a relatively common cause of hirsutism. The dexamethasone androgen-suppression test (0.5 mg PO every 6 h × 4 days, with free testosterone levels obtained before and after administration of dexamethasone) may distinguish ovarian from adrenal overproduction. Incomplete suppression suggests ovarian androgen excess. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency can be excluded by a 17-hydroxyprogesterone level that is <6 nmol/L (<2 μg/L) either in the morning during the follicular phase or 1 h after administration of 250 μg of cosyntropin. CT may localize an adrenal mass, and ultrasound may identify an ovarian mass, if evaluation suggests these possibilities.

TREATMENT HIRSUTISM

Treatment of a remediable underlying cause (e.g., Cushing's syndrome, adrenal or ovarian tumor) also improves hirsutism. In idiopathic hirsutism or PCOS, symptomatic physical or pharmacologic treatment is indicated. Nonpharmacologic treatments include (1) bleaching; (2) depilatory such as shaving and chemical treatments; and (3) epilatory such as plucking, waxing, electrolysis, and laser therapy. Pharmacologic therapy includes oral contraceptives with a low androgenic progestin and spironolactone (100–200 mg/d PO), often in combination. Flutamide is also effective as an antiandrogen, but its use is

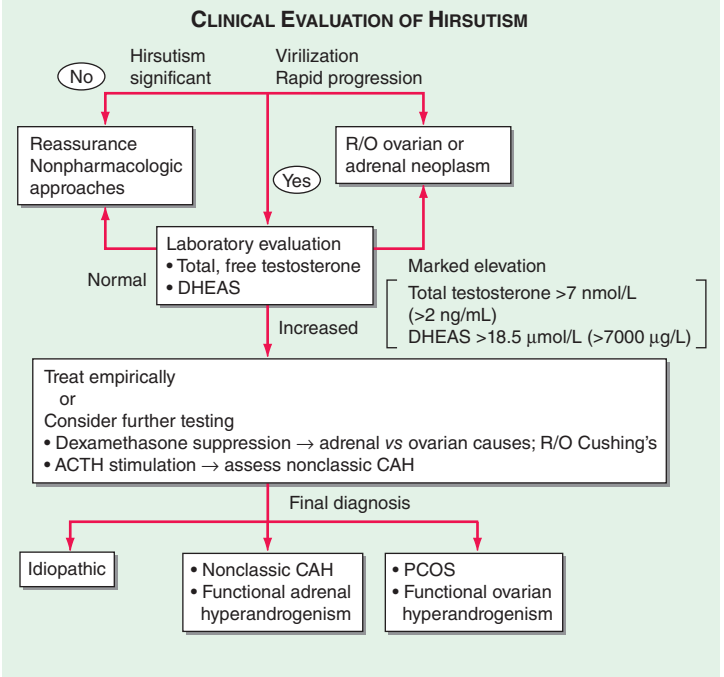


FIGURE 175-2 Algorithm for the evaluation and differential diagnosis of hirsutism. ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; DHEAS, sulfated form of dehydroepiandrosterone; PCOS, polycystic ovarian syndrome; R/O, rule out.

limited by hepatotoxicity. Glucocorticoids (dexamethasone, 0.25–0.5 mg at bedtime, or prednisone, 5–10 mg at bedtime) are the mainstay of treatment in pts with congenital adrenal hyperplasia. Attenuation of hair growth with pharmacologic therapy is typically not evident until 6 months after initiation of medical treatment and therefore should be used in conjunction with nonpharmacologic treatments.

MENOPAUSE

Etiology

Menopause is defined as the final episode of menstrual bleeding and occurs at a median age of 51 years. It is the consequence of depletion of ovarian follicles or of oophorectomy. The onset of *perimenopause*, when fertility wanes and menstrual irregularity increases, precedes the final menses by 2–8 years.

Clinical Features

The most common menopausal symptoms are vasomotor instability (hot flashes and night sweats), mood changes (nervousness, anxiety, irritability, and depression), insomnia, and atrophy of the urogenital epithelium and skin. FSH levels are elevated to ≥40 IU/L with estradiol levels that are <30 pg/mL.

TREATMENT MENOPAUSE

During perimenopause, low-dose combined oral contraceptives may be of benefit. The rational use of postmenopausal hormone therapy requires balancing the potential benefits and risks. Concerns include increased risks of endometrial cancer, breast cancer, thromboembolic disease, and gallbladder disease, as well as probably increased risks of stroke, cardiovascular events, and ovarian cancer. Benefits include a delay in postmenopausal bone loss and probably decreased risks of colorectal cancer and diabetes mellitus. Short-term therapy (<5 years) may be beneficial in controlling intolerable symptoms of menopause, as long as no contraindications exist. These include unexplained vaginal bleeding, active liver disease, venous thromboembolism, history of endometrial cancer (except stage I without deep invasion), breast cancer, preexisting cardiovascular disease, and diabetes. Hypertriglyceridemia (>400 mg/dL) and active gallbladder disease are relative contraindications. Alternative therapies for symptoms include venlafaxine, fluoxetine, paroxetine, gabapentin, clonidine, vitamin E, or soy-based products. Vaginal estradiol tablets may be used for genitourinary symptoms. Long-term therapy (≥5 years) should be undertaken only after careful consideration, particularly in light of alternative therapies for osteoporosis (bisphosphonates, raloxifene) and of the risks of venous thromboembolism and breast cancer. Estrogens should be given in the minimal effective doses (conjugated estrogen, 0.625 mg/d PO; micronized estradiol, 1.0 mg/d PO; or transdermal estradiol, 0.05–1.0 mg once or twice a week). Women with an intact uterus should be given estrogen in combination with a progestin (medroxyprogesterone either cyclically, 5–10 mg/d PO for days 15–25 each month, or continuously, 2.5 mg/d PO) to avoid the increased risk of endometrial carcinoma seen with unopposed estrogen use.

CONTRACEPTION

The most widely used methods for fertility control include (1) barrier methods, (2) oral contraceptives, (3) intrauterine devices, (4) long-acting progestins, (5) sterilization, and (6) abortion.

Oral contraceptive agents are widely used for both prevention of pregnancy and control of dysmenorrhea and anovulatory bleeding. Combination oral contraceptive agents contain synthetic estrogen (ethinyl estradiol or mestranol) and synthetic progestins. Some progestins possess an inherent androgenic action. Low-dose norgestimate and third-generation progestins (desogestrel, gestodene, drospirenone) have a less androgenic profile; levonorgestrel appears to be the most androgenic of the progestins and should be avoided in pts with hyperandrogenic symptoms. The three major formulation types include fixed-dose estrogen-progestin, phasic estrogen-progestin, and progestin only.

Despite overall safety, oral contraceptive users are at risk for venous thromboembolism, hypertension, and cholelithiasis. Risks for myocardial infarction and stroke are increased with smoking and aging. Side effects, including breakthrough bleeding, amenorrhea, breast tenderness, and weight gain, are often responsive to a change in formulation.

Absolute contraindications to the use of oral contraceptives include previous thromboembolic disorders, cerebrovascular or coronary artery disease, carcinoma of the breasts or other estrogen-dependent neoplasia, liver disease, hypertriglyceridemia, heavy smoking with age over 35, undiagnosed uterine bleeding, or known or suspected pregnancy. Relative contraindications include hypertension and anticonvulsant drug therapy.

New methods include a weekly contraceptive patch, a monthly contraceptive injection, and a monthly vaginal ring. Long-term progestins may be administered in the form of Depo-Provera or a subdermal progestin implant.

Emergency contraceptive pills, containing progestin only, can be used within 72 h of unprotected intercourse for prevention of pregnancy. Plan B is an emergency contraceptive kit specifically designed for postcoital contraception. Mifepristone (RU486) also may be used but is not available in most countries.

INFERTILITY

Etiology

Infertility is defined as the inability to conceive after 12 months of unprotected sexual intercourse. The causes of infertility are outlined in Fig. 175-3. Male infertility is discussed in Chap. 174.

Clinical Features

The initial evaluation includes discussion of the appropriate timing of intercourse, semen analysis in the male, confirmation of ovulation in the female, and, in the majority of situations, documentation of tubal patency in the female. Abnormalities in menstrual function constitute the most common cause of female infertility (Fig. 175-1). A history of regular, cyclic, predictable, spontaneous menses usually indicates ovulatory cycles, which may be confirmed by urinary ovulation predictor kits, basal body temperature graphs, or plasma progesterone measurements during the luteal phase of the cycle. An FSH level <10 IU/mL on day 3 of the cycle predicts adequate ovarian oocyte reserve. Tubal disease can be evaluated by obtaining a hysterosalpingogram or by diagnostic laparoscopy. Endometriosis may be suggested by history and examination, but is often clinically silent and can only be excluded definitively by laparoscopy.

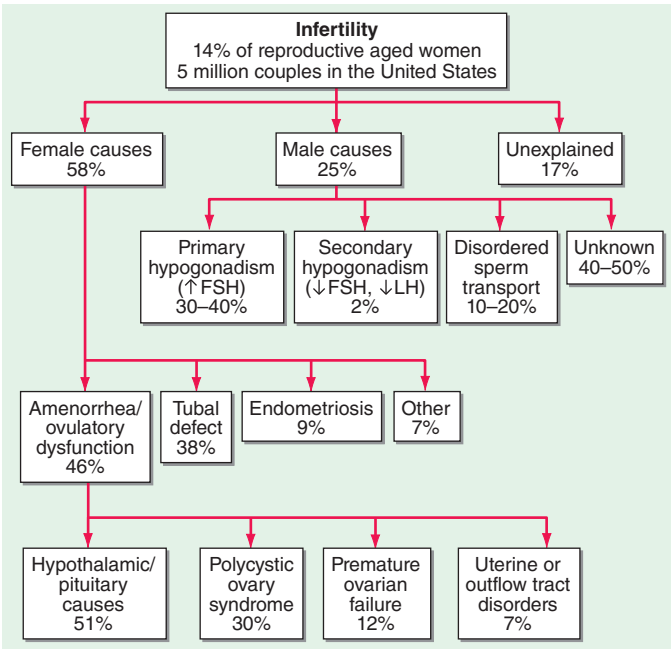


FIGURE 175-3 Causes of infertility. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

TREATMENT INFERTILITY

The treatment of infertility should be tailored to the problems unique to each couple. Treatment options include expectant management, clomiphene citrate with or without intrauterine insemination (IUI), gonadotropins with or without IUI, and in vitro fertilization (IVF). In specific situations, surgery, gonadotropin therapy, intracytoplasmic sperm injection (ICSI), or assisted reproductive technologies with donor egg or sperm may be required.

For a more detailed discussion, see Ehrmann DA: Hirsutism, Chap. 68, p. 331; Hall JE: Menstrual Disorders and Pelvic Pain, Chap. 69, p. 335; Hall JE: Disorders of the Female Reproductive System, Chap. 412, p. 2375; Manson JE, Bassuk SS: Menopause and Postmenopausal Hormone Therapy, Chap. 413, p. 2381, in HPIM-19; Hall JE: Infertility and Contraception, Chap. 414, p. 2387.

176 Hypercalcemia and Hypocalcemia

HYPERCALCEMIA

Hypercalcemia from any cause can result in fatigue, depression, mental confusion, anorexia, nausea, constipation, renal tubular defects, polyuria, a short QT interval, and arrhythmias. CNS and GI symptoms can occur at levels of serum calcium >2.9 mmol/L (>11.5 mg/dL), and nephrocalcinosis and impairment of renal function occur when serum calcium is >3.2 mmol/L (>13 mg/dL). Severe hypercalcemia, usually defined as >3.7 mmol/L (>15 mg/dL), can be a medical emergency, leading to coma and cardiac arrest.

Etiology

The regulation of the calcium homeostasis is depicted in **Fig. 176-1**. The causes of hypercalcemia are listed in **Table 176-1**. Hyperparathyroidism and malignancy account for >90% of cases.

Primary hyperparathyroidism is a generalized disorder of bone metabolism due to increased secretion of parathyroid hormone (PTH) by an adenoma (80%) or rarely a carcinoma in a single gland, or by parathyroid hyperplasia (15%). Familial hyperparathyroidism may be part of multiple endocrine neoplasia type 1 (MEN 1), which also includes pituitary and pancreatic islet tumors, or of MEN 2A, in which hyperparathyroidism occurs with pheochromocytoma and medullary carcinoma of the thyroid.

Hypercalcemia associated with malignancy is often severe and difficult to manage. Mechanisms for this include excess production and release of PTH-related protein

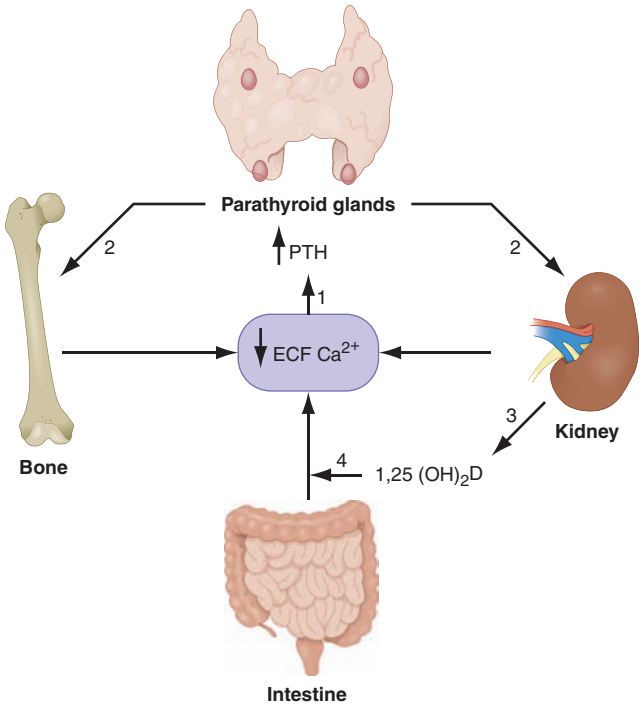


FIGURE 176-1 Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range (8.9–10.1 mg/dL [2.2–2.5 m*M*]). A decrease in extracellular fluid (ECF) calcium (Ca^{2+}) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal 1,25$(OH)_2$D production (3). 1,25$(OH)_2$D, in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

(PTHrP) in lung, kidney, and squamous cell carcinoma (humoral hypercalcemia of malignancy); local bone destruction in myeloma and breast carcinoma; activation of lymphocytes leading to release of cytokines in myeloma and lymphoma; or an increased synthesis of 1,25$(OH)_2$D in lymphoma.

Several other conditions have been associated with hypercalcemia. These include sarcoidosis and other granulomatous diseases, which lead to increased synthesis of 1,25$(OH)_2$D; vitamin D intoxication from chronic ingestion of large vitamin doses (50–100 × physiologic requirements); lithium therapy, which results in hyperfunctioning of the parathyroid glands; and familial hypocalciuric hypercalcemia (FHH) due autosomal dominant inheritance of an inactivating mutation in the calcium-sensing receptor, which results in inappropriately normal or even high secretion of PTH, despite hypercalcemia and enhanced renal calcium resorption. Severe secondary hyperparathyroidism associated with end-stage renal disease may progress to tertiary hyperthyroidism, in which PTH hypersecretion becomes autonomous, causes hypercalcemia, and is no longer responsive to medical therapy.

TABLE 176-1 CLASSIFICATION OF CAUSES OF HYPERCALCEMIA

I. Parathyroid-related
  A. Primary hyperparathyroidism
    1. Solitary adenomas or rarely carcinoma
    2. Multiple endocrine neoplasia
  B. Lithium therapy
  C. Familial hypocalciuric hypercalcemia
II. Malignancy-related
  A. Solid tumor with humoral mediation of hypercalcemia (lung, kidney, squamous cell carcinoma)
  B. Solid tumor with metastases (breast)
  C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)
III. Vitamin D–related
  A. Vitamin D intoxication
  B. ↑ $1,25(OH)_2D$; sarcoidosis and other granulomatous diseases
  C. ↑ $1,25(OH)_2D$; impaired $1,25(OH)_2D$ metabolism due to 24-hydroxylase deficiency
IV. Associated with high bone turnover
  A. Hyperthyroidism
  B. Immobilization
  C. Thiazides
  D. Vitamin A intoxication
  E. Fat necrosis
V. Associated with renal failure
  A. Severe secondary or tertiary hyperparathyroidism
  B. Aluminum intoxication
  C. Milk-alkali syndrome

Clinical Features

Most pts with mild to moderate hyperparathyroidism are asymptomatic, even when the disease involves the kidneys and the skeletal system. Pts frequently have hypercalciuria and polyuria, and calcium can be deposited in the renal parenchyma (nephrocalcinosis) or form calcium oxalate stones. The characteristic skeletal lesion is osteopenia or osteoporosis; rarely, the more severe disorder osteitis fibrosa cystica occurs as a manifestation of long-standing, more severe hyperparathyroidism. Increased bone resorption primarily involves cortical rather than trabecular bone. Hypercalcemia may be intermittent or sustained, and serum phosphate is usually low but may be normal.

Diagnosis

Primary hyperparathyroidism is confirmed by demonstration of an inappropriately high PTH level for the degree of hypercalcemia. Hypercalciuria helps to distinguish this disorder from FHH, in which PTH levels are usually in the normal range and the urine calcium level is low. Differentiation between primary hyperparathyroidism and FHH is important because the latter does not respond to parathyroid surgery. Levels of PTH are low in hypercalcemia of malignancy (Table 176-2).

Total serum calcium should be corrected when serum albumin is abnormal (addition of 0.2 m*M* [0.8 mg/dL] to calcium value for every 1.0-g/dL decrement in

TABLE 176-2 DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA: LABORATORY CRITERIA

	Blood[a]			
	Ca	P_i	$1,25(OH)_2D$	iPTH
Primary hyperparathyroidism	↑	↓	↑↔	↑(↔)
Malignancy-associated hypercalcemia:				
Humoral hypercalcemia	↑↑	↓	↓↔	↓
Local destruction (osteolytic metastases)	↑	↔	↓↔	↓

[a]Symbols in parentheses refer to values rarely seen in the particular disease.
Abbreviations: P_i, inorganic phosphate; iPTH, immunoreactive parathyroid hormone.
Source: JT Potts Jr: HPIM-12, p. 1911.

albumin below 4.1 g/dL, or the converse for an increase in albumin). Alternatively, ionized calcium can be measured. Third-generation PTH assays should be used for PTH measurement, especially in pts with renal impairment.

TREATMENT HYPERCALCEMIA

The type of treatment is based on the severity of the hypercalcemia and the nature of the associated symptoms. Table 176-3 shows general recommendations

TABLE 176-3 THERAPIES FOR SEVERE HYPERCALCEMIA

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
Hydration with saline (≤6 L/d)	Hours	During infusion	Rehydrates; rapid action	Volume overload; electrolyte disturbance
Forced diuresis (furosemide along with aggressive hydration)	Hours	During treatment	Rapid action	Monitoring required to avoid dehydration
Pamidronate 30–90 mg IV over 4 h	1–2 days	10–14 days	High potency; intermediate onset of action	Fever in 20%, ↓ Ca, ↓ phosphate, ↓ Mg, rarely jaw necrosis
Zoledronate 4–8 mg IV over 15 min	1–2 days	>3 weeks	High potency; prolonged action; rapid infusion	Minor: Fever; rare ↓ Ca, ↓ phosphate, jaw necrosis
Calcitonin (2–8 U/kg SC q6-12h)	Hours	1–2 days	Rapid onset	Limited effect; rapid tachyphylaxis
Glucocorticoids (prednisone 10–25 mg PO qid)	Days	Days-weeks	Useful in myeloma, lymphoma, breast CA, sarcoid, vitamin D intox	Effects limited to certain disorders; glucocorticoid side effects
Dialysis	Hours	During use–2 days	Useful in renal failure; immediate effect	Complex procedure

that apply to therapy of severe hypercalcemia (levels of >3.2 mmol/L [>13 mg/dL]) from any cause.

In pts with severe primary hyperparathyroidism, surgical parathyroidectomy should be performed promptly. Asymptomatic disease may not require surgery; usual surgical indications include age <50, nephrolithiasis, creatinine clearance <60 mL/min, reduction in bone mass (T score <–2.5), or serum calcium >0.25 mmol/L (>1 mg/dL) above the normal range. A minimally invasive approach may be used if preoperative localization via sestamibi scans with single-photon emission computed tomography (SPECT) or neck ultrasound demonstrates a solitary adenoma and intraoperative PTH assays are available. Otherwise, neck exploration is required. Surgery in a center experienced in parathyroid interventions is recommended. Postoperative management requires close monitoring of calcium and phosphorus, as transient hypocalcemia is common. Calcium supplementation is given for symptomatic hypocalcemia.

Hypercalcemia of malignancy is managed by treating the underlying tumor. Adequate hydration and parenteral bisphosphonates can be used to reduce calcium levels. Long-term control of hypercalcemia is difficult unless the underlying cause can be eliminated.

No therapy is recommended for FHH. Secondary hyperparathyroidism should be treated with phosphate restriction, the use of nonabsorbable antacids or sevelamer, and calcitriol. Tertiary hyperparathyroidism requires parathyroidectomy.

HYPOCALCEMIA

Chronic hypocalcemia is less common than hypercalcemia, but is usually symptomatic and requires treatment. Symptoms include peripheral and perioral paresthesia, muscle spasms, carpopedal spasm, tetany, laryngeal spasm, seizure, and respiratory arrest. Increased intracranial pressure and papilledema may occur with long-standing hypocalcemia, and other manifestations may include irritability, depression, psychosis, intestinal cramps, and chronic malabsorption. Chvostek's and Trousseau's signs are frequently positive, and the QT interval is prolonged. Both hypomagnesemia and alkalosis lower the threshold for tetany.

Etiology

Transient hypocalcemia often occurs in critically ill pts with burns, sepsis, and acute renal failure; following transfusion with citrated blood; or with medications such as protamine and heparin. Hypoalbuminemia can reduce serum calcium below normal, although ionized calcium levels remain normal. The above-mentioned correction (see "Hypercalcemia") can be used to assess whether the serum calcium concentration is abnormal when serum proteins are low. Alkalosis increases calcium binding to proteins, and in this setting direct measurements of ionized calcium should be used.

The causes of hypocalcemia can be divided into those in which PTH is absent (hereditary or acquired hypoparathyroidism, hypomagnesemia), PTH is ineffective (chronic renal failure, vitamin D deficiency, anticonvulsant therapy, intestinal malabsorption, pseudohypoparathyroidism), or PTH is overwhelmed (severe, acute hyperphosphatemia in tumor lysis, acute renal failure, or rhabdomyolysis; hungry bone syndrome following parathyroidectomy). The most common forms of chronic severe hypocalcemia are autoimmune hypoparathyroidism and postoperative hypoparathyroidism following neck surgery. Chronic renal insufficiency is associated with mild hypocalcemia compensated for by secondary hyperparathyroidism. The cause of hypocalcemia associated with acute pancreatitis is unclear.

TREATMENT HYPOCALCEMIA

Symptomatic hypocalcemia may be treated with IV calcium gluconate (bolus of 1–2 g IV over 10–20 min followed by infusion of 10 ampoules of 10% calcium gluconate diluted in 1 L D_5W infused at 30–100 mL/h). Management of chronic hypocalcemia requires a high oral calcium intake, usually with vitamin D supplementation. Hypoparathyroidism requires administration of calcium (1–3 g/d) and calcitriol (0.25–1 μg/d), adjusted according to serum calcium levels and urinary excretion. Restoration of magnesium stores may be required to reverse hypocalcemia in the setting of severe hypomagnesemia.

HYPOPHOSPHATEMIA

Mild hypophosphatemia is not usually associated with clinical symptoms. In severe hypophosphatemia, pts may have muscle weakness, numbness, paresthesia, and confusion. Rhabdomyolysis may develop during rapidly progressive hypophosphatemia. Respiratory insufficiency can result from diaphragm muscle weakness.

Etiology

The causes of hypophosphatemia include decreased intestinal absorption (vitamin D deficiency, phosphorus-binding antacids, malabsorption); urinary losses (hyperparathyroidism, hyperglycemic states, X-linked hypophosphatemic rickets, oncogenic osteomalacia, alcoholism, or certain toxins); and shifts of phosphorus from extracellular to intracellular compartments (administration of insulin in diabetic ketoacidosis or by hyperalimentation or refeeding in a malnourished pt). In syndromes of severe primary renal phosphate wasting (X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, oncogenic osteomalacia), the phosphatonin hormone FGF23 (fibroblast growth factor 23) plays a key pathogenetic role.

TREATMENT HYPOPHOSPHATEMIA

Mild hypophosphatemia can be replaced orally with milk, carbonated beverages, or Neutra-Phos or K-Phos (up to 2 g/d in divided doses). For severe hypophosphatemia (0.75 mmol/L; [<2.0 mg/dL]), IV phosphate may be administered at initial doses of 0.2–0.8 mmol/kg of elemental phosphorus over 6 h. The total body phosphate depletion cannot be predicted from the serum phosphate level; careful monitoring of therapy is therefore required. Hypocalcemia should be corrected first, and the dose reduced 50% in hypercalcemia. Serum calcium and phosphate levels should be measured every 6–12 h; a serum calcium × phosphate product of >50 must be avoided.

HYPERPHOSPHATEMIA

In adults, hyperphosphatemia is defined as a level >1.8 mmol/L (>5.5 mg/dL). The most common causes are acute and chronic renal failure, but it may also be seen in hypoparathyroidism, vitamin D intoxication, acromegaly, acidosis, rhabdomyolysis, and hemolysis. The clinical consequences of severe hyperphosphatemia are hypocalcemia and calcium phosphate deposition in tissues. Depending on the location of tissue calcifications, serious chronic or acute complications may ensue (e.g., nephrocalcinosis, cardiac arrhythmias). Therapy consists of treating the underlying disorder and limiting dietary phosphorus intake and absorption. Oral aluminum phosphate binders or sevelamer may be used, and hemodialysis should be considered in severe cases.

HYPOMAGNESEMIA

Hypomagnesemia usually indicates significant whole body magnesium depletion. Muscle weakness, prolonged PR and QT intervals, and cardiac arrhythmias are the most common manifestations of hypomagnesemia. Magnesium is important for effective PTH secretion as well as the renal and skeletal responsiveness to PTH. Therefore, hypomagnesemia is often associated with hypocalcemia.

Etiology

Hypomagnesemia generally results from a derangement in renal or intestinal handling of magnesium and is classified as primary (hereditary) or secondary (acquired). Hereditary causes include both disorders of absorption (rare) and those of renal loss (e.g., Bartter's and Gitelman syndromes). Secondary causes are much more common, with renal losses being due to volume expansion, hypercalcemia, osmotic diuresis, loop diuretics, alcohol, aminoglycosides, cisplatin, cyclosporine, and amphotericin B, and gastrointestinal losses most commonly resulting from vomiting and diarrhea.

TREATMENT HYPOMAGNESEMIA

For mild deficiency, oral replacement in divided doses totaling 20–30 mmol/d (40–60 meq/d) is effective, although diarrhea may result. Parenteral magnesium administration is usually needed for serum levels <0.5 mmol/L (<1.2 mg/dL), with a continuous infusion of magnesium chloride IV to deliver 50 mmol/d over a 24-h period (dose reduced by 50–75% in renal failure). Therapy may be required for several days in order to replete tissue magnesium stores; serum Mg should be monitored every 12–24 h during treatment. Other electrolyte disturbances should be treated simultaneously. Pts with associated seizures or acute arrhythmias can be given 1–2 g of magnesium sulfate IV over 5–10 min.

HYPERMAGNESEMIA

Hypermagnesemia is rare but can be seen in renal failure when pts are taking magnesium-containing antacids, laxatives, enemas, or infusions, or in acute rhabdomyolysis. The most readily detectable clinical sign of hypermagnesemia is the disappearance of deep tendon reflexes, but hypocalcemia, hypotension, paralysis of respiratory muscles, complete heart block, and cardiac arrest can occur. Treatment includes stopping the preparation, clearing the intestines of residual offending laxatives or antacids with magnesium-free enemas or cathartics, dialysis against a low magnesium bath, or, if associated with life-threatening complications, 100–200 mg of elemental calcium IV over 1–2 h.



For a more detailed discussion, see Bringhurst FR, Demay MB, Krane SM, Kronenberg HM: Bone and Mineral Metabolism in Health and Disease, Chap. 423, p. 2454; Khosla S: Hypercalcemia and Hypocalcemia, Chap. 65, p. 313; Potts JT Jr, Jüppner H: Disorders of the Parathyroid Gland and Calcium Homeostasis, Chap. 424, p. 2466, in HPIM-19.

177 Osteoporosis and Osteomalacia

OSTEOPOROSIS

Osteoporosis is defined as a reduction in the strength of bone that leads to increased risk of fractures. It is defined operationally as a bone density that falls 2.5 SD below the mean for a young normal individual (a T-score of <–2.5). Those with a T-score of <1.0 (osteopenia) have low bone density and are at increased risk for osteoporosis. The most common sites for osteoporosis-related fractures are the vertebrae, hip, and distal radius.

Osteoporosis is a common condition in the elderly; women are at particularly high risk. In the United States, 8 million women and 2 million men have osteoporosis; an additional 18 million have osteopenia. The annual incidence of osteoporosis-related fractures is at least 2 million; almost half of them are vertebral crush fractures, followed in frequency by hip and wrist fractures. Hip fractures are associated with significant morbidity (thromboembolism) and a 5–20% mortality within a year.

Etiology

Low bone density may result from low peak bone mass or increased bone loss. Risk factors for an osteoporotic fracture are listed in Table 177-1, and conditions associated with osteoporosis are listed in Table 177-2. Certain drugs, primarily glucocorticoids, cyclosporine, cytotoxic drugs, thiazolidinediones, anticonvulsants, aluminum, heparin, excessive levothyroxine, GnRH agonists, and aromatase inhibitors also have detrimental effects on the skeleton.

Clinical Features

Pts with multiple vertebral crush fractures may have loss of height, kyphosis, and secondary pain from altered biomechanics of the back. Thoracic fractures can be associated with restrictive lung disease, whereas lumbar fractures are sometimes associated with abdominal symptoms or nerve compression leading to sciatica.

TABLE 177-1 RISK FACTORS FOR OSTEOPOROSIS FRACTURE

Nonmodifiable	Estrogen deficiency
Personal history of fracture as an adult	Early menopause (<45 years) or bilateral ovariectomy
History of fracture in first-degree relative	Prolonged premenopausal amenorrhea (>1 year)
Female sex	Low calcium intake
Advanced age	Alcoholism
White race	Impaired eyesight despite adequate correction
Dementia	
Potentially modifiable	Recurrent falls
Current cigarette smoking	Inadequate physical activity
Low body weight (<58 kg [127 lb])	Poor health/frailty

TABLE 177-2 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES

Lifestyle factors		
Alcohol abuse	High salt intake	Falling
Low calcium intake	Inadequate physical activity	Excessive thinness
Vitamin D insufficiency	Immobilization	Prior fractures
Excess vitamin A	Smoking (active or passive)	
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos syndrome	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan's syndrome	Riley-Day syndrome
Hemochromatosis	Menkes' steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Athletic amenorrhea
		Panhypopituitarism
Anorexia nervosa and bulimia	Premature menopause	
	Premature ovarian failure	
Turner's & Klinefelter's syndromes		
Endocrine disorders		
Adrenal insufficiency	Cushing's syndrome	Central adiposity
Diabetes mellitus (types 1 and 2)	Hyperparathyroidism	Thyrotoxicosis
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
Gastrointestinal surgery	Pancreatic disease	
Hematologic disorders		
Multiple myeloma	Monoclonal gammopathies	Sickle cell disease
Hemophilia	Leukemia and lymphomas	Systemic mastocytosis
Thalassemia		
Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Other rheumatic and autoimmune diseases		

(*Continued*)

TABLE 177-2 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES (*CONTINUED*)

Central nervous system disorders		
Epilepsy	Parkinson's disease	Stroke
Multiple sclerosis	Spinal cord injury	
Miscellaneous conditions and diseases		
AIDS/HIV	Congestive heart failure	Posttransplant bone disease
Alcoholism	Depression	Sarcoidosis
Amyloidosis	End-stage renal disease	Weight loss
Chronic metabolic acidosis	Hypercalciuria	
Chronic obstructive lung disease	Idiopathic scoliosis	
	Muscular dystrophy	
Medications		
Aluminum (in antacids)	Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 months)	Tamoxifen (premenopausal use)
Anticoagulants (heparin)	Gonadotropin-releasing hormone antagonists and agonists	Thiazolidinediones (such as pioglitazone and rosiglitazone)
Anticonvulsants	Lithium	Thyroid hormones (in excess)
Aromatase inhibitors	Methotrexate	Parenteral nutrition
Barbiturates	Proton pump inhibitors	
Cancer chemotherapeutic drugs	Selective serotonin reuptake inhibitors	
Cyclosporine A and tacrolimus		
Depo-medroxyprogesterone (premenopausal contraception)		

Source: From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

Dual-energy x-ray absorptiometry (DEXA) has become the standard for measuring bone density. Women age 65 and older should be screened routinely for osteoporosis, and screening should begin at age 60 for women with increased risk. Indications for bone mass measurement are summarized in **Table 177-3**. A general laboratory evaluation includes complete blood count, serum and 24-h urine calcium, 25(OH) D level, and renal and hepatic function tests. Further testing is based on clinical suspicion and may include thyroid-stimulating hormone (TSH), urinary free cortisol, parathyroid hormone (PTH), serum and urine electrophoresis, and testosterone levels (in men). Tissue transglutaminase Ab testing may identify asymptomatic celiac disease. Markers of bone resorption (e.g., urine cross-linked *N*-telopeptide) may be helpful in detecting an early response to antiresorptive therapy if measured prior to and 4–6 months after initiating therapy.

TREATMENT OSTEOPOROSIS

Treatment involves the management of acute fractures, modifying risk factors, and treating any underlying disorders that lead to reduced bone mass. Treatment decisions are based on an individual's risk factors, but active treatment

TABLE 177-3 INDICATIONS FOR BONE DENSITY TESTING

Consider BMD testing in the following individuals:

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged 50–69 with clinical risk factors for fracture
- Adults who have a fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥5-mg prednisone or equivalent for ≥3 months) associated with low bone mass or bone loss

Abbreviation: BMD, bone mineral density.
Source: From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

is generally recommended if the T-score is ≤2.5. Risk factor reduction is a key part of management; smoking cessation and reduced alcohol intake should be encouraged; offending drugs should be discontinued or doses minimized (e.g., glucocorticoids), an exercise program should be instituted, and fall prevention strategies should be put in place. Oral calcium (1–1.2 g/d of elemental calcium in divided doses) and vitamin D (400–800 IU/d) should be initiated in all pts with osteoporosis. Adequate vitamin D status should be verified by measuring serum 25(OH)D, the value of which should be at least 75 nmol/L (30 ng/mL). Some pts may require higher vitamin D supplements than those recommended above. Moderate sun exposure also generates vitamin D, although recommending outdoor exposure is controversial because of concerns about skin cancer. Bisphosphonates (alendronate, 70 mg PO weekly; risedronate, 35 mg PO weekly; ibandronate, 150 mg PO monthly or 3 mg IV every 3 mo; zoledronic acid, 5 mg IV annually) inhibit bone resorption, augment bone density, and decrease fracture rates. Oral bisphosphonates are poorly absorbed and should be taken in the morning on an empty stomach with 0.25 L (8 oz) of tap water. Long-term bisphosphonate treatment may be associated with atypical femur fractures; a tentative recommendation is to limit therapy to 5 years. Osteonecrosis of the jaw is a rare complication of bisphosphonate treatment mainly seen with high-dose IV zoledronic acid or pamidronate administered in cancer pts. Estrogen decreases the rate of bone reabsorption, but therapy should be carefully weighed in the context of increased risks of cardiovascular disease and breast cancer. Raloxifene (60 mg/d PO), a selective estrogen receptor modulator (SERM), is an alternative antiresorptive agent that can be used in lieu of estrogen. It increases bone density and decreases total and LDL cholesterol without stimulating endometrial hyperplasia, although it may precipitate hot flashes. A new antiresorptive agent is denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast differentiation factor. It is approved for pts at high risk for fracture and is given as an injection twice a year (60 mg SC every 6 months). Clinical experience with denosumab is still limited.

The only available drug that induces bone *formation* is teriparatide [PTH(1-34)] 20 μg SC qd. It is indicated for treatment of severe osteoporosis for a maximum of 2 years. Teriparatide therapy must be followed by antiresorptive agent therapy to prevent rapid loss of the newly formed bone.

OSTEOMALACIA

Etiology

Defective mineralization of the organic matrix of bone results in *osteomalacia*. The childhood form of osteomalacia is called rickets. Osteomalacia is caused by inadequate intake or malabsorption of vitamin D (chronic pancreatic insufficiency, gastrectomy, malabsorption) and disorders of vitamin D metabolism (anticonvulsant therapy, chronic renal failure, genetic disorders of vitamin D activation or action). Osteomalacia can also be caused by long-standing hypophosphatemia, which can be due to renal phosphate wasting (e.g., X-linked hypophosphatemic rickets or oncogenic osteomalacia) or excessive use of phosphate binders.

Clinical Features

Skeletal deformities may be overlooked until fractures occur after minimal trauma. Symptoms include diffuse skeletal pain and bony tenderness and may be subtle. Proximal muscle weakness is a feature of vitamin D deficiency and may mimic primary muscle disorders. A decrease in bone density is usually associated with loss of trabeculae and thinning of the cortices. Characteristic x-ray findings are radiolucent bands (looser's zones or pseudofractures) ranging from a few millimeters to several centimeters in length, usually perpendicular to the surface of the femur, pelvis, and scapula. Changes in serum calcium, phosphorus, 25(OH)D, and $1,25(OH)_2D$ levels vary depending on the cause. The most specific test for vitamin D deficiency in an otherwise healthy individual is a low serum 25(OH)D level. Even modest vitamin D deficiency leads to compensatory secondary hyperparathyroidism characterized by increased levels of PTH and alkaline phosphatase, hyperphosphaturia, and low serum phosphate. With advancing osteomalacia, hypocalcemia may develop due to impaired calcium mobilization from undermineralized bone. 1,25-Dihydroxyvitamin D levels may be preserved, reflecting upregulation of 1α-hydroxylase activity.

TREATMENT OSTEOMALACIA

In osteomalacia due to vitamin D deficiency (serum 25(OH)D <50 nmol/L [<20 ng/mL]), vitamin D_2 (ergocalciferol) is given orally in doses of 50,000 IU weekly for 8 weeks, followed by maintenance therapy with 800 IU daily. Osteomalacia due to malabsorption requires larger doses of vitamin D (up to 50,000 IU/d orally or 250,000 IU IM biannually). In pts taking anticonvulsants or those with disorders of abnormal vitamin D activation, vitamin D should be administered in doses that maintain the serum calcium and 25(OH)D levels in the normal range. Calcitriol (0.25–0.5 μg/d PO) is effective in treating hypocalcemia or osteodystrophy caused by chronic renal failure. Vitamin D deficiency should always be repleted in conjunction with calcium supplementation (1.5–2.0 g of elemental calcium daily). Serum and urinary calcium measurements are efficacious for monitoring resolution of vitamin D deficiency, with a goal 24-h urinary calcium excretion of 100–250 mg/24 h.



For a more detailed discussion, see Bringhurst FR, Demay MB, Krane SM, Kronenberg HM: Bone and Mineral Metabolism in Health and Disease, Chap. 423, p. 2454; Lindsay R, Cosman F: Osteoporosis, Chap. 425, p. 2488, in HPIM-19.

178 Hypercholesterolemia and Hypertriglyceridemia

Hyperlipoproteinemia may be characterized by hypercholesterolemia, isolated hypertriglyceridemia, or both. Genetic causes of hyperlipoproteinemia are summarized in Table 178-1. Diabetes mellitus, obesity, ethanol consumption, oral contraceptives, glucocorticoids, renal disease, hepatic disease, and hypothyroidism can cause secondary hyperlipoproteinemias or worsen underlying hyperlipoproteinemic states.

Standard lipoprotein analysis assesses total cholesterol, HDL cholesterol, and triglycerides with a calculation of LDL cholesterol levels using the following equation: LDL cholesterol = total cholesterol – HDL cholesterol – (triglycerides/5). The LDL cholesterol concentration can be estimated using this method only if triglycerides are <4.0 mmol/L (<350 mg/dL). Both LDL and HDL cholesterol levels are temporarily decreased for several weeks after myocardial infarction or acute inflammatory states, but can be accurately measured if blood is obtained within 8 h of the event.

ISOLATED HYPERCHOLESTEROLEMIA

Elevated levels of fasting plasma total cholesterol (>5.2 mmol/L [>200 mg/dL]) in the presence of normal levels of triglycerides are almost always associated with increased concentrations of plasma LDL cholesterol. Elevations of LDL cholesterol can result from single-gene defects, from polygenic disorders, or from the secondary effects of other disease states.

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

FH is a codominant genetic disorder due to mutations in the gene for the LDL receptor. Plasma LDL levels are elevated at birth and remain so throughout life. In untreated heterozygous adults, total cholesterol levels range from 7.1 to 12.9 mmol/L (275–500 mg/dL). Plasma triglyceride levels are typically normal, and HDL cholesterol levels are normal or reduced. Heterozygotes, especially men, are prone to accelerated atherosclerosis and premature coronary artery disease (CAD). *Tendon xanthomas* (most commonly of the Achilles tendons and the extensor tendons of the knuckles), *tuberous xanthomas* (softer, painless nodules on the ankles and buttocks), and *xanthelasmas* (deposits on the eyelids) are common. In its homozygous form, FH leads to severe atherosclerosis during childhood.

FAMILIAL DEFECTIVE APO B-100

This autosomal dominant disorder impairs the synthesis and/or function of apo B-100, thereby reducing the affinity for the LDL receptor, slowing LDL catabolism, and causing a phenocopy of FH.

POLYGENIC HYPERCHOLESTEROLEMIA

Most moderate hypercholesterolemia (<9.1 mmol/L [<350 mg/dL]) arises from an interaction of multiple genetic defects and environmental factors such as diet, age, and exercise. Plasma HDL and triglyceride levels are normal, and xanthomas are not present.

TREATMENT ISOLATED HYPERCHOLESTEROLEMIA

Therapy for all of these disorders includes restriction of dietary cholesterol and HMG-CoA reductase inhibitors (statins). Cholesterol absorption inhibitors and bile acid sequestrants or nicotinic acid may also be required (Table 178-2).

TABLE 178-1 PRIMARY HYPERLIPOPROTEINEMIAS CAUSED BY KNOWN SINGLE-GENE MUTATIONS

Genetic Disorder	Protein (Gene) Defect	Lipoproteins Elevated	Clinical Findings	Genetic Transmission	Estimated Incidence
Hypertriglyceridemia					
Lipoprotein lipase deficiency	LPL (*LPL*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	~1/1,000,000
Familial apo CII deficiency	Apo CII (*APOC2*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
Apo A-V deficiency	Apo A-V (*APOA5*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
GPIHBP1 deficiency	*GPIHBP1*	Chylomicrons	Eruptive xanthomas, pancreatitis	AR	<1/1,000,000
Combined Hyperlipidemia					
Familial hepatic lipase deficiency	Hepatic lipase (*LIPC*)	VLDL remnants, HDL	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (*APOE*)	Chylomicron remnants, VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR	~1/10,000
Hypercholesterolemia					
Familial hypercholesterolemia	LDL receptor (*LDLR*)	LDL	Tendon xanthomas, CHD	AD	~1/250 to 1/500
Familial defective apoB-100	ApoB-100 (*APOB*)	LDL	Tendon xanthomas, CHD	AD	<~1/1500
Autosomal dominant hypercholesterolemia, type 3	PCSK9 (*PCSK9*)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	ARH (*LDLRAP*)	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	*ABCG5* or *ABCG8*	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Abbreviations: AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.

TABLE 178-2 SUMMARY OF THE MAJOR APPROVED DRUGS USED FOR THE TREATMENT OF DYSLIPIDEMIA

Drug	Major Indications	Starting Dose	Maximal Dose	Mechanism	Common Side Effects
HMG-CoA reductase inhibitors (statins)	Elevated LDL-C; increased CV risk			↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production	Myalgias, arthralgias, elevated transaminases, dyspepsia
Lovastatin		20–40 mg daily	80 mg daily		
Pravastatin		40–80 mg daily	80 mg daily		
Simvastatin		20–40 mg daily	80 mg daily		
Fluvastatin		20–40 mg daily	80 mg daily		
Atorvastatin		20–40 mg daily	80 mg daily		
Rosuvastatin		5–20 mg daily	40 mg daily		
Pitavastatin		1–2 mg daily	4 mg daily		
Cholesterol absorption inhibitor	Elevated LDL-C			↓ Cholesterol absorption, ↑ LDL receptors	Elevated transaminases
Ezetimibe		10 mg daily	10 mg daily		
Bile acid sequestrants	Elevated LDL-C			↑ Bile acid excretion and ↑ LDL receptors	Bloating, constipation, elevated triglycerides
Cholestyramine		4 g daily	32 g daily		

Colestipol		5 g daily	40 g daily		
Colesevelam		3750 mg daily	4375 mg daily		
MTP inhibitor Lomitapide	HoFH	5 mg daily	60 mg daily	↓ VLDL production	Nausea, diarrhea, increased hepatic fat
apoB inhibitor Mipomersen	HoFH	200 mg SC weekly	200 mg SC weekly	↓ VLDL production	Injection site reactions, flu-like symptoms, increased hepatic fat
Nicotinic acid	Elevated LDL-C, elevated TG			↓ VLDL production	Cutaneous flushing, GI upset, elevated glucose, uric acid, and elevated liver function tests
Immediate-release		100 mg tid	1 g tid		
Sustained-release		250 mg bid	1.5 g bid		
Extended-release		500 mg qhs	2 g qhs		
Fibric acid derivatives	Elevated TG			↑ LPL, ↓ VLDL synthesis	Dyspepsia, myalgia, gallstones, elevated transaminases
Gemfibrozil		600 mg bid	600 mg bid		
Fenofibrate		145 mg qd	145 mg qd		
Omega-3 fatty acids Omega-3 acid ethyl esters	Elevated TG	4 g daily	4 g daily	↑ TG catabolism	Dyspepsia, fishy odor to breath
Icosapent ethyl		4 g daily	4 g daily		

Abbreviations: CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; TG, triglyceride; VLDL, very-low-density lipoprotein.

ISOLATED HYPERTRIGLYCERIDEMIA

The diagnosis of hypertriglyceridemia is made by measuring plasma lipid levels after an overnight fast (≥12 h). Hypertriglyceridemia in adults is defined as a triglyceride level >2.3 mmol/L (>200 mg/dL). An isolated increase in plasma triglycerides indicates that chylomicrons and/or very low-density lipoprotein (VLDL) are increased. Plasma is usually clear when triglyceride levels are <4.5 mmol/L (<400 mg/dL) and cloudy when levels are higher due to VLDL (and/or chylomicron) particles becoming large enough to scatter light. When chylomicrons are present, a creamy layer floats to the top of plasma after refrigeration for several hours. Tendon xanthomas and xanthelasmas do not occur with isolated hypertriglyceridemia, but *eruptive xanthomas* (small orange-red papules) can appear on the trunk and extremities and *lipemia retinalis* (orange-yellow retinal vessels) may be seen when the triglyceride levels are >11.3 mmol/L (>1000 mg/dL). Pancreatitis is associated with these high concentrations.

FAMILIAL HYPERTRIGLYCERIDEMIA

In this relatively common (~1 in 500), likely polygenic disorder, increased plasma VLDL causes elevated plasma triglyceride concentrations. Obesity, hyperglycemia, and hyperinsulinemia are characteristic, and diabetes mellitus, ethanol consumption, oral contraceptives, and hypothyroidism may exacerbate the condition. The diagnosis is suggested by the triad of elevated plasma triglycerides (2.8–11.3 mmol/L [250–1000 mg/dL]), normal or only mildly increased cholesterol levels (<6.5 mmol/L [<250 mg/dL]), and reduced plasma HDL. Secondary forms of hypertriglyceridemia due to the conditions listed above should be ruled out before making the diagnosis of familial hypertriglyceridemia. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. Familial dysbetalipoproteinemia and familial combined hyperlipidemia (FCHL) should be ruled out, as these two conditions are associated with accelerated atherosclerosis.

LIPOPROTEIN LIPASE DEFICIENCY

This rare autosomal recessive disorder results from the absence or deficiency of lipoprotein lipase, which in turn impairs the metabolism of chylomicrons. Accumulation of chylomicrons in plasma causes recurrent bouts of pancreatitis, usually beginning in childhood, and hepatosplenomegaly is present. Accelerated atherosclerosis is not a feature.

APO CII DEFICIENCY

This rare autosomal recessive disorder is due to the absence of apo CII, an essential cofactor for lipoprotein lipase. As a result, chylomicrons and triglycerides accumulate and cause manifestations similar to those in lipoprotein lipase deficiency.

TREATMENT ISOLATED HYPERTRIGLYCERIDEMIA

Pts with severe hypertriglyceridemia should be placed on a fat-free diet with fat-soluble vitamin supplementation. Pts with moderate hypertriglyceridemia should restrict fat, carbohydrate, and alcohol intake. In those with familial hypertriglyceridemia, fibric acid derivatives, omega-3 fatty acids, or niacin can be administered if dietary measures fail (Table 178-2).

HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA

Elevations of both triglycerides and cholesterol are caused by elevations in both VLDL and LDL or in VLDL remnant particles.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

This inherited disorder, present in 1/200 persons, can cause different lipoprotein abnormalities in affected individuals, including hypercholesterolemia (elevated LDL), hypertriglyceridemia (elevated triglycerides and VLDL), or both. Atherosclerosis is accelerated. A mixed dyslipidemia (plasma triglycerides 2.3–9.0 mmol/L [200–800 mg/dL], cholesterol levels 5.2–10.3 mmol/L [200–400 mg/dL], and HDL levels <10.3 mmol/L [<40 mg/dL] in men and <12.9 mmol/L [<50 mg/dL] in women) and a family history of hyperlipidemia and/or premature cardiovascular disease suggest the diagnosis of FCHL. Many of these pts also have the metabolic syndrome (Chap. 118), and it may be difficult to differentiate familial from secondary causes of hyperlipidemia. All pts should restrict dietary cholesterol and fat and avoid alcohol and oral contraceptives; pts with diabetes should be treated aggressively. An HMG-CoA reductase inhibitor is usually required, and many pts will require a second drug (cholesterol absorption inhibitor, niacin, or fibrate) for optimal control.

DYSBETALIPOPROTEINEMIA

This rare genetic disorder is associated with homozygosity for an apoprotein variant (apoE2) that has reduced affinity for the LDL receptor. Development of disease requires additional environmental and/or genetic factors. Plasma cholesterol (6.5–13.0 mmol/L [250–500 mg/dL]) and triglycerides (2.8–5.6 mmol/L [250–500 mg/dL]) are increased due to accumulation of VLDL and chylomicron remnant particles. Pts usually present in adulthood with xanthomas and premature coronary and peripheral vascular disease. Cutaneous xanthomas are distinctive, in the form of *palmar* and *tuberoeruptive xanthomas*. Triglycerides and cholesterol are both elevated. Diagnosis is established by lipoprotein electrophoresis (showing a broad beta band) or a ratio of VLDL (by ultracentrifugation) to total plasma triglycerides of >0.3. The disorder is associated with accelerated atherosclerosis. Dietary modifications should be instituted, and HMG-CoA reductase inhibitors, fibrates, and/or niacin may be necessary. Comorbidities, such as diabetes mellitus, obesity, or hypothyroidism, should be optimally managed.

PREVENTION OF THE COMPLICATIONS OF ATHEROSCLEROSIS

Abundant and compelling data demonstrate that interventions to reduce LDL-C substantially reduces the risk of cardiovascular disease, including MI and stroke, as well as total mortality. Thus, is it imperative that patients with hypercholesterolemia be assessed for cardiovascular risk and for the need for intervention. Patients at high risk for cardiovascular disease who have plasma LDL-C levels in the "normal" range also benefit from intervention to reduce LDL-C levels.

Lifestyle The first approach to a patient with hypercholesterolemia and high cardiovascular risk is to make any necessary lifestyle changes. In obese patients, efforts should be made to reduce body weight to the ideal level. Dietary counseling to reduce the content of saturated fats, trans fats, and cholesterol in the diet. Regular aerobic exercise has relatively little impact on reducing plasma LDL-C levels, though has cardiovascular benefits independent of LDL lowering.

Pharmacologic therapy for hypercholesterolemia The decision to use LDL-lowering drug therapy—with a statin being first-line therapy—depends on the level of LDL-C as well as the level of cardiovascular risk. In general, patients with a Mendelian disorder of elevated LDL-C such as FH must be treated to reduce the very high lifetime risk of cardiovascular disease, and treatment should be initiated as early as possible in adulthood, and in some cases during childhood. Otherwise, the decision to initiate LDL-lowering drug therapy is generally determined by the level of cardiovascular risk. In patients with established CVD, statin therapy is well supported by clinical trial data and should be used regardless of the LDL-C

level. For patients >40 years old without clinical CVD, the AHA/ACC risk calculator (http://professional.heart.org/professional/GuidelinesStatements/Prevention-Guidelines/UCM_457698_Prevention-Guidelines.jsp) can be used to determine the 10-year absolute risk for CVD, and current guidelines suggest that a 10-year risk >7.5% merits consideration of statin therapy regardless of plasma LDL-C level. For younger patients, the assessment of lifetime risk of CVD may help inform the decision to start a statin.

For a more detailed discussion, see Rader DJ, Hobbs HH: Disorders of Lipoprotein Metabolism, Chap. 421, p. 2435; in HPIM-19.

179 Hemochromatosis, Porphyrias, and Wilson's Disease

HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage that results in increased intestinal iron absorption with Fe deposition and damage to many tissues. The classic clinical constellation of hemochromatosis is a pt presenting with bronze skin, liver disease, diabetes, arthropathy, cardiac conduction abnormalities, and hypogonadism. Two major causes of hemochromatosis exist: hereditary (due to inheritance of mutant *HFE* genes) and secondary iron overload (usually the result of ineffective erythropoiesis, such as thalassemia or sideroblastic anemia). *HFE* encodes a protein that is involved in cellular iron sensing and in regulating intestinal iron absorption. *HFE* mutations are very common in populations of Northern European origin (1 in 10 is a carrier). Heterozygotes are asymptomatic; homozygotes show a disease penetrance of ~30%. There is progressive iron overload, with clinical manifestations appearing after age 30–40, typically earlier in men than in women. Alcoholic liver disease and chronic excessive Fe ingestion may also be associated with a moderate increase in hepatic Fe and elevated body Fe stores.

Clinical Features

Early symptoms include weakness, lassitude, weight loss, a bronze pigmentation or darkening of skin, abdominal pain, and loss of libido. Hepatomegaly occurs in 95% of pts, sometimes in the presence of normal LFTs. If untreated, liver disease progresses to cirrhosis, and further to hepatocellular carcinoma in ~30% of pts with cirrhosis. Other manifestations include skin pigmentation (bronzing), diabetes mellitus (65% of pts), arthropathy (25–59%), cardiac arrhythmias and CHF (15%), and hypogonadotropic hypogonadism. Diabetes mellitus is more common in pts with a family history of diabetes, and hypogonadism may be an isolated early manifestation. Typical signs of portal hypertension and decompensated hepatic cirrhosis may appear late in the clinical course. Adrenal insufficiency, hypothyroidism, and hypoparathyroidism rarely occur.

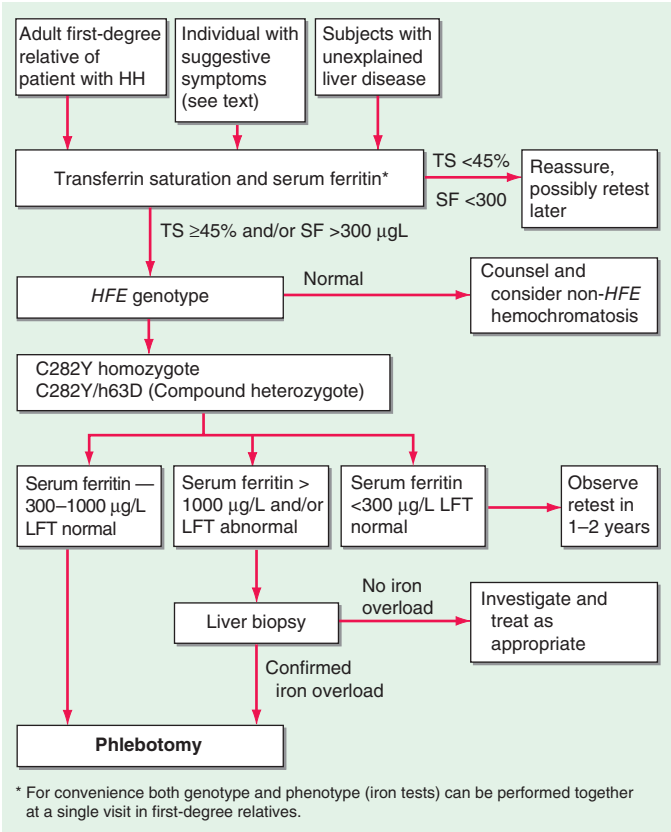


FIGURE 179-1 Algorithm for screening for *HFE*-associated hemochromatosis. HH, hereditary hemochromatosis, homozygous subject (C282Y +/+); LFT, liver function tests; SF, serum ferritin concentration; TS, transferrin saturation. *(From EJ Eijkelkamp et al: Can J Gastroenterol 14:2, 2000; with permission.)*

Diagnosis

Serum Fe, percent transferrin saturation, and serum ferritin levels are increased. In an otherwise-healthy person, a fasting serum transferrin saturation >50% is abnormal and suggests homozygosity for hemochromatosis. In most untreated pts with hemochromatosis, the serum ferritin level is also greatly increased. If either the percent transferrin saturation or the serum ferritin level is abnormal, genetic testing for hemochromatosis should be performed. All first-degree relatives of pts with hemochromatosis should be tested for the C282Y and H63D mutations in *HFE*. Liver biopsy may be required in affected individuals to evaluate possible cirrhosis and to quantify tissue iron. An algorithm for evaluating pts with possible hemochromatosis is shown in Fig. 179-1. Death in untreated pts results from cardiac failure (30%), cirrhosis (25%), and hepatocellular carcinoma (30%); the latter may develop despite adequate Fe removal.

TREATMENT HEMOCHROMATOSIS

Therapy involves removal of excess body Fe, usually by intermittent phlebotomy, and supportive treatment of damaged organs. Since one unit of blood contains ~250 mg Fe, and since up to 25 g of Fe must be removed, phlebotomy is performed weekly for 1–2 years. Less frequent phlebotomy is then used to maintain serum Fe at 9–18 μmol/L (50–100 μg/dL). Chelating agents such as deferoxamine (infused subcutaneously using a portable pump) remove 10–20 mg iron per day, a fraction of that mobilized by weekly phlebotomy. Chelation therapy is indicated, however, when phlebotomy is inappropriate, such as with anemia or hypoproteinemia. Alcohol consumption should be eliminated. End-stage liver disease may require liver transplantation.

PORPHYRIAS

The porphyrias are inherited disturbances in heme biosynthesis. Each of the nine disorders causes a unique pattern of overproduction, accumulation, and excretion of intermediates of heme synthesis. These disorders are classified as either hepatic or erythropoietic, depending on the primary site of overproduction and accumulation of the porphyrin precursor or porphyrin. The major manifestations of the hepatic porphyrias are neurologic (neuropathic abdominal pain, neuropathy, and mental disturbances), whereas the erythropoietic porphyrias characteristically cause cutaneous photosensitivity. Laboratory testing is required to confirm or exclude the various types of porphyria. However, a definite diagnosis requires demonstration of the specific enzyme deficiency or gene defect. Only the three most common porphyrias are discussed here.

ACUTE INTERMITTENT PORPHYRIA

This is an autosomal dominant disorder with variable expressivity caused by partial (50%) deficiency in hydroxymethylbilane synthase. It has a prevalence of 1–3 in 100,000 but is much more common in certain parts of the world (Northern Sweden, Great Britain). Manifestations include colicky abdominal pain, vomiting, constipation, port wine–colored urine, and neurologic and psychiatric disturbances. Acute attacks rarely occur before puberty and may last from days to months. Photosensitivity does not occur. Clinical and biochemical manifestations may be precipitated by barbiturates, anticonvulsants, estrogens, oral contraceptives, the luteal phase of the menstrual cycle, alcohol, or low-calorie diets. Diagnosis is established by demonstrating elevation of urinary porphobilinogen (PBG) and γ-aminolevulinic acid (ALA) during an acute attack. Genetic testing, if available, should be used to confirm the diagnosis.

TREATMENT ACUTE INTERMITTENT PORPHYRIA

As soon as possible after the onset of an attack, 3–4 mg of heme, in the form of heme arginate, heme albumin, or hematin, should be infused daily for 4 days. Heme acts by inhibiting ALA synthase, thereby restraining ALA and PBG production. Administration of IV glucose at rates up to 20 g/h or parenteral nutrition, if oral feeding is not possible for long periods, can be effective in acute attacks. Narcotic analgesics may be required during acute attacks for abdominal pain, and phenothiazines are useful for nausea, vomiting, anxiety, and restlessness. Treatment between attacks involves adequate nutritional intake, avoidance of drugs known to exacerbate the disease, and prompt treatment of other intercurrent diseases or infections. Liver transplantation has been effective in selected patient and gene replacement trials are underway.

PORPHYRIA CUTANEA TARDA

This is the most common porphyria (2–4 in 100,000) and is characterized by cutaneous photosensitivity and, usually, hepatic disease. It is due to partial deficiency (familial, sporadic, or acquired) of hepatic uroporphyrinogen decarboxylase. Photosensitivity causes facial pigmentation, increased fragility of skin, erythema, and vesicular and ulcerative lesions, typically involving face, forehead, and forearms. Neurologic manifestations are not observed. Contributing factors include excess alcohol, iron, and estrogens. Pts with liver disease are at risk for cirrhosis and hepatocellular carcinoma. Plasma and urine uroporphyrin and 7-carboxylate porphyrin are increased.

TREATMENT PORPHYRIA CUTANEA TARDA

Avoidance of precipitating factors, including abstinence from alcohol, estrogens, iron supplements, and other exacerbating drugs, is the first line of therapy. A complete response can almost always be achieved by repeated phlebotomy (every 1–2 weeks) until hepatic iron is reduced. Chloroquine or hydroxychloroquine may be used in low doses (e.g., 125-mg chloroquine phosphate twice weekly) to promote porphyrin excretion in pts unable to undergo or unresponsive to phlebotomy.

ERYTHROPOIETIC PROTOPORPHYRIA

Erythropoietic protoporphyria is an autosomal dominant disorder due to partial deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway. Its prevalence is 1 in 100,000. Porphyrins (primarily protoporphyrin IX) from bone marrow erythrocytes and plasma are deposited in the skin and lead to cutaneous photosensitivity. Skin photosensitivity usually begins in childhood. The skin manifestations differ from those of other porphyrias, in that vesicular lesions are uncommon. Redness, swelling, burning, and itching can develop within minutes of sun exposure and resemble angioedema. Symptoms may seem out of proportion to the visible skin lesions. Chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. Liver function is usually normal, but liver disease and gallstones may occur. Protoporphyrin levels are increased in bone marrow, circulating erythrocytes, plasma, bile, and feces; protoporphyrin in erythrocytes is free rather than zinc complexed as it is in other types of porphyria or hematologic disorders. Urinary porphyrin levels are normal. Diagnosis is confirmed by identifying a mutation in the ferrochelatase gene.

TREATMENT ERYTHROPOIETIC PROTOPORPHYRIA

Avoidance of sun exposure is essential. Oral β-carotene (120–180 mg/d) improves tolerance to sunlight in many pts. The dosage may be adjusted to maintain serum carotene levels between 10 and 15 μmol/L (600–800 μg/dL). Cholestyramine or activated charcoal may promote fecal excretion of protoporphyrin. Plasmapheresis or IV heme therapy may be beneficial.

WILSON'S DISEASE

Wilson's disease is a rare inherited disorder of copper metabolism, resulting in the toxic accumulation of copper in the liver, brain, and other organs. Individuals with Wilson's disease have mutations in the *ATP7B* gene, which encodes a membrane-bound copper-transporting adenosine triphosphatase (ATPase). Deficiency of this protein impairs copper excretion into the bile and copper incorporation into ceruloplasmin, leading to its rapid degradation.

Clinical Features

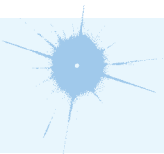
Clinical manifestations typically appear in the mid- to late-teen years but may occur later. Hepatic disease may present as hepatitis, cirrhosis, or hepatic decompensation. In other pts, neurologic or psychiatric disturbances are the first clinical sign and are always accompanied by Kayser-Fleischer rings (corneal deposits of copper). Dystonia, incoordination, or tremor may be present, and dysarthria and dysphagia are common. Autonomic disturbances also may be present. Microscopic hematuria is common. In about 5% of pts, the first manifestation may be primary or secondary amenorrhea or repeated spontaneous abortions.

Diagnosis

Serum ceruloplasmin levels are often low but may be normal in up to 10% of pts. Urine copper levels are elevated. The "gold standard" for diagnosis is an elevated copper level on liver biopsy. Genetic testing can be confirmatory but the disorder can be caused by a large number of different mutations.

TREATMENT WILSON'S DISEASE

Hepatitis or cirrhosis without decompensation should be treated with zinc acetate (50-mg elemental Zn PO three times a day). Zinc is effective by blocking intestinal copper absorption and inducing metallothionein, which sequesters copper in a nontoxic complex. For pts with hepatic decompensation, the chelator trientene (500 mg PO twice a day) plus zinc (separated by at least 1 h to avoid zinc chelation in the intestinal lumen) is recommended, although liver transplantation should be considered for severe hepatic decompensation. For initial neurologic therapy, trientine and zinc are recommended for 8 weeks, followed by therapy with zinc alone. Tetrathiomolybdate is an alternative therapeutic option available in the future. Penicillamine is no longer first-line therapy. Zinc treatment does not require monitoring for toxicity, and 24-h urine copper can be followed for a therapeutic response. Trientine may induce bone marrow suppression and proteinuria. With chelation therapy, measuring free serum copper levels (adjusting total serum copper for ceruloplasmin copper) rather than urine copper is used to monitor therapeutic response. Anticopper therapy must be lifelong.



For a more detailed discussion, see Powell LW: Hemochromatosis, Chap. 428, p. 2514; Desnick RJ, Balwani M: The Porphyrias, Chap. 430, p. 2521; Brewer GJ: Wilson's Disease, Chap. 429, p. 2519, in HPIM-19.

180 The Neurologic Examination

MENTAL STATUS EXAMINATION

- *The bare minimum: During the interview, look for difficulties with communication and determine whether the pt has recall and insight into recent and past events.*

The mental status examination is underway as soon as the physician begins observing and talking with the pt. The goal is to evaluate attention, orientation, memory, insight, judgment, and grasp of general information. Attention: ask pt to respond every time a specific item recurs in a list. Orientation: ask about the day, date, and location. Memory: ask pt to immediately recall a sequence of numbers and test recall of a series of objects after defined times (e.g., 5 and 15 min). Remote memory is also evaluated by assessing pt's ability to provide a cogent chronologic history of the illness or personal life events. Recall of historic events or dates of current events can be used to assess knowledge. Evaluation of language function should include assessment of spontaneous speech, naming, repetition, reading, writing, and comprehension. Additional tests such as ability to draw and copy, perform calculations, interpret proverbs or logic problems, identify right versus left, name and identify body parts, etc., are also important.

A useful screening examination of cognitive function is the mini-mental status examination (MMSE), a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 minutes later); and language (e.g., name pencil and watch; repeat "no if's and's or but's"; follow a three-step command; obey a written command; and write a sentence and copy a design).

CRANIAL NERVE (CN) EXAMINATION

- *The bare minimum: Check the fundi, visual fields (VFs), pupil size and reactivity, extraocular movements, and facial movements.*

CN I

Occlude each nostril sequentially and ask pt to gently sniff and identify a mild test stimulus, such as toothpaste or coffee.

CN II

Check visual acuity with eyeglasses or contact lens correction using a Snellen chart or similar tool. Map VFs by confrontation testing in each quadrant of VF for each eye individually. The best method is to sit facing pt (2–3 ft apart) and then have pt cover one eye gently and fix uncovered eye on examiner's nose. A small white object (e.g., a cotton-tipped applicator) is then moved slowly from periphery of field toward center until seen. Pt's VF should be mapped against examiner's for comparison. Formal perimetry and tangent screen examination are essential to identify small defects. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc recorded. The retinal vessels should be checked for size, regularity, arteriovenous (AV) nicking at crossing points,

hemorrhage, exudates, and aneurysms. The retina, including the macula, should be examined for abnormal pigmentation and other lesions.

CN III, IV, VI

Describe size, regularity, and shape of pupils; reaction (direct and consensual) to light; and convergence (pt follows an object as it moves closer). Check for lid drooping, lag, or retraction. Ask pt to follow your finger (and report any double vision) as you move it horizontally to left and right and vertically with each eye first fully adducted then fully abducted. Check for failure to move fully in particular directions and for presence of regular, rhythmic, involuntary oscillations of eyes (nystagmus). Test quick voluntary eye movements (saccades) as well as pursuit (e.g., follow the finger).

CN V

Feel the masseter and temporalis muscles as pt bites down and test jaw opening, protrusion, and lateral motion against resistance. Examine sensation over entire face. Testing of the corneal reflex is indicated when suggested by the history.

CN VII

Look for asymmetry of face at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, frowning; check puff, whistle, lip pursing, and chin muscle contraction. Observe for differences in strength of lower and upper facial muscles. Taste on the anterior two-thirds of tongue can be affected by lesions of the seventh CN proximal to the chorda tympani.

CN VIII

Check ability to hear tuning fork, finger rub, watch tick, and whispered voice at specified distances with each ear. Check for air versus mastoid bone conduction (Rinne) and lateralization of a tuning fork placed on center of forehead (Weber). Accurate, quantitative testing of hearing requires formal audiometry. Remember to examine tympanic membranes.

CN IX, X

Check for symmetric elevation of palate-uvula with phonation ("ahh"), as well as position of uvula and palatal arch at rest. Sensation in region of tonsils, posterior pharynx, and tongue may also require testing. Pharyngeal ("gag") reflex is evaluated by stimulating posterior pharyngeal wall on each side with a blunt object (e.g., tongue blade). Direct examination of vocal cords by laryngoscopy is necessary in some situations.

CN XI

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid muscle) against resistance.

CN XII

Examine bulk and power of tongue. Look for atrophy, deviation from midline with protrusion, tremor, and small flickering or twitching movements (fasciculations).

MOTOR EXAMINATION

- *The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper limb strength by checking for pronator drift and strength of wrist or finger extensors. Test for lower limb strength by asking pt to walk normally and on heels and toes and testing power of the toe extensors.*

Power should be systematically tested for major movements at each joint (**Table 180-1**). Strength should be recorded using a reproducible scale (e.g., 0 = no movement,

TABLE 180-1 MUSCLES THAT MOVE JOINTS

	Muscle	Nerve	Segmental Innervation	Function
Shoulder	Supraspinatus	Suprascapular n.	C5,6	Abduction of upper arm
	Deltoid	Axillary n.	C5,6	Abduction of upper arm
Forearm	Biceps	Musculocutaneous n.	C5,6	Flexion of the supinated forearm
	Brachioradialis	Radial n.	C5,6	Forearm flexion with arm between pronation and supination
	Triceps	Radial n.	C6,7,8	Extension of forearm
	Ext. carpi radialis	Radial n.	C5,6	Extension and abduction of hand at the wrist
	Ext. carpi ulnaris	P. interosseous n.	C7,8	Extension and adduction of hand at the wrist
	Ext. digitorum	P. interosseous n.	C7,8	Extension of fingers at the MCP joints
	Supinator	P. interosseous n.	C6,7	Supination of the extended forearm
	Flex. carpi radialis	Median n.	C6,7	Flexion and abduction of hand at the wrist
	Flex. carpi ulnaris	Ulnar n.	C7,8,T1	Flexion and adduction of hand at the wrist
	Pronator teres	Median n.	C6,7	Pronation of the forearm
Wrist	Ext. carpi ulnaris	Ulnar n.	C7,8,T1	Extension/adduction at the wrist
	Flex. carpi radialis	Median n.	C6,7	Flexion/abduction at the wrist
Hand	Lumbricals	Median + ulnar n.	C8,T1	Extension of fingers at PIP joint with the MCP joint extended and fixed
	Interossei	Ulnar n.	C8,T1	Abduction/adduction of the fingers
	Flex. digitorum	Median + A. interosseous n.	C7,C8,T1	Flexion of the fingers

(*Continued*)

TABLE 180-1 MUSCLES THAT MOVE JOINTS (*CONTINUED*)

	Muscle	Nerve	Segmental Innervation	Function
Thumb	Opponens pollicis	Median n.	C8,T1	Touching the base of the 5th finger with thumb
	Ext. pollicis	P. interosseous n.	C7,8	Extension of the thumb
	Add. pollicis	Ulnar n.	C8,T1	Adduction of the thumb
	Abd. pollicis	Median n.	C8,T1	Abduction of the thumb
	Flex. pollicis br.	Ulnar n.	C8,T1	Flexion of the thumb
Thigh	Iliopsoas	Femoral n.	L1,2,3	Flexion of the thigh
	Glutei	Sup. + inf. gluteal n.	L4,L5,S1,S2	Abduction, extension, and internal rotation of the leg
	Quadriceps	Femoral n.	L2,3,4	Extension of the leg at the knee
	Adductors	Obturator n.	L2,3,4	Adduction of the leg
	Hamstrings	Sciatic n.	L5,S1,S2	Flexion of the leg at the knee
Foot	Gastrocnemius	Tibial n.	S1,S2	Plantar flexion of the foot
	Tibialis ant.	Deep peroneal n.	L4,5	Dorsiflexion of the foot
	Peronei	Deep peroneal n.	L5,S1	Eversion of the foot
	Tibialis post.	Tibial n.	L4,5	Inversion of the foot
Toes	Ext. hallucis l.	Deep peroneal n.	L5,S1	Dorsiflexion of the great toe

Abbreviation: MCP, metacarpophalangeal; PIP, proximal interphalangeal.

1 = flicker or trace of contraction with no associated movement at a joint, 2 = movement present but cannot be sustained against gravity, 3 = movement against gravity but not against applied resistance, 4 = movement against some degree of resistance, and 5 = full power; 4 values can be supplemented with + and – signs to provide additional gradations). Speed of movement, ability to relax contractions promptly, and fatigue with repetition should all be noted. Loss in bulk and size of muscle (atrophy) should be noted, as well as the presence of irregular involuntary contraction (twitching) of groups of muscle fibers (fasciculations). Any involuntary movements should be noted at rest, during maintained posture, and with voluntary action.

REFLEXES

- *The bare minimum: Tap the biceps, patellar, and Achilles reflexes.*

Important muscle-stretch reflexes to test routinely and the spinal cord segments involved in their reflex arcs include biceps (C5, 6); brachioradialis (C5, 6); triceps (C7, 8); patellar (L3, 4); and Achilles (S1, 2). A common grading scale is 0 = absent, 1 = present but diminished, 2 = normal, 3 = hyperactive, and 4 = hyperactive with clonus (repetitive rhythmic contractions with maintained stretch). The plantar reflex should be tested by using a blunt-ended object such as the point of a key to stroke the outer border of the sole of the foot from the heel toward the base of the great toe. An abnormal response (Babinski sign) is extension (dorsiflexion) of the great toe at the metatarsophalangeal joint. In some cases, this may be associated with abduction (fanning) of other toes and variable degrees of flexion at ankle, knee, and hip. Normal response is plantar flexion of the toes. Superficial abdominal and anal reflexes are important in certain situations; unlike muscle stretch reflexes, these cutaneous reflexes disappear with CNS lesions.

SENSORY EXAMINATION

- *The bare minimum: Ask whether the pt can feel light touch and the temperature of a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands.*

For most purposes it is sufficient to test sensation to pinprick, touch, position, and vibration in each of the four extremities (**Figs. 180-1** and **180-2**). The Romberg maneuver, primarily a test of proprioception, is tested as follows: pt is asked to stand with feet together while eyes are open, and eyes are then closed; loss of balance with the eyes closed is an abnormal response. Specific problems often require more thorough evaluation. Pts with cerebral lesions may have abnormalities in "discriminative sensation" such as the ability to perceive double simultaneous stimuli, to localize stimuli accurately, to identify closely approximated stimuli as separate (two-point discrimination), to identify objects by touch alone (stereognosis), or to judge weights, evaluate texture, or identify letters or numbers written on the skin surface (graphesthesia).

COORDINATION AND GAIT

- *The bare minimum: Test rapid alternating movements of the hands and feet, and the finger-to-nose maneuver. Observe the pt while he or she is walking along a straight line.*

The ability to move the index finger accurately from the nose to the examiner's outstretched finger and the ability to slide the heel of each foot from the knee down the shin are tests of coordination. Additional tests (drawing objects in the air, following a moving finger, tapping with index finger against thumb or alternately against each

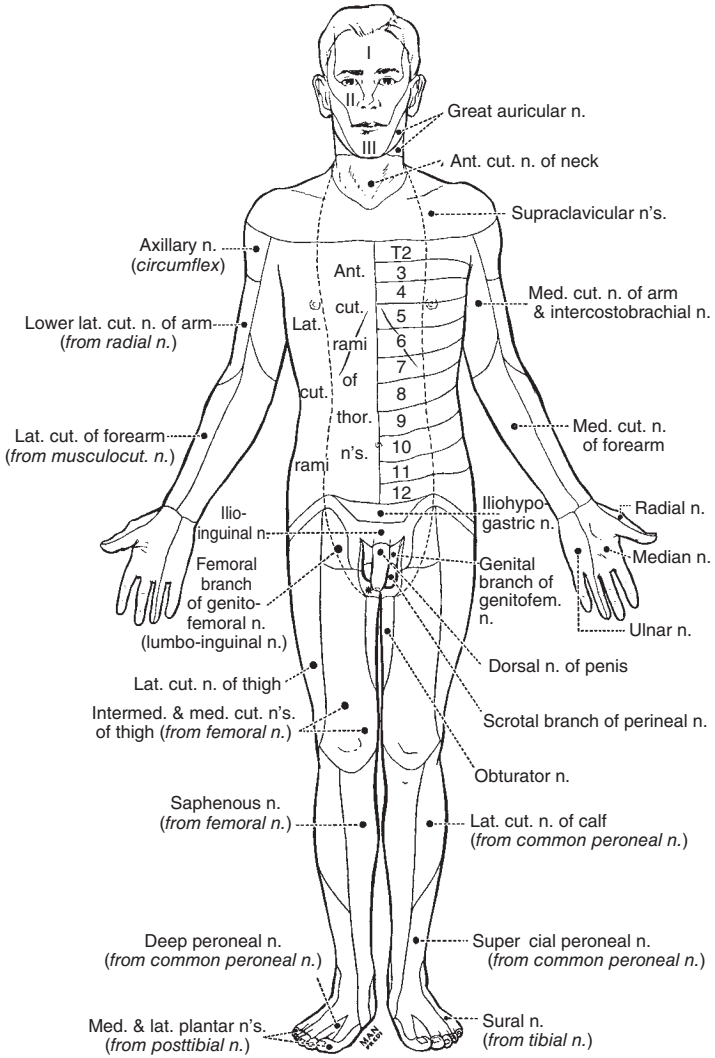


FIGURE 180-1 The cutaneous fields of peripheral nerves. *(Reproduced by permission from W Haymaker, B Woodhall: Peripheral Nerve Injuries, 2nd ed. Philadelphia, Saunders, 1953.)*

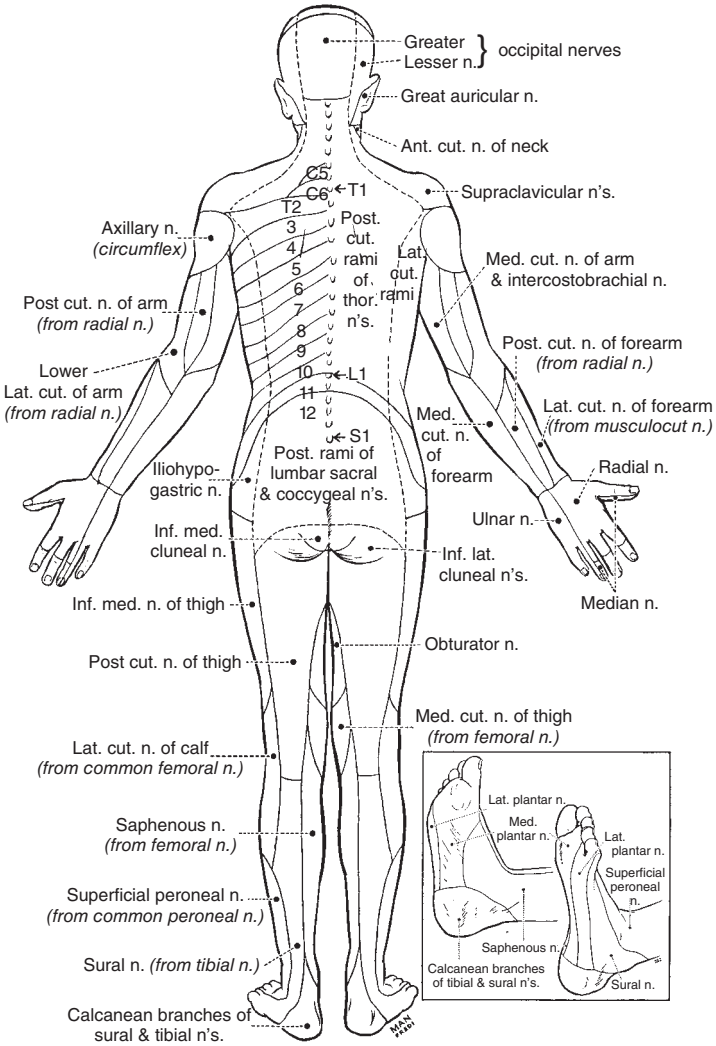


FIGURE 180-1 (*Continued*)

individual finger) may also be useful. The ability to walk normally, on a straight line (tandem walk), and to turn should all be observed.

THE NEUROLOGIC METHOD AND LOCALIZATION

The clinical data obtained from the neurologic examination coupled with a careful history are interpreted to arrive at an anatomic localization that best explains the clinical findings (Table 180-2), to narrow the list of diagnostic possibilities, and to select the diagnostic tests most likely to be informative.

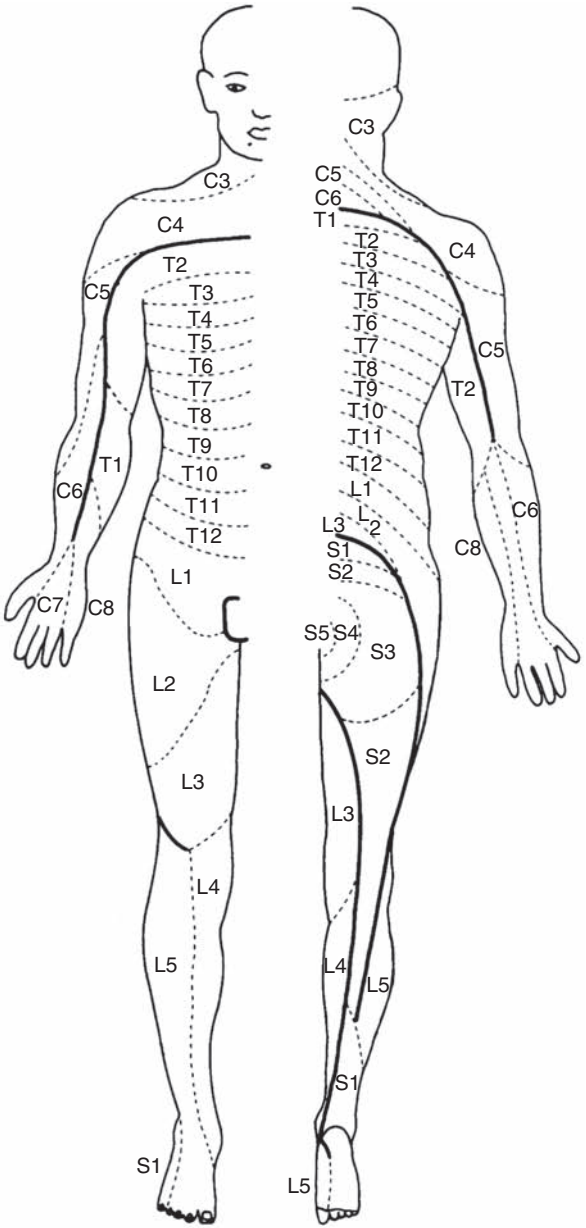
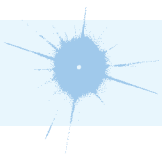


FIGURE 180-2 Distribution of the sensory spinal roots on the surface of the body (dermatomes). *(From D Sinclair: Mechanisms of Cutaneous Sensation. Oxford, UK, Oxford University Press, 1981; with permission from Dr. David Sinclair.)*

TABLE 180-2 FINDINGS HELPFUL FOR LOCALIZATIONS WITHIN THE NERVOUS SYSTEM

	Signs
Cerebrum	Abnormal mental status or cognitive impairment
	Seizures
	Unilateral weakness[a] and sensory abnormalities including head and limbs
	Visual field abnormalities
	Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)
Brainstem	Isolated cranial nerve abnormalities (single or multiple)
	"Crossed" weakness[a] and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg
Spinal cord	Back pain or tenderness
	Weakness[a] and sensory abnormalities sparing the head
	Mixed upper and lower motor neuron findings
	Sensory level
	Sphincter dysfunction
Spinal roots	Radiating limb pain
	Weakness[b] or sensory abnormalities following root distribution (see Figs. 180-1 and 180-2)
	Loss of reflexes
Peripheral nerve	Mid or distal limb pain
	Weakness[b] or sensory abnormalities following nerve distribution (see Figs. 180-1 and 180-2)
	"Stocking or glove" distribution of sensory loss
	Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs
	Increasing weakness with exertion
	Sparing of sensation
Muscle	Bilateral proximal or distal weakness
	Sparing of sensation

[a]Weakness along with other abnormalities having an "upper motor neuron" pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.
[b]Weakness along with other abnormalities having a "lower motor neuron" pattern, i.e., flaccidity and hyporeflexia.



For a more detailed discussion, see Lowenstein DH, Martin JB, Hauser SL: Approach to the Patient with Neurologic Disease, Chap. 437, p. 2535, in HPIM-19.

181 Seizures and Epilepsy

A *seizure* is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. *Epilepsy* is diagnosed when there are recurrent seizures due to a chronic, underlying process.

APPROACH TO THE PATIENT: Seizure

Seizure classification: Essential for diagnosis, therapy, and prognosis (Table 181-1). Seizures are focal or generalized: *focal seizures* originate in networks limited to one cerebral hemisphere, and *generalized seizures* rapidly engage networks distributed across both hemispheres. *Focal seizures* are further divided based on presence or absence of cognitive impairment.

Generalized seizures may occur as a primary disorder or result from secondary generalization of a focal seizure. *Tonic-clonic seizures* (grand mal) cause sudden loss of consciousness, loss of postural control, and tonic muscular contraction producing teeth-clenching and rigidity in extension (tonic phase), followed by rhythmic muscular jerking (clonic phase). Tongue-biting and incontinence may occur during the seizure. Recovery of consciousness is typically gradual over many minutes to hours. Headache and confusion are common postictal phenomena. In *absence seizures* (petit mal) there is sudden, brief impairment of consciousness without loss of postural control. Events rarely last longer than 5–10 s but can recur many times per day. Minor motor symptoms are common, while complex automatisms and clonic activity are not. Other types of generalized seizures include tonic, atonic, and myoclonic seizures.

Etiology: Seizure type and age of pt provide important clues to etiology (Table 181-2).

TABLE 181-1 CLASSIFICATION OF SEIZURES

1. **Focal seizures**
   (Can be further described as having motor, sensory, autonomic, cognitive, or other features)
2. **Generalized seizures**
   a. Absence
      Typical
      Atypical
   b. Tonic clonic
   c. Clonic
   d. Tonic
   e. Atonic
   f. Myoclonic
3. **May be focal, generalized, or unclear**
   Epileptic spasms

TABLE 181-2 CAUSES OF SEIZURES

Neonates (<1 month)	Perinatal hypoxia and ischemia
	Intracranial hemorrhage and trauma
	CNS infection
	Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency)
	Drug withdrawal
	Developmental disorders
	Genetic disorders
Infants and children (>1 month and <12 years)	Febrile
	Genetic disorders (metabolic, degenerative, primary epilepsy syndromes)
	CNS infection
	Developmental disorders
	Trauma
Adolescents (12–18 years)	Trauma
	Genetic disorders
	Infection
	Illicit drug use
	Brain tumor
Young adults (18–35 years)	Trauma
	Alcohol withdrawal
	Illicit drug use
	Brain tumor
	Autoantibodies
Older adults (>35 years)	Cerebrovascular disease
	Brain tumor
	Alcohol withdrawal
	Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia)
	Alzheimer's disease and other degenerative CNS diseases
	Autoantibodies

CLINICAL EVALUATION

Careful history is essential since diagnosis of seizures and epilepsy is often based solely on clinical grounds. Differential diagnosis (Table 181-3) includes syncope or psychogenic seizures ("pseudoseizures"). General examination includes search for infection, trauma, toxins, systemic illness, neurocutaneous abnormalities, and vascular disease. A number of drugs lower the seizure threshold (Table 181-4).

TABLE 181-3 DIFFERENTIAL DIAGNOSIS OF SEIZURES

Syncope	**Transient ischemic attack (TIA)**
Vasovagal syncope	Basilar artery TIA
Cardiac arrhythmia	**Sleep disorders**
Valvular heart disease	Narcolepsy/cataplexy
Cardiac failure	Benign sleep myoclonus
Orthostatic hypotension	**Movement disorders**
Psychological disorders	Tics
Psychogenic seizure	Nonepileptic myoclonus
Hyperventilation	Paroxysmal choreoathetosis
Panic attack	**Special considerations in children**
Metabolic disturbances	Breath-holding spells
Alcoholic blackouts	Migraine with recurrent abdominal pain and cyclic vomiting
Delirium tremens	Benign paroxysmal vertigo
Hypoglycemia	Apnea
Hypoxia	Night terrors
Psychoactive drugs (e.g., hallucinogens)	Sleepwalking
Migraine	
Confusional migraine	
Basilar migraine	

Asymmetries in neurologic exam suggest brain tumor, stroke, trauma, or other focal lesions. An algorithmic approach is shown in Fig. 181-1.

LABORATORY EVALUATION

Routine blood studies are indicated to identify the more common metabolic causes of seizures such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and urine should be obtained especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of CNS infection such as meningitis or encephalitis; it is mandatory in HIV-infected pts even in the absence of symptoms or signs suggesting infection. Testing for autoantibodies in the serum and CSF should be considered in pts presenting with an aggressive form of epilepsy associated with cognitive disturbances.

Electroencephalography

All pts should be evaluated as soon as possible with an EEG, which measures electrical activity of the brain by recording from electrodes placed on the scalp. The presence of *electrographic seizure activity* during the clinically evident event (i.e., abnormal, repetitive, rhythmic activity having an abrupt onset and termination) clearly establishes the diagnosis. The absence of electrographic seizure activity does not exclude a seizure disorder, however. The EEG is always abnormal during generalized tonic-clonic seizures. Continuous monitoring for prolonged periods may be required to capture the EEG abnormalities. The EEG can show abnormal discharges during the interictal period that support the diagnosis of epilepsy and is useful for classifying seizure disorders, selecting anticonvulsant medications, and determining prognosis.

TABLE 181-4 DRUGS AND OTHER SUBSTANCES THAT CAN CAUSE SEIZURES

Alkylating agents (e.g., busulfan, chlorambucil)
Antimalarials (chloroquine, mefloquine)
Antimicrobials/antivirals
β-lactam and related compounds
Quinolones
Acyclovir
Isoniazid
Ganciclovir
Anesthetics and analgesics
Meperidine
Fentanyl
Tramadol
Local anesthetics
Dietary supplements
Ephedra (ma huang)
Gingko
Immunomodulatory drugs
Cyclosporine
OKT3 (monoclonal antibodies to T cells)
Tacrolimus
Interferons
Psychotropics
Antidepressants (e.g., bupropion)
Antipsychotics (e.g., clozapine)
Lithium
Radiographic contrast agents
Drug withdrawal
Alcohol
Baclofen
Barbiturates (short-acting)
Benzodiazepines (short-acting)
Zolpidem
Drugs of abuse
Amphetamine
Cocaine
Phencyclidine
Methylphenidate
Flumazenil[a]

[a]In benzodiazepine-dependent patients.

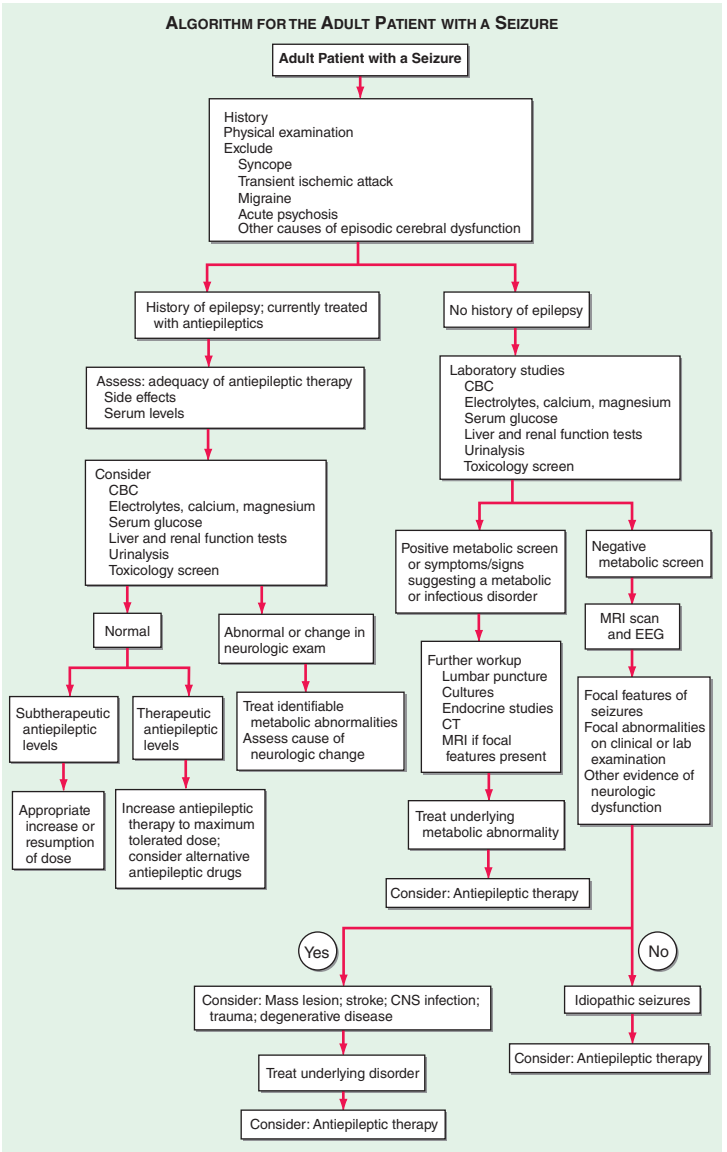


FIGURE 181-1 Evaluation of the adult pt with a seizure.

Brain Imaging

All pts with unexplained new-onset seizures should have a brain imaging study (MRI or CT) to search for an underlying structural abnormality; the only exception may be children who have an unambiguous history and examination suggestive of a

TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS

Generic Name	Trade Name	Principal Uses	Typical Dose; Dose Interval	Half-Life	Therapeutic Range	Adverse Effects		Drug Interactions[a]
						Neurologic	Systemic	
Carbamazepine	Tegretol[c]	Tonic-clonic Focal-onset	600–1800 mg/d (15–35 mg/kg, child); bid (capsules or tablets), tid-qid (oral suspension)	10–17 h (variable due to auto-induction: complete 3–5 wk after initiation)	4–12 μg/mL	Ataxia Dizziness Diplopia Vertigo	Aplastic anemia Leukopenia Gastrointestinal irritation Hepatotoxicity Hyponatremia	Level decreased by enzyme-inducing drugs[b] Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine
Clobazam	Onfi	Lennox-Gastaut syndrome	10–40 mg/d (5–20 mg/d for patients <30 kg body weight); bid	36–42 h (71–82 h for less active metabolite)	Not established	Fatigue Sedation Ataxia Aggression Insomnia	Constipation Anorexia Skin rash	Level increased by CYP2C19 inhibitors
Clonazepam	Klonopin	Absence Atypical absence Myoclonic	1–12 mg/d; qd-tid	24–48 h	10–70 ng/mL	Ataxia Sedation Lethargy	Anorexia	Level decreased by enzyme-inducing drugs[b]

(*Continued*)

TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)

Generic Name	Trade Name	Principal Uses	Typical Dose; Dose Interval	Half-Life	Therapeutic Range	Adverse Effects		Drug Interactions[a]
						Neurologic	Systemic	
Ethosuximide	Zarontin	Absence	750–1250 mg/d (20-40 mg/kg); qd-bid	60 h, adult 30 h, child	40–100 µg/mL	Ataxia Lethargy Headache	Gastrointestinal irritation Skin rash Bone marrow suppression	Level decreased by enzyme-inducing drugs[b] Level increased by valproic acid
Ezogabine	Potiga	Focal-onset	800–1200 mg/d; tid	7–11 h	Not established	Dizziness Fatigue Sedation Confusion Vertigo Tremor	Retinal abnormalities Skin discoloration Cardiac conduction (QT interval prolongation) Urinary retention	Level decreased by enzyme-inducing drugs[b]
Felbamate	Felbatol	Focal-onset Lennox-Gastaut syndrome Tonic-clonic	2400–3600 mg/d, tid-qid	16–22 h	30–60 µg/mL	Insomnia Dizziness Sedation Headache	Aplastic anemia Hepatic failure Weight loss Gastrointestinal irritation	Increases phenytoin, valproic acid, active carbamazepine metabolite
Gabapentin	Neurontin	Focal-onset	900–2400 mg/d; tid-qid	5–9 h	2–20 µg/mL	Sedation Dizziness Ataxia Fatigue	Gastrointestinal irritation Weight gain Edema	No known significant interactions

Lacosamide	Vimpat	Focal-onset	200–400 mg/d; bid	13 h	Not established	Dizziness Ataxia Diplopia Vertigo	Gastrointestinal irritation Cardiac conduction (PR interval prolongation)	Level decreased by enzyme-inducing drugs[b]
Lamotrigine	Lamictal[c]	Focal-onset Tonic-clonic Atypical absence Myoclonic Lennox-Gastaut syndrome	150–500 mg/d; bid (immediate release), daily (extended release) (lower daily dose for regimens with valproic acid; higher daily dose for regimens with an enzyme inducer)	25 h 14 h (with enzyme-inducers), 59 h (with valproic acid)	2.5–20 µg/mL	Dizziness Diplopia Sedation Ataxia Headache	Skin rash Stevens-Johnson syndrome	Level decreased by enzyme-inducing drugs[b] and oral contraceptives Level increased by valproic acid
Levetiracetam	Keppra[c]	Focal-onset	1000–3000 mg/d; bid (immediate release), daily (extended release)	6–8 h	5–45 µg/mL	Sedation Fatigue Incoordination Mood changes	Anemia Leukopenia	No known significant interactions

(*Continued*)

TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)

Generic Name	Trade Name	Principal Uses	Typical Dose; Dose Interval	Half-Life	Therapeutic Range	Adverse Effects		Drug Interactions[a]
						Neurologic	Systemic	
Oxcarbazepine[c]	Trileptal	Focal-onset Tonic-clonic	900–2400 mg/d (30–45 mg/kg, child); bid	10–17 h (for active metabolite)	10–35 μg/mL	Fatigue Ataxia Dizziness Diplopia Vertigo Headache	See carbamazepine	Level decreased by enzyme-inducing drugs[b] May increase phenytoin
Phenobarbital	Luminal	Tonic-clonic Focal-onset	60–180 mg/d; qd-tid	90 h	10–40 μg/mL	Sedation Ataxia Confusion Dizziness Decreased libido Depression	Skin rash	Level increased by valproic acid, phenytoin
Phenytoin (diphenylhydantoin)	Dilantin	Tonic-clonic Focal-onset	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-tid	24 h (wide variation, dose-dependent)	10–20 μg/mL	Dizziness Diplopia Ataxia Incoordination Confusion	Gingival hyperplasia Lymphadenopathy Hirsutism Osteomalacia Facial coarsening Skin rash	Level increased by isoniazid, sulfonamides, fluoxetine Level decreased by enzyme-inducing drugs[b] Altered folate metabolism

Primidone	Mysoline	Tonic-clonic Focal-onset	750–1000 mg/d; bid-tid	Primidone, 8–15 h Phenobarbital, 90 h	Primidone, 4–12 µg/mL Phenobarbital, 10–40 µg/mL	Same as phenobarbital		Level increased by valproic acid Level decreased by phenytoin (increased conversion to phenobarbital)
Rufinamide	Banzel	Lennox-Gastaut syndrome	3200 mg/d (45 mg/kg, child); bid	6–10 h	Not established	Sedation Fatigue Dizziness Ataxia Headache Diplopia	Gastrointestinal irritation Leukopenia Cardiac conduction (QT interval shortening)	Level decreased by enzyme-inducing drugs[b] Level increased by valproic acid May increase phenytoin
Tiagabine	Gabitril	Focal-onset	32–56 mg/d; bid-qid (as adjunct to enzyme-inducing antiepileptic drug regimen)	2–5 h (with enzyme inducer), 7–9 h (without enzyme inducer)	Not established	Confusion Sedation Depression Dizziness Speech or language problems Paresthesias Psychosis	Gastrointestinal irritation	Level decreased by enzyme-inducing drugs[b]

(*Continued*)

TABLE 181-5 DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (*CONTINUED*)

Generic Name	Trade Name	Principal Uses	Typical Dose; Dose Interval	Half-Life	Therapeutic Range	Adverse Effects		Drug Interactions[a]
						Neurologic	Systemic	
Topiramate	Topamax	Focal-onset Tonic-clonic Lennox-Gastaut syndrome	200–400 mg/d; bid (immediate release), daily (extended release)	20 h (immediate release), 30 h (extended release)	2–20 μg/mL	Psychomotor slowing Sedation Speech or language problems Fatigue Paresthesias	Renal stones (avoid use with other carbonic anhydrase inhibitors) Glaucoma Weight loss Hypohidrosis	Level decreased by enzyme-inducing drugs[b]
Valproic acid (valproate sodium, divalproex sodium)	Depakene Depakote[c]	Tonic-clonic Absence Atypical absence Myoclonic Focal-onset Atonic	750–2000 mg/d (20–60 mg/kg); bid-qid (immediate and delayed release), daily (extended release)	15 h	50–125 μg/mL	Ataxia Sedation Tremor	Hepatotoxicity Thrombocytopenia Gastrointestinal irritation Weight gain Transient alopecia Hyperammonemia	Level decreased by enzyme-inducing drugs[b]
Zonisamide	Zonegran	Focal-onset Tonic-clonic	200–400 mg/d; qd-bid	50–68 h	10–40 μg/mL	Sedation Dizziness Confusion Headache Psychosis	Anorexia Renal stones Hypohidrosis	Level decreased by enzyme-inducing drugs[b]

[a]Examples only; please refer to other sources for comprehensive listings of all potential drug-drug interactions.
[b]Phenytoin, carbamazepine, phenobarbital. [c]Extended-release product available.

TABLE 181-6 SELECTION OF ANTIEPILEPTIC DRUGS

Generalized-Onset Tonic-Clonic	Focal	Typical Absence	Atypical Absence, Myoclonic, Atonic
First-Line			
Lamotrigine	Lamotrigine	Valproic acid	Valproic acid
Valproic acid	Carbamazepine	Ethosuximide	Lamotrigine
	Oxcarbazepine	Lamotrigine	Topiramate
	Phenytoin		
	Levetiracetam		
Alternatives			
Zonisamide[a]	Topiramate	Lamotrigine	Clonazepam
Phenytoin	Zonisamide[a]	Clonazepam	Felbamate
Carbamazepine	Valproic acid		Clobazam
Oxcarbazepine	Tiagabine[a]		Rufinamide
Topiramate	Gabapentin[a]		
Phenobarbital	Lacosamide[a]		
Primidone	Exogabine[a]		
Felbamate	Phenobarbital		
	Primidone		
	Felbamate		

[a]As adjunctive therapy.

benign, generalized seizure disorder such as absence epilepsy. Newer MRI methods have increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of cortical neuronal migration.

TREATMENT SEIZURES AND EPILEPSY

- Acute management of seizures
  - Pt should be placed in semiprone position with head to the side to avoid aspiration.
  - Tongue blades or other objects should not be forced between clenched teeth.
  - Oxygen should be given via face mask.
  - Reversible metabolic disorders (e.g., hypoglycemia, hyponatremia, hypocalcemia, drug or alcohol withdrawal) should be promptly corrected.
  - Treatment of status epilepticus is discussed in Chap. 22.
- Longer-term therapy includes treatment of underlying conditions, avoidance of precipitating factors, prophylactic therapy with antiepileptic medications or surgery, and addressing various psychological and social issues.
- Choice of antiepileptic drug therapy depends on a variety of factors including seizure type, dosing schedule, and potential side effects (Tables 181-5 and 181-6).
- Therapeutic goal is complete cessation of seizures without side effects using a single drug (monotherapy) and a dosing schedule that is easy for the pt to follow.
  - If ineffective, medication should be increased to maximal tolerated dose based primarily on clinical response rather than serum levels.

– If still unsuccessful, a second drug should be added, and when control is obtained, the first drug can be slowly tapered. Some pts will require polytherapy with two or more drugs, although monotherapy should be the goal.
– Pts with certain epilepsy syndromes (e.g., temporal lobe epilepsy) are often refractory to medical therapy and benefit from surgical excision of the seizure focus.

For a more detailed discussion, see Lowenstein DH: Seizures and Epilepsy, Chap. 445, p. 2542, in HPIM-19.

182 Dementia

Dementia

Dementia is an acquired deterioration in cognitive ability that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia; 10% of persons over age 70 and 20–40% of individuals over age 85 have clinically identifiable memory loss. Other mental faculties are also affected in dementia, such as language, visuospatial ability, calculation, judgment, and problem solving. Neuropsychiatric and social deficits develop in many dementia syndromes, resulting in depression, withdrawal, hallucinations, delusions, agitation, insomnia, and disinhibition. Dementia is usually chronic and progressive.

Diagnosis

Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and the Cognistat are useful screening tests and can follow progression. A functional assessment should also be performed to help determine the day-to-day impact of the disorder.

APPROACH TO THE PATIENT: **Dementia**

Differential Diagnosis: Dementia has many causes (Table 182-1). It is essential to exclude treatable etiologies; the most common potentially reversible diagnoses are depression, hydrocephalus, and alcohol dependence. The major degenerative dementias can usually be distinguished by distinctive symptoms, signs, and neuroimaging features (Table 182-2).

History: A subacute onset of confusion may represent delirium and should trigger the search for intoxication, infection, or metabolic derangement (Chap. 16). An elderly person with slowly progressive memory loss over several years is likely to have Alzheimer's disease (AD). A change in personality, disinhibition, gain of weight, or compulsive eating suggests frontotemporal dementia (FTD), not AD;

TABLE 182-1 DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism[a]
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication[a]
Diffuse white matter disease (Binswanger's)	
Less Common Causes of Dementia	
Vitamin deficiencies	Toxic disorders
Thiamine (B_1): Wernicke's encephalopathy[a]	Drug, medication, and narcotic poisoning[a]
B_{12} (subacute combined degeneration)[a]	Heavy metal intoxication[a]
Nicotinic acid (pellagra)[a]	Organic toxins
Endocrine and other organ failure	Psychiatric
Hypothyroidism[a]	Depression (pseudodementia)[a]
Adrenal insufficiency and Cushing's syndrome[a]	Schizophrenia[a]
Hypo- and hyperparathyroidism[a]	Conversion disorder[a]
Renal failure[a]	Degenerative disorders
Liver failure[a]	Huntington's disease
Pulmonary failure[a]	Multisystem atrophy
Chronic infections	Hereditary ataxias (some forms)
HIV	Frontotemporal lobar degeneration spectrum
Neurosyphilis[a]	Multiple sclerosis
Papovavirus (JC virus) (progressive multifocal leukoencephalopathy)	Adult Down's syndrome with Alzheimer's disease
Tuberculosis, fungal, and protozoal[a]	ALS-parkinsonism-dementia complex of Guam
Whipple's disease[a]	Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
Head trauma and diffuse brain damage	Miscellaneous
Chronic traumatic encephalopathy	Sarcoidosis[a]
Chronic subdural hematoma[a]	Vasculitis[a]
Postanoxia	CADASIL, etc.
Postencephalitis	Acute intermittent porphyria[a]
Normal-pressure hydrocephalus[a]	Recurrent nonconvulsive seizures[a]
Intracranial hypotension	Additional conditions in children or adolescents
Neoplastic	Pantothenate kinase–associated neurodegeneration
Primary brain tumor[a]	Subacute sclerosing panencephalitis
Metastatic brain tumor[a]	Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)
Paraneoplastic/autoimmune limbic encephalitis[a]	

[a]Potentially reversible dementia.

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

TABLE 182-2 CLINICAL DIFFERENTIATION OF THE MAJOR DEMENTIAS

Disease	First Symptom	Mental Status	Neuropsychiatry	Neurology	Imaging
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement.

apathy, loss of executive function, progressive abnormalities in speech, or relative sparing of memory or visuospatial abilities also suggests FTD. Dementia with Lewy bodies (DLB) is suggested by the early presence of visual hallucinations, parkinsonism, tendency to delirium, sensitivity to psychoactive medications, or a REM behavior disorder (RBD, the loss of skeletal muscle paralysis during dreaming).

A history of stroke suggests vascular dementia, which may also occur with hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. Rapid progression of dementia with myoclonus suggests a prion disease such as Creutzfeldt-Jakob disease (CJD). A rapidly progressive dementia with psychiatric symptoms and seizures suggests paraneoplastic *encephalitis associated with NMDA receptor antibodies*; affected pts are often young women with ovarian teratoma. Gait disturbance is prominent with vascular dementia, Parkinson's disease, DLB, or normal-pressure hydrocephalus. Multiple sex partners or IV drug use should trigger search for an infection, especially HIV or syphilis. A history of head trauma could indicate chronic subdural hematoma, chronic traumatic encephalopathy, or normal-pressure hydrocephalus. Alcoholism may suggest malnutrition and thiamine deficiency. A history of gastric surgery may result in loss of intrinsic factor and vitamin B_{12} deficiency. A careful review of medications, especially of sedatives and tranquilizers, may raise the issue of drug intoxication. A family history of dementia is found in Huntington's disease and in familial forms of AD, FTD, DLB, or prion disorders. Insomnia or weight loss is often seen with depression-related cognitive impairments, which can also be caused by the recent death of a loved one.

Examination: It is essential to document the dementia, look for other signs of nervous system involvement, and search for clues of a systemic disease that might be responsible for the cognitive disorder. Typical AD does not affect motor systems until late in the course. In contrast, FTD pts often develop axial rigidity, supranuclear gaze palsy, or features of amyotrophic lateral sclerosis. In DLB, initial symptoms may be the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, and festinating gait). Unexplained falls, axial rigidity, dysphagia, and gaze deficits suggest progressive supranuclear palsy (PSP).

Focal neurologic deficits may occur in vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B_{12} deficiency. A peripheral neuropathy could also indicate an underlying vitamin deficiency or heavy metal intoxication. Dry cool skin, hair loss, and bradycardia suggest hypothyroidism. Confusion associated with repetitive stereotyped movements may indicate ongoing seizure activity. Hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Such sensory deficits are common in the elderly.

Choice of Diagnostic Studies: A reversible or treatable cause must not be missed, yet no single etiology is common; thus a screen must employ multiple tests, each of which has a low yield. **Table 182-3** lists most screening tests for dementia. Guidelines recommend the routine measurement of a complete blood count, electrolytes, renal and thyroid function, a vitamin B_{12} level, and a neuroimaging study (CT or MRI). Lumbar puncture need not be done routinely but is indicated if infection or inflammation is a consideration; CSF levels of tau protein and amyloid β_{42} show differing patterns with the various dementias although their sensitivity and specificity are not yet sufficiently high to warrant routine use. An EEG is rarely helpful except to suggest a prion disease or an underlying nonconvulsive seizure disorder. The role of functional-metabolic imaging in the diagnosis of dementia is still under study; amyloid imaging has recently shown promise for the diagnosis of AD; currently the main clinical value is to exclude AD as the likely cause of dementia in pts who have negative scans. Brain biopsy may be indicated to diagnose vasculitis, potentially treatable neoplasms, or unusual infections.

TABLE 182-3 EVALUATION OF THE PATIENT WITH DEMENTIA

Routine Evaluation	Optional Focused Tests	Occasionally Helpful Tests
History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B_{12}	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
		Lab screen for autoantibodies

Diagnostic Categories

Reversible Causes	Irreversible/Degenerative Dementias	Psychiatric Disorders
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Autoimmune encephalopathy		

Associated Treatable Conditions	
Depression	Agitation
Seizures	Caregiver "burnout"
Insomnia	Drug side effects

Abbreviations: PET, positron emission tomography; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

ALZHEIMER'S DISEASE

Most common cause of dementia; 10% of all persons over age 70 have significant memory loss, and in more than half the cause is AD. Cost is >$50,000 annually for a single pt with advanced AD.

Clinical Manifestations

Cognitive changes follow a characteristic pattern beginning with memory impairment and spreading to language and visuospatial deficits, although 20% present with non-memory complaints such as word-finding, organizational, or navigational difficulty. Memory loss is often not recognized initially, in part due to preservation of social

graces until later phases; impaired activities of daily living (keeping track of finances, appointments) draw attention of friends/family. Once the memory loss becomes noticeable to the pt and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term *mild cognitive impairment* (MCI) is applied; roughly 50% will progress to AD over 4 years. Disorientation, poor judgment, poor concentration, aphasia, and apraxia are increasingly evident as the disease progresses. Pts may be frustrated or unaware of deficit. In end-stage AD, pts become rigid, mute, incontinent, and bedridden. Help may be needed with the simplest tasks, such as eating, dressing, and toilet function. Often, death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. Typical duration is 8–10 years, but the course can range from 1 to 25 years.

Pathogenesis

Risk factors for AD: old age, positive family history, and a history of head trauma with concussion. Pathology: neuritic plaques composed in part of Aβ amyloid, derived from amyloid precursor protein (APP); neurofibrillary tangles composed of abnormally phosphorylated tau protein. The apolipoprotein E (apoE) ε4 allele accelerates age of onset of AD and is associated with sporadic and late-onset familial cases. ApoE testing is not indicated as a predictive test. Rare genetic causes of AD are Down syndrome and mutations in APP, presenilin-1, and presenilin-2 genes; all increase production of Aβ amyloid. Genetic testing available for presenilin mutations; likely to be revealing only in early-age-of-onset familial AD.

TREATMENT ALZHEIMER'S DISEASE

- AD cannot be cured, and no highly effective drug exists. The focus is on judicious use of cholinesterase inhibitor drugs; symptomatic management of behavioral problems; and building rapport with the pt, family members, and other caregivers.
- Donepezil, rivastigmine, galantamine, and memantine are approved by the FDA for treatment of AD. Due to hepatotoxicity, tacrine is no longer used. With the exception of memantine, their action is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine. Memantine appears to act by blocking overexcited *N*-methyl-D-aspartate (NMDA) channels.
  - These compounds are only modestly effective and offer little or no benefit in the late stages of AD; they are associated with improved caregiver ratings of pts' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years.
  - Donepezil (Aricept), target dose 10 mg/d PO, has the advantages of few side effects and single daily dosage.
- There is no role for hormone replacement therapy in prevention of AD in women, and no benefit has been found in the treatment of established AD with estrogen.
- Randomized trials of *Ginkgo biloba* have found it to be ineffective. Retrospective studies suggest that NSAIDs and statin medications may have a protective effect on dementia if used prior to the onset of the disease but do not benefit established AD.
- Other experimental approaches target amyloid either through diminishing its production or promoting clearance by passive immunization with monoclonal antibodies. New trials have targeted cognitively normal elderly who are amyloid positive with PET.
- Depression, common in early stages of AD, may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs)

are often used due to their low anticholinergic side effects. Management of behavioral problems in conjunction with family and caregivers is essential. Mild sedation may help insomnia.

- Control of agitation usually involves low doses of atypical antipsychotic medications, but recent trials have shown mild efficacy with significant side effects related to sleep and gait; in addition, all of the antipsychotics carry a black box warning in the elderly, increasing the risk of cardiovascular complications and death, and therefore should be used with caution.
- Notebooks and posted daily reminders can function as memory aids in early stages. Kitchens, bathrooms, and bedrooms need evaluation for safety. Pts must eventually stop driving. Caregiver burnout is common; nursing home placement may be necessary. Local and national support groups (Alzheimer's Disease and Related Disorders Association) are valuable resources.

OTHER CAUSES OF DEMENTIA

Frontotemporal Dementia

Often begins in the fifth to seventh decades; in this age group it is nearly as prevalent as AD. Unlike AD, behavioral symptoms may predominate in the early stages of FTD. Extremely heterogeneous; presents with combinations of disinhibition, dementia, apraxia, parkinsonism, and motor neuron disease. May be sporadic or inherited. Treatment is symptomatic; no therapies known to slow progression or improve cognitive symptoms. Many of the behaviors that accompany FTD such as depression, hyperorality, compulsions, and irritability may be helped with SSRIs.

Dementia with Lewy Bodies

Characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often RBD. Dementia can precede or follow the appearance of parkinsonism; when it occurs after an established diagnosis of Parkinson's disease, many use the term Parkinson's disease dementia (PDD). Lewy bodies are intraneuronal cytoplasmic inclusions. Anticholinesterase compounds often provide significant benefit due to a severe cholinergic deficit in DLB. Exercise programs to maximize motor function and protect against fall-related injury, and antidepressants to treat depressive syndromes may be helpful. Antipsychotics in low doses to alleviate psychosis may be considered, although DLB pts are extremely sensitive to these agents and may experience worsening of extrapyramidal symptoms.

Vascular Dementia

Typically follows a pattern of either multiple strokelike episodes (multi-infarct dementia) or diffuse white matter disease (leukoaraiosis, subcortical arteriosclerotic encephalopathy, Binswanger's disease) (Fig. 182-1). Unlike AD, focal neurologic signs (e.g., hemiparesis) may be apparent at presentation. Treatment focuses on underlying causes of atherosclerosis.

Normal-Pressure Hydrocephalus (NPH)

Uncommon; presents as a gait disorder (ataxic or apractic), dementia, and urinary incontinence. Gait improves in some pts following ventricular shunting; dementia and incontinence do not improve. The diagnosis is difficult to make, and the clinical picture may overlap with several other causes of dementia including AD; historically many individuals treated for NPH have suffered from other dementias.

Huntington's Disease

Chorea, behavioral disturbance, and a frontal/executive disorder (Chap. 54). Typical onset fourth to fifth decade but can present at almost any age. Autosomal dominant

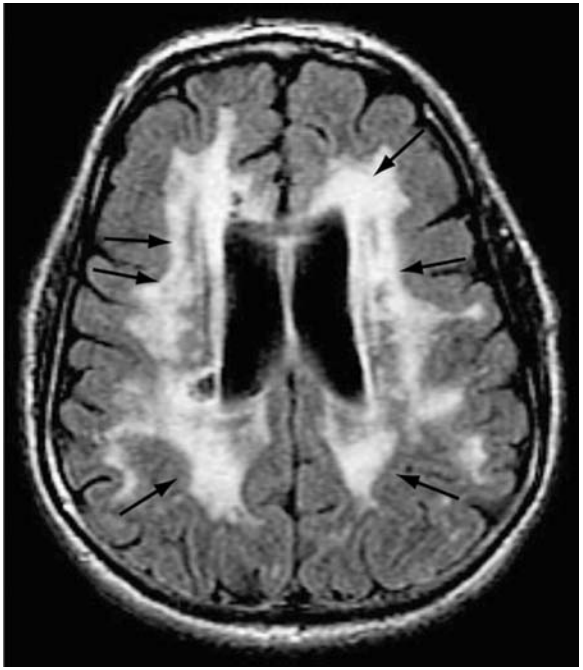


FIGURE 182-1 Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (*arrows*) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in pts with dementia of a vascular etiology.

inheritance due to expanded trinucleotide repeat in gene encoding the protein huntingtin. Diagnosis confirmed with genetic testing coupled with genetic counseling. Symptomatic treatment of movements and behaviors; SSRIs may help depression.

Creutzfeldt-Jakob Disease

Prion disorders such as CJD are rare (~1 per million). CJD is a rapidly progressive disorder with dementia, focal cortical signs, rigidity, and myoclonus; death in <1 year from first symptom. The markedly abnormal periodic discharges on EEG and cortical ribboning and basal ganglia hyperintensities on diffusion-weighted and fluid-attenuated inversion recovery MRI are diagnostic features. No proven treatments exist.



For a more detailed discussion, see Seeley WW, Miller BL: Dementia, Chap. 35, p. 170, in HPIM-19; Seeley WW, Miller BL: Alzheimer's Disease and Other Dementias, Chap. 448, p. 2598, in HPIM-19.

183 Parkinson's Disease

CLINICAL FEATURES

Parkinsonism is a general term used to define a syndrome manifest as bradykinesia (slowness of voluntary movements) with rigidity and/or tremor; it has a wide differential diagnosis (Table 183-1). *Parkinson's disease* (PD) is idiopathic parkinsonism without evidence of more widespread neurologic involvement. PD afflicts >1 million individuals in the United States. Mean age of onset is about 60 years; course progressive over 10–25 years. Tremor ("pill rolling" of hands) at rest (4–6 Hz). Presentation with tremor confined to one limb or one side of body is common. Other findings: rigidity ("cogwheeling"—increased ratchet-like resistance to passive limb movements), bradykinesia, fixed expressionless face (facial masking) with reduced frequency of blinking, hypophonic voice, drooling, impaired rapid alternating movements, micrographia (small handwriting), reduced arm swing, and flexed "stooped" posture with walking, shuffling gait, difficulty initiating or stopping walking, en-bloc turning (multiple small steps required to turn), retropulsion (tendency to fall backwards). Nonmotor aspects of PD include depression and anxiety, cognitive impairment, sleep disturbances, sensation of inner restlessness, loss of smell (*anosmia*), and disturbances of autonomic function. Normal muscular strength, deep tendon reflexes, and sensory examination. Diagnosis based on history and examination; neuroimaging, EEG, and CSF studies usually normal for age.

TABLE 183-1 DIFFERENTIAL DIAGNOSIS OF PARKINSONISM

Parkinson's Disease	Atypical Parkinsonism	Secondary Parkinsonism	Other Neurodegenerative Disorders
Genetic	Multiple-system atrophy (MSA)	Drug-induced	Wilson's disease
Sporadic	Cerebellar type (MSA-c)	Tumor	Huntington's disease
Dementia with Lewy bodies	Parkinson type (MSA-p)	Infection	Neurodegeneration with brain iron accumulation
	Progressive supranuclear palsy	Vascular	
	Corticobasal ganglionic degeneration	Normal-pressure hydrocephalus	SCA 3 (spinocerebellar ataxia)
	Frontotemporal dementia	Trauma Liver failure	Fragile X–associated ataxia-tremor-parkinsonism
		Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Prion disease
			Dystonia-parkinsonism (DYT3)
			Alzheimer's disease with parkinsonism

Abbreviations: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

PATHOPHYSIOLOGY

Most PD cases occur sporadically and are of unknown cause. Degeneration of pigmented pars compacta neurons of the substantia nigra in the midbrain resulting in lack of dopaminergic input to striatum; accumulation of cytoplasmic intraneural inclusion granules (Lewy bodies). Cause of cell death is unknown, but it may result from generation of free radicals and oxidative stress, inflammation, or mitochondrial dysfunction; no environmental factor has yet been conclusively determined to cause typical PD. Rare genetic forms of parkinsonism exist (~5% of cases); most common are mutations in glucocerebrosidase, *LRRK2,* α-synuclein or parkin genes. Early age of onset suggests a possible genetic cause of PD, although *LLRK2* mutations cause PD in the same age range as sporadic.

DIFFERENTIAL DIAGNOSIS

Atypical parkinsonism refers to a group of neurodegenerative conditions usually associated with more widespread neurodegeneration than is found in PD including multiple-system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and frontotemporal dementia (FTD). Secondary parkinsonism can be associated with drugs (neuroleptics as well as GI medications such as metoclopramide, all of which block dopamine), infection, or exposure to toxins such as carbon monoxide or manganese. Some features to suggest that parkinsonism might be due to a condition other than PD are shown in **Table 183-2**.

TABLE 183-2 FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM

Symptoms/Signs	Alternative Diagnosis to Consider
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired down gaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

TREATMENT PARKINSON'S DISEASE (SEE FIG. 183-1, TABLE 183-3)

Goals are to maintain function and avoid drug-induced complications; start therapy when symptoms interfere with quality of life. Bradykinesia, tremor, rigidity, and abnormal posture respond early in illness; cognitive symptoms, hypophonia, autonomic dysfunction, and balance difficulties respond poorly.

LEVODOPA

- Routinely administered in combination with a decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting. In the United States, levodopa is combined with carbidopa (Sinemet).
- Levodopa is also available in controlled-release formulations and in with a catechol-O-methyl transferase (COMT) inhibitor (see below).
- Levodopa remains the most effective symptomatic treatment for PD, and lack of response to the medication despite an adequate trial should cause the diagnosis to be questioned.
- Side effects include nausea, vomiting, and orthostatic hypotension that can be avoided by gradual titration.
- Levodopa-induced motor complications consist of fluctuations in motor response and involuntary movements known as dyskinesias.
- When pts initially take the drug, the benefits are long-lasting; with continued treatment, the duration of benefit following an individual dose becomes progressively shorter ("wearing-off effect").

DOPAMINE AGONISTS

- A diverse group of drugs that act directly on dopamine receptors. Second-generation non-ergot dopamine agonists are commonly used (e.g., pramipexole, ropinirole, rotigotine).
- Compared with levodopa, dopamine agonists are longer acting and thus provide a more uniform stimulation of dopamine receptors; less prone to induce dyskinesias compared with levodopa.
- They are effective as monotherapeutic agents and as adjuncts to carbidopa/levodopa therapy.
- Side effects include nausea, vomiting, and postural hypotension. Hallucinations and cognitive impairment are more common than with levodopa, so caution is urged in those older than 70.
- Sedation with sudden episodes of falling asleep while driving have been reported.
- Associated with impulse-control disorders including pathologic gambling, hypersexuality, and compulsive eating and shopping.

MAO-B INHIBITORS

- Block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter; generally safe and well tolerated.
- Provide modest antiparkinson benefits when used as monotherapy in early disease.
- Recent work has examined whether these drugs could have a disease-modifying effect; however, long-term significance is uncertain.

COMT INHIBITORS

- When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized by COMT; inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability.
- Combining levodopa with a COMT inhibitor reduces wearing-off time.

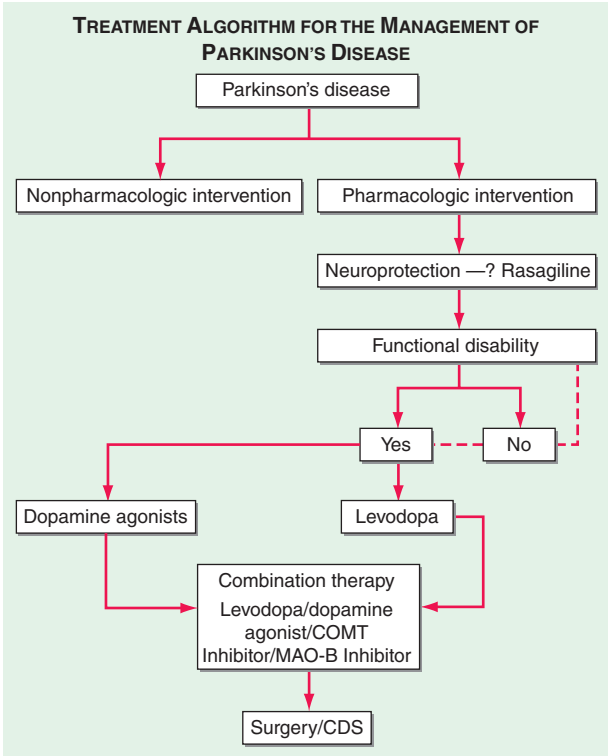


FIGURE 183-1 Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: No drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonists ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because pts may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: Many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected pts because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger pts with functionally significant disability to reduce the risk of motor complications; and levodopa for pts with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: Motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: Interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (*Adapted from C Olanow et al: Neurology 72:S1, 2009.*)

TABLE 183-3 DRUGS COMMONLY USED FOR TREATMENT OF PARKINSON'S DISEASE[a]

Agent	Available Dosages	Typical Dosing
Levodopa[a]		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/d 2–4 times/d
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250	
Carbidopa/levodopa/ entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC		2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	1.0 mg QAM

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

OTHER MEDICAL THERAPIES

- Anticholinergics (trihexyphenidyl, benztropine) have their major clinical effect on tremor. Use in the elderly is limited due to propensity for inducing urinary dysfunction, glaucoma, and particularly cognitive impairment.
- The mechanism of action of amantadine is unknown; it has N-methyl-D-aspartate (NMDA) antagonist properties; it is most commonly used as an anti-dyskinesia agent in pts with advanced PD. Side effects include livedo reticularis, weight gain, and impaired cognitive function; discontinue slowly as pts can experience withdrawal symptoms.

SURGICAL TREATMENTS

- In refractory cases, surgical treatment of PD should be considered.

- Deep-brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna (GPi) has largely replaced ablation surgery (e.g., pallidotomy or thalamotomy).
- DBS is primarily indicated for pts who suffer disability resulting from severe tremor or levodopa-induced motor complications; the procedure is profoundly beneficial to many pts.
- Contraindications to surgery include atypical PD, advanced cognitive impairment, major psychiatric illness, substantial medical comorbidities, and advanced age (a relative factor).
- Experimental surgical procedures including cell-based therapies, gene therapies, and trophic factors are under investigation.

For a more detailed discussion, see Olanow CW, Schapira AHV, Obeso JA: Parkinson's Disease and Other Movement Disorders, Chap. 449, p. 2609, in HPIM-19.

184 Ataxic Disorders

CLINICAL PRESENTATION

Symptoms and signs may include gait impairment, visual blurring due to nystagmus, unclear ("scanning") speech, hand incoordination, and tremor with movement. *Differential diagnosis*: Unsteady gait associated with vertigo from vestibular nerve or labyrinthine disease can resemble gait instability of cerebellar disease but produces a perception of movement, dizziness, or light-headedness. Sensory disturbances also can simulate cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Bilateral proximal leg weakness also can rarely mimic cerebellar ataxia.

APPROACH TO THE PATIENT: **Ataxia**

Causes are best grouped by determining whether ataxia is symmetric or focal and by the time course (**Table 184-1**). Also important to distinguish whether ataxia is present in isolation or is part of a multisystem neurologic disorder. Acute symmetric ataxia is usually due to medications, toxins including alcohol, viral infection, or a postinfectious syndrome (especially varicella). Subacute or chronic symmetric ataxia can result from hypothyroidism, vitamin deficiencies, infections (Lyme disease, tabes dorsalis, prions), alcohol, other toxins, or an inherited condition (see below). An immune-mediated progressive ataxia is associated with antigliadin antibodies; biopsy of the small intestine may reveal villous atrophy of gluten enteropathy. Elevated serum anti–glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. Progressive nonfamilial cerebellar ataxia after age 45 suggests a paraneoplastic syndrome, either subacute cortical cerebellar

TABLE 184-1 ETIOLOGY OF CEREBELLAR ATAXIA

Symmetric and Progressive Signs			Focal and Ipsilateral Cerebellar Signs		
Acute (Hours to Days)	**Subacute (Days to Weeks)**	**Chronic (Months to Years)**	**Acute (Hours to Days)**	**Subacute (Days to Weeks)**	**Chronic (Months to Years)**
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen) Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome	Intoxication: mercury, solvents, gasoline, glue; cytotoxic chemotherapeutic, hemotherapeutic drugs Alcoholic-nutritional (vitamin B_1 and B_{12} deficiency) Lyme disease	Paraneoplasticsyndrome Antigliadin antibody syndrome Hypothyroidism Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent) AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months) Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)

degeneration (ovarian, breast, lung, Hodgkin's) or opsoclonus-myoclonus (neuroblastoma, breast, lung).

Unilateral ataxia suggests a focal lesion in the ipsilateral cerebellar hemisphere or its connections. An important cause of acute unilateral ataxia is stroke. Mass effect from cerebellar hemorrhage or swelling from cerebellar infarction can compress brainstem structures, producing altered consciousness and ipsilateral pontine signs (small pupils, sixth or seventh nerve palsies); limb ataxia may not be prominent. Other diseases producing asymmetric or unilateral ataxia include tumors, multiple sclerosis, progressive multifocal leukoencephalopathy (immunodeficiency states), and congenital malformations.

INHERITED ATAXIAS

May be autosomal dominant, autosomal recessive, or mitochondrial (maternal inheritance); more than 30 disorders recognized (see Chap. 451e in HPIM-19). Friedreich's ataxia is most common; autosomal recessive, onset before age 25; ataxia with areflexia, upgoing toes, vibration and position sense deficits, cardiomyopathy, hammer toes, scoliosis; linked to expanded trinucleotide repeat in the intron of gene encoding frataxin; a second form is associated with genetically determined vitamin E deficiency syndrome. Common dominantly inherited ataxias are spinocerebellar ataxia (SCA)1 (olivopontocerebellar atrophy; "ataxin-1" gene) (Fig. 184-1), SCA2 (ataxin-2; pts from Cuba and India) and SCA3 (Machado-Joseph disease); all may

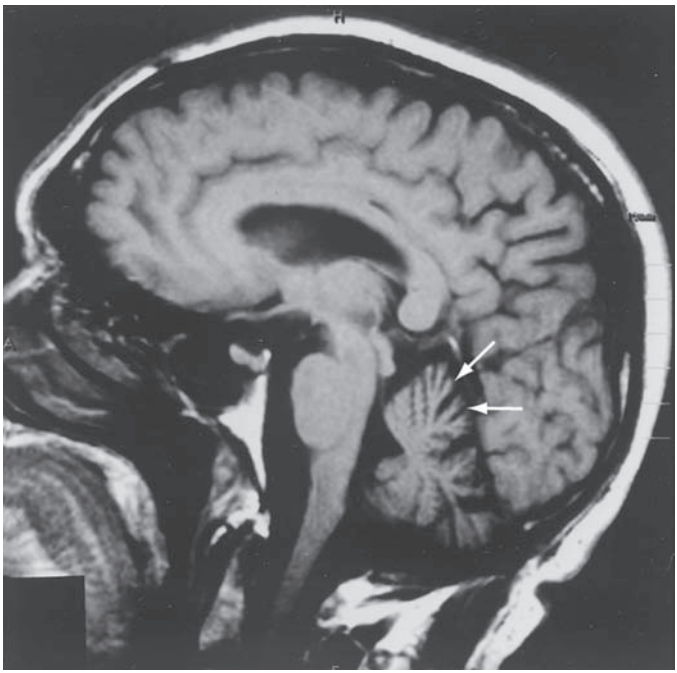


FIGURE 184-1 Sagittal MRI of the brain of a 60-year-old man with gait ataxia and dysarthria due to SCA1, illustrating cerebellar atrophy (*arrows*). SCA1, spinocerebellar ataxia type 1.

manifest as ataxia with brainstem and/or extrapyramidal signs; SCA3 may also have dystonia and amyotrophy; genes for each disorder contain unstable trinucleotide repeats in coding region.

EVALUATION

Diagnostic approach is determined by the nature of the ataxia (Table 184-1). For symmetric ataxias, drug and toxicology screens; vitamin B_1, B_{12}, and E levels; thyroid function tests; antibody tests for syphilis and Lyme infection; antigliadin and anti-GAD antibodies; paraneoplastic antibodies (Chap. 77); and CSF studies often indicated. Genetic testing is available for many inherited ataxias. For unilateral or asymmetric ataxias, brain MRI or CT scan is the initial test of choice; CT is insensitive for nonhemorrhagic lesions of the cerebellum.

TREATMENT ATAXIA

- The most important goal is to identify treatable entities including hypothyroidism, vitamin deficiency, and infectious causes.
- Ataxia with antigliadin antibodies and gluten enteropathy may improve with a gluten-free diet.
- Paraneoplastic disorders are often refractory to therapy, but some pts improve following removal of the tumor or immunotherapy (Chap. 77).
- Vitamins B_1, B_{12}, and E should be administered to pts with deficient levels.
- The deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in pts with ataxia of any cause.
- There is no proven therapy for any of the autosomal dominant ataxias; family and genetic counseling are important.
- There is preliminary evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in Friedreich's ataxia; there is no evidence that it improves neurologic function.
- Cerebellar hemorrhage and other mass lesions of the posterior fossa may require emergent surgical treatment to prevent fatal brainstem compression.

For a more detailed discussion, see Rosenberg RN: Ataxic Disorders, Chap. 450, p. 2626, in HPIM-19.

185 ALS and Other Motor Neuron Diseases

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease (Table 185-1). ALS is caused by degeneration of motor neurons at all levels of the CNS, including anterior horns of the spinal cord, brainstem motor nuclei, and motor cortex. Familial ALS (FALS) represents 5–10% of the total and is inherited usually as an autosomal dominant disorder.

TABLE 185-1 SPORADIC MOTOR NEURON DISEASES

Chronic	Entity
Upper and lower motor neuron	Amyotrophic lateral sclerosis
Predominantly upper motor neuron	Primary lateral sclerosis
Predominantly lower motor neuron	Multifocal motor neuropathy with conduction block
	Motor neuropathy with paraproteinemia or cancer
	Motor predominant peripheral neuropathies
Other	
Associated with other neurodegenerative disorders	
Secondary motor neuron disorders (see Table 185-2)	
Acute	
Poliomyelitis	
Herpes zoster	
Coxsackie virus	
West Nile virus	

CLINICAL FEATURES

Onset is usually midlife, with most cases progressing to death in 3–5 years. In most societies there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. Presentation is variable depending on whether upper motor or lower motor neurons are more prominently involved initially.

Common initial symptoms are weakness, muscle wasting, stiffness and cramping, and twitching in muscles of hands and arms, often first in the intrinsic hand muscles. Legs are less severely involved than arms, with complaints of leg stiffness, cramping, and weakness common. Symptoms of brainstem involvement include dysphagia, which may lead to aspiration pneumonia and compromised energy intake; there may be prominent wasting of the tongue leading to difficulty in articulation (dysarthria), phonation, and deglutition. Weakness of ventilatory muscles leads to respiratory insufficiency. Additional features that characterize ALS are lack of sensory abnormalities, pseudobulbar palsy (e.g., involuntary laughter, crying), and absence of bowel or bladder dysfunction. Dementia is not a component of sporadic ALS; in some families ALS is co-inherited with frontotemporal dementia characterized by behavioral abnormalities due to frontal lobe dysfunction (Chap. 182).

PATHOPHYSIOLOGY

Pathologic hallmark is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons). Although at onset ALS may involve selective loss of only upper or lower motor neurons, it ultimately causes progressive loss of both; the absence of clear involvement of both motor neuron types should call into question the diagnosis of ALS.

LABORATORY EVALUATION

EMG provides objective evidence of extensive muscle denervation not confined to the territory of individual peripheral nerves and nerve roots. CSF is usually normal. Muscle enzymes (e.g., CK) may be elevated.

Several types of secondary motor neuron disorders that resemble ALS are treatable (Table 185-2); therefore all pts should have a careful search for these disorders.

TABLE 185-2 ETIOLOGY OF MOTOR NEURON DISORDERS

Diagnostic Category	Investigation
Structural lesions	MRI scan of head (including foramen magnum and cervical spine)
Parasagittal or foramen magnum tumors	
Cervical spondylosis	
Chiari malformation of syrinx	
Spinal cord arteriovenous malformation	
Infections	CSF examination, culture
Bacterial—tetanus, Lyme	Lyme titer
Viral—poliomyelitis, herpes zoster	Anti-viral antibody
Retroviral—myelopathy	HTLV-1 titers
Intoxications, physical agents	24-h urine for heavy metals
Toxins—lead, aluminum, others	Serum lead level
Drugs—strychnine, phenytoin	
Electric short, x-irradiation	
Immunologic mechanisms	Complete blood count[a]
Plasma cell dyscrasias	Sedimentation rate[a]
Autoimmune polyradiculopathy	Total protein[a]
Motor neuropathy with conduction block	Anti-GM1 antibodies[a]
Paraneoplastic	Anti-Hu antibody
Paracarcinomatous	MRI scan, bone marrow biopsy
Metabolic	Fasting blood sugar[a]
Hypoglycemia	Routine chemistries including calcium[a]
Hyperparathyroidism	PTH
Hyperthyroidism	Thyroid function[a]
Deficiency of folate, vitamin B_{12}, vitamin E	Vitamin B_{12}, vitamin E, folate[a]
Malabsorption	Serum zinc, copper[a]
Deficiency of copper, zinc	24-h stool fat, carotene, prothrombin time
Mitochondrial dysfunction	Fasting lactate, pyruvate, ammonia
	Consider mtDNA

(*Continued*)

TABLE 185-2 ETIOLOGY OF MOTOR NEURON DISORDERS (*CONTINUED*)

Diagnostic Category	Investigation
Hyperlipidemia	Lipid electrophoresis
Hyperglycinuria	Urine and serum amino acids
	CSF amino acids
Hereditary disorders	WBC DNA for mutational analysis
Superoxide dismutase	
TDP43	
FUS/TLS	
Androgen receptor defect (Kennedy's disease)	
Hexosaminidase deficiency	
Infantile a-glucosidase deficiency (Pompe's disease)	

[a]Should be obtained in all cases.
Abbreviations: FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; PTH, parathyroid.

MRI or CT myelography is often required to exclude compressive lesions of the foramen magnum or cervical spine. When involvement is restricted to lower motor neurons only, another important entity is multifocal motor neuropathy with conduction block (MMN). A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma; an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease may also cause an axonal, lower motor neuropathy, typically with intense proximal limb pain and a CSF pleocytosis. Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis.

Pulmonary function studies may aid in management of ventilation. Swallowing evaluation identifies those at risk for aspiration. Genetic testing is available for superoxide dismutase 1 (SOD1) (20% of FALS) and for rare mutations in other genes.

TREATMENT AMYOTROPHIC LATERAL SCLEROSIS

- There is no treatment that arrests the underlying pathologic process in ALS.
- The drug riluzole produces modest lengthening of survival; in one trial the survival rate at 18 months with riluzole (100 mg/d) was similar to placebo at 15 months. It may act by diminishing glutamate release and thereby decreasing excitotoxic neuronal cell death. Side effects of riluzole include nausea, dizziness, weight loss, and elevation of liver enzymes.
- Multiple therapies are presently in clinical trials for ALS including small molecules, mesenchymal stem cells, and immunosuppression; interventions such as antisense oligonucleotides that diminish expression of mutant SOD1 protein are nearing trial for SOD1-mediated ALS.
- A variety of rehabilitative aids may substantially assist ALS pts. Foot-drop splints facilitate ambulation, and finger extension splints can potentiate grip.
- Respiratory support may be life-sustaining. For pts who decide against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia.

Also beneficial are respiratory devices that produce an artificial cough; these help to clear airways and prevent aspiration pneumonia.

- When bulbar disease prevents normal chewing and swallowing, gastrostomy is helpful in restoring normal nutrition and hydration.
- Speech synthesizers can augment speech when there is advanced bulbar palsy.
- Web-based information on ALS is offered by the Amyotrophic Lateral Sclerosis Association (*www.alsa.org*).

For a more detailed discussion, see Brown RH Jr: Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases, Chap. 452, p. 2631, in HPIM-19.

186 Autonomic Nervous System Disorders

The autonomic nervous system (ANS) (**Fig. 186-1**) innervates the entire neuraxis and permeates all organ systems. It regulates bp, heart rate, sleep, and bladder and bowel function. It operates automatically, so that its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia.

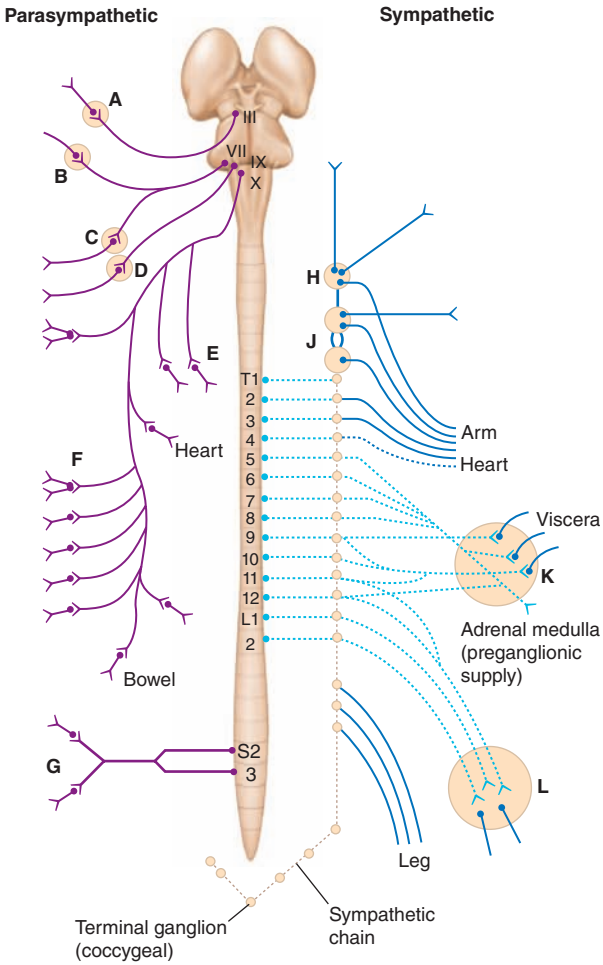
Key features of the ANS are summarized in **Table 186-1**. Responses to sympathetic or parasympathetic activation often have opposite effects; partial activation of both systems allows for simultaneous integration of multiple body functions.

Consider disorders of autonomic function in the differential diagnosis of pts with unexplained orthostatic hypotension (OH), sleep dysfunction, impotence, bladder dysfunction (urinary frequency, hesitancy, or incontinence), diarrhea, constipation, upper gastrointestinal symptoms (bloating, nausea, vomiting of old food), impaired lacrimation, or altered sweating (hyperhidrosis or hypohidrosis).

OH is often the most disabling feature of autonomic dysfunction. Syncope results when the drop in bp impairs cerebral perfusion (**Chap. 50**). Other manifestations of impaired baroreflexes are supine hypertension, a fixed heart rate regardless of posture, postprandial hypotension, and a high nocturnal bp. Many pts with OH have a preceding diagnosis of hypertension. Most causes of OH are not neurologic in origin; these must be distinguished from neurogenic causes.

APPROACH TO THE PATIENT: Autonomic Nervous System Disorders

The first step in the evaluation of OH is to exclude treatable causes. History should include a review of medications that may cause OH (e.g., diuretics, antihypertensives, antidepressants, ethanol, narcotics, insulin, dopamine agonists, barbiturates, and calcium channel-blocking agents); precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. History may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's



Parasympathetic system
from cranial nerves III, VII, IX, X and from sacral nerves 2 and 3

Sympathetic system
from T1 to L2
Preganglionic fibers
Postganglionic fibers

- **A** Ciliary ganglion
- **B** Sphenopalatine (pterygopalatine) ganglion
- **C** Submandibular ganglion
- **D** Otic ganglion
- **E** Vagal ganglion cells in the heart wall
- **F** Vagal ganglion cells in bowel wall
- **G** Pelvic ganglia
- **H** Superior cervical ganglion
- **J** Middle cervical ganglion and inferior cervical (stellate) ganglion including T1 ganglion
- **K** Coeliac and other abdominal ganglia
- **L** Lower abdominal sympathetic ganglia

FIGURE 186-1 Schematic representation of the autonomic nervous system. *(From M. Moskowitz: Clin Endocrinol Metab 6:745, 1977.)*

TABLE 186-1 FUNCTIONAL CONSEQUENCES OF NORMAL ANS ACTIVATION

	Sympathetic	Parasympathetic
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding (decreased tone)
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	—
Pupils	Dilation	Constriction
Adrenal glands	Catecholamine release	—
Sexual function	Ejaculation, orgasm	Erection
Lacrimal glands	—	Tearing
Parotid glands	—	Salivation

Abbreviation: ANS, autonomic nervous system.

disease) or identify causative mechanisms (e.g., cardiac pump failure, reduced intravascular volume). Any relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought.

Physical examination includes measurement of supine and standing pulse and bp. OH is defined as a sustained drop in systolic (≥20 mmHg) or diastolic (≥10 mmHg) bp within 2–3 min of standing. In nonneurogenic causes of OH (such as hypovolemia), the bp drop is accompanied by a compensatory increase in heart rate of >15 beats/min. A clue to neurogenic OH is aggravation or precipitation of OH by autonomic stressors (such as a meal, hot tub/hot bath, and exercise). Neurologic evaluation should include a mental status examination (to exclude neurodegenerative disorders), cranial nerve examination (impaired downgaze in progressive supranuclear palsy), pupils (Horner's or Adie's pupils), motor tone (Parkinson's), and sensory examination (polyneuropathies). In pts without a clear initial diagnosis, follow-up evaluations every few months or whenever symptoms worsen may reveal the underlying cause.

Autonomic testing : Autonomic function tests are helpful when history and physical examination findings are inconclusive, to detect subclinical involvement, or to follow the course of an autonomic disorder. Heart rate variation with deep breathing is a measure of vagal function. The Valsalva maneuver measures changes in heart rate and bp while a constant expiratory pressure of 40 mmHg is maintained for 15 s. The Valsalva ratio is the maximum heart rate during the maneuver divided by the minimum heart rate following the maneuver; the ratio reflects cardiovagal function. Tilt-table beat-to-beat bp measurements in the supine, 70° tilt, and tilt-back positions can be used to evaluate orthostatic failure in bp control in pts with unexplained syncope. Most pts with syncope do not have autonomic failure; the tilt-table test can be used to diagnose vasovagal syncope with high sensitivity, specificity, and reproducibility.

Other tests of autonomic function include the quantitative sudomotor axon reflex test (QSART) and the thermoregulatory sweat test (TST). The QSART provides quantitative measure of regional autonomic function mediated by

acetylcholine (ACh)-induced sweating. The TST provides a qualitative measure of sweating in response to a standardized elevation of body temperature. For a more complete discussion of autonomic function tests, see Chap. 454, HPIM-19.

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Autonomic disorders may occur with many disorders of the central and/or peripheral nervous systems (Table 186-2). Diseases of the CNS may cause ANS dysfunction at many levels, including hypothalamus, brainstem, or spinal cord.

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder comprising autonomic failure (OH and/or a neurogenic bladder) combined with either parkinsonism (MSA-p) or cerebellar signs (MSA-c), often with progressive cognitive dysfunction. Dysautonomia is also common in advanced Parkinson's disease and in dementia with Lewy bodies.

Spinal cord injury may produce autonomic hyperreflexia affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. With spinal cord lesions above T6, increased autonomic discharges (autonomic dysreflexia) can be elicited by stimulation of bladder, skin, or muscles. Bladder distention from palpation, catheter insertion, catheter obstruction, or urinary infection is a common and correctable trigger of autonomic dysreflexia. Dangerous increases or decreases in body temperature can result from an inability to experience the sensory accompaniments of heat or cold exposure below the level of injury.

Peripheral neuropathies affecting small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves are the most common cause of chronic autonomic insufficiency (Chap. 193). Autonomic involvement in *diabetes mellitus* typically begins ~10 years after onset of diabetes and slowly progresses. Diabetic enteric neuropathy produces gastroparesis, nausea and vomiting, malnutrition, achlorhydria, and bowel incontinence. Impotence, urinary incontinence, pupillary abnormalities, and OH may occur as well. Prolongation of the QT interval increases risk of sudden death. Autonomic neuropathy occurs in sporadic and familial forms of *amyloidosis*. Pts typically present with distal, painful polyneuropathy. *Alcoholic polyneuropathy* produces symptoms of autonomic failure when the neuropathy is severe, and autonomic involvement contributes to the high mortality rates associated with alcoholism. Attacks of *acute intermittent porphyria* (AIP) are associated with tachycardia, sweating, urinary retention, and hypertension; other prominent symptoms include anxiety, abdominal pain, nausea, and vomiting. BP fluctuation and cardiac arrhythmias can be severe in *Guillain-Barré syndrome*. *Autoimmune autonomic ganglionopathy* presents as the subacute development of autonomic failure with OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), flaccid bladder, loss of sweating, sicca complex, and a tonic pupil. Onset may follow a viral infection; serum antibodies to the ganglionic ACh receptor (A_3 AChR) are diagnostic, and some pts appear to respond to immunotherapy. Rare pts develop *dysautonomia* as a paraneoplastic disorder (Chap. 77). There are five known hereditary sensory and autonomic neuropathies (*HSAN I–V*).

Botulism is associated with blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, urinary retention, and constipation. *Postural orthostatic tachycardia syndrome* (POTS) presents with symptoms of orthostatic intolerance (not OH), including shortness of breath, light-headedness, and exercise intolerance accompanied by an increase in heart rate but no drop in bp. *Primary hyperhidrosis* affects 0.6–1.0% of the population; the usual symptoms are excessive sweating of the palms and soles. Onset is in adolescence, and symptoms tend to improve with age. Although not dangerous, this condition is socially embarrassing; treatment with sympathectomy or local injection of botulinum toxin is often effective.

TABLE 186-2 CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS

I. Autonomic disorders with brain involvement
  A. Associated with multisystem degeneration
    1. Multisystem degeneration: autonomic failure clinically prominent
      a. Multiple system atrophy
      b. Parkinson's disease with autonomic failure
      c. Diffuse Lewy body disease (some cases)
    2. Multisystem degeneration: autonomic failure clinically not usually prominent
      a. Parkinson's disease
      b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, FXTAS)
  B. Unassociated with multisystem degeneration (focal CNS disorders)
    1. Disorders mainly due to cerebral cortex involvement
      a. Frontal cortex lesions causing urinary/bowel incontinence
      b. Focal seizures (temporal lobe or anterior cingulate)
      c. Cerebral infarction of the insula
    2. Disorders of the limbic and paralimbic circuits
      a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)
      b. Autonomic seizures
      c. Limbic encephalitis
    3. Disorders of the hypothalamus
      a. Thiamine deficiency (Wernicke-Korsakoff syndrome)
      b. Diencephalic syndrome
      c. Neuroleptic malignant syndrome
      d. Serotonin syndrome
      e. Fatal familial insomnia
      f. ADH syndromes (diabetes insipidus, inappropriate ADH secretion)
      g. Disturbances of temperature regulation (hyperthermia, hypothermia)
      h. Disturbances of sexual function
      i. Disturbances of appetite
      j. Disturbances of bp/HR and gastric function
      k. Horner's syndrome
    4. Disorders of the brainstem and cerebellum
      a. Posterior fossa tumors
      b. Syringobulbia and Arnold-Chiari malformation
      c. Disorders of bp control (hypertension, hypotension)
      d. Cardiac arrhythmias
      e. Central sleep apnea

(*Continued*)

TABLE 186-2 CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS (*CONTINUED*)

- f. Baroreflex failure
- g. Horner's syndrome
- h. Vertebrobasilar and lateral medullary (Wallenberg's) syndromes
- i. Brainstem encephalitis

II. Autonomic disorders with spinal cord involvement
- A. Traumatic quadriplegia
- B. Syringomyelia
- C. Subacute combined degeneration
- D. Multiple sclerosis and neuromyelitis optica
- E. Amyotrophic lateral sclerosis
- F. Tetanus
- G. Stiff-person syndrome
- H. Spinal cord tumors

III. Autonomic neuropathies
- A. Acute/subacute autonomic neuropathies
  1. Subacute AAG
     - a. Subacute paraneoplastic autonomic neuropathy
     - b. Guillain-Barré syndrome
     - c. Botulism
     - d. Porphyria
     - e. Drug-induced autonomic neuropathies-stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists
     - f. Toxin-induced autonomic neuropathies
     - g. Subacute cholinergic neuropathy
- B. Chronic peripheral autonomic neuropathies
  1. Distal small fiber neuropathy
  2. Combined sympathetic and parasympathetic failure
     - a. Amyloid
     - b. Diabetic autonomic neuropathy
     - c. Autoimmune autonomic ganglionopathy (paraneoplastic and idiopathic)
     - d. Sensory neuronopathy with autonomic failure
     - e. Familial dysautonomia (Riley-Day syndrome)
     - f. Diabetic, uremic, or nutritional deficiency
     - g. Dysautonomia of old age
  3. Disorders of reduced orthostatic intolerance: reflex syncope, POTS, associated with prolonged bed rest, associated with space flight, chronic fatigue

Abbreviations: AAG, autoimmune autonomic ganglionopathy; ADH, antidiuretic hormone; FXTAS, fragile X–associated tremor/ataxia syndrome; HR, heart rate; POTS, postural orthostatic tachycardia syndrome.

COMPLEX REGIONAL PAIN SYNDROME (REFLEX SYMPATHETIC DYSTROPHY AND CAUSALGIA)

Complex regional pain syndrome (CRPS) type I is a regional pain syndrome that usually develops after tissue trauma. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. Symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a peripheral nerve, usually a major nerve trunk. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

- Early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for CRPS type I.
- Other treatments include the use of adrenergic blockers, NSAIDs, calcium channel blockers, phenytoin, opioids, and calcitonin.
- Stellate ganglion blockade is a commonly used invasive therapeutic technique that often provides temporary pain relief, but the efficacy of repetitive blocks is uncertain.

TREATMENT AUTONOMIC NERVOUS SYSTEM DISORDERS

- Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate symptoms. For example, OH can be related to angiotensin-converting enzyme inhibitors, calcium channel blocking agents, tricyclic antidepressants, levodopa, alcohol, or insulin.
- Nonpharmacologic approaches are summarized in **Table 186-3**. Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine (containing >170 meq of Na^+) each 24 h is essential. Sleeping with the head of the bed elevated will minimize the effects of supine nocturnal hypertension.
- Prolonged recumbency should be avoided. Pts are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning. Compressive garments such as compression stockings and abdominal binders may be helpful if they can be tolerated. Anemia should be corrected, if necessary, with erythropoietin; the increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension. Postprandial OH may respond to frequent, small, low-carbohydrate meals.
- If these measures are not sufficient, drug treatment might be necessary.
- Midodrine is a directly acting α_1-agonist that does not cross the blood-brain barrier. The dose is 5–10 mg orally three times a day, but some pts respond best

TABLE 186-3 INITIAL TREATMENT OF ORTHOSTATIC HYPOTENSION (OH)

Pt education: mechanisms and stressors of OH
High salt diet (10–20 g/d)
High fluid intake (2 L/d)
Elevate head of bed 10 cm (4 in.) to minimize supine hypertension
Maintain postural stimuli
Learn physical counter-maneuvers
Compression garments
Correct anemia

to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6 P.M. Side effects include pruritus, uncomfortable piloerection, and supine hypertension.

- Droxidopa was recently approved for treatment of neurogenic OH associated with autonomic failure, Parkinson's disease, or MSA; the oral form is converted to norepinephrine and has been shown to be effective in short-term clinical trials.
- Pyridostigmine appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal supine).
- Fludrocortisone (0.1–0.3 mg PO twice daily) will reduce OH, but it aggravates supine hypertension. Susceptible pts may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia.

For a more detailed discussion, see Low PA, Engstrom JW: Disorders of the Autonomic Nervous System, Chap. 454, p. 2637, in HPIM-19.

187 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders

Disorders of vision and ocular movement are discussed in Chap. 52 and dizziness and vertigo in Chap. 51.

FACIAL PAIN OR NUMBNESS (TRIGEMINAL NERVE [V])

(See Fig. 187-1)

Trigeminal Neuralgia (Tic Douloureux)

Frequent, excruciating paroxysms of pain in lips, gums, cheek, or chin (rarely in ophthalmic division of fifth nerve) lasting seconds to minutes. Typically presents in middle or old age. Pain is often stimulated at trigger points. Sensory deficit cannot be demonstrated. Must be distinguished from other forms of facial pain arising from diseases of jaw, teeth, or sinuses. Rare causes are herpes zoster or a tumor. An onset in young adulthood or if bilateral raises the possibility of multiple sclerosis (Chap. 190).

TREATMENT TRIGEMINAL NEURALGIA

- Carbamazepine is effective in 50–75% of cases. Begin at 100-mg single daily dose taken with food and advance by 100 mg every 1–2 days until substantial (>50%) pain relief occurs. Most pts require 200 mg four times a day; doses >1200 mg daily usually provide no additional benefit.
- Oxcarbazepine (300–1200 mg bid) is an alternative with less bone marrow toxicity and probably similar efficacy.
- For nonresponders, lamotrigine (400 mg daily), phenytoin (300–400 mg/d), or baclofen (initially 5–10 mg three times a day) can be tried.

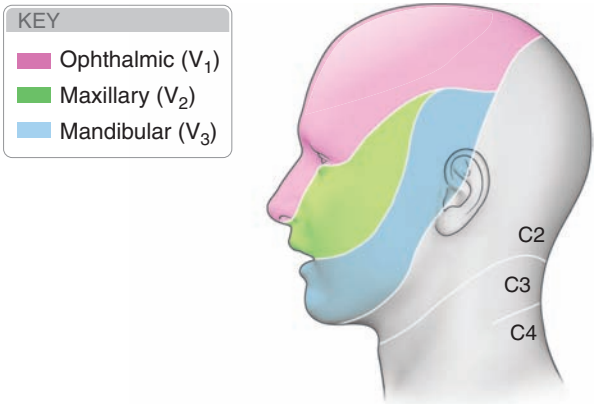


FIGURE 187-1 The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves. *(Adapted from Waxman SG: Clinical Neuroanatomy, 26th ed. http://www.accessmedicine.com. Copyright The McGraw-Hill Companies, Inc. All rights reserved.)*

- When medications fail, surgical microvascular decompression to relieve pressure on the trigeminal nerve can be offered.
- Other options include gamma knife radiosurgery and radiofrequency thermal rhizotomy.

Trigeminal Neuropathy

Usually presents as facial sensory loss or weakness of jaw muscles. Causes are varied (Table 187-1), including tumors of middle cranial fossa or trigeminal nerve, metastases to base of skull, or lesions in cavernous sinus (affecting first and second divisions of fifth nerve) or superior orbital fissure (affecting first division of fifth nerve).

FACIAL WEAKNESS (FACIAL NERVE [VII]) (SEE FIG. 187-2)

Look for hemifacial weakness that includes muscles of forehead and orbicularis oculi. If lesion is in middle ear portion, taste is lost over the anterior two-thirds of tongue and there may be hyperacusis; if lesion is at internal auditory meatus, there may be involvement of auditory and vestibular nerves; pontine lesions usually affect abducens (sixth cranial) nerve and often corticospinal tract. Peripheral nerve lesions with incomplete recovery may produce continuous contractions of affected musculature (*facial myokymia*); contraction of all facial muscles on attempts to move one group selectively (*synkinesis*); hemifacial spasms; or anomalous tears when facial muscles activated as in eating (*crocodile tears*).

Bell's Palsy

Most common form of idiopathic facial paralysis; affects 1 in 60 persons over a lifetime. Association with herpes simplex virus type 1. Risk factors include pregnancy and diabetes mellitus. Weakness evolves gradually with maximal weakness by 48 h, sometimes preceded by retroaural pain. Hyperacusis may be present. Full recovery within several weeks or months in 80%; incomplete paralysis in first week is the most favorable prognostic sign.

Diagnosis can be made clinically in pts with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) no lesions

TABLE 187-1 TRIGEMINAL NERVE DISORDERS

Nuclear (brainstem) lesions	Peripheral nerve lesions
Multiple sclerosis	Nasopharyngeal carcinoma
Stroke	Trauma
Syringobulbia	Guillain-Barré syndrome
Glioma	Sjögren's syndrome
Lymphoma	Collagen-vascular diseases
Preganglionic lesions	Sarcoidosis
Acoustic neuroma	Leprosy
Meningioma	Drugs (stilbamidine, trichloroethylene)
Metastasis	Idiopathic trigeminal neuropathy
Chronic meningitis	
Cavernous carotid aneurysm	
Gasserian ganglion lesions	
Trigeminal neuroma	
Herpes zoster	
Infection (spread from otitis media or mastoiditis)	

of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. In uncertain cases, an ESR, testing for diabetes mellitus, a Lyme titer, angiotensin-converting enzyme level and chest imaging study for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated.

TREATMENT BELL'S PALSY

- Protect the eye with paper tape to depress the upper eyelid during sleep and prevent corneal drying.
- Massage of the weakened muscle may help symptomatically as well.
- Prednisone (60–80 mg/d over 5 days, tapered off over the next 5 days) modestly shortens the recovery period and improves functional outcome.
- Large randomized trials found no added benefit for valacyclovir or acyclovir compared with glucocorticoids alone.

Other Facial Nerve Disorders

Ramsay Hunt syndrome is caused by herpes zoster infection of geniculate ganglion; distinguished from Bell's palsy by a vesicular eruption in pharynx and external auditory canal, and by frequent involvement of eighth cranial nerve. *Acoustic neuromas* often compress the seventh nerve. *Infarcts*, *demyelinating lesions of multiple sclerosis*, and *tumors* are common pontine causes. *Bilateral facial weakness* may occur in Guillain-Barré syndrome, sarcoidosis, Lyme disease, and leprosy. *Hemifacial spasm* may occur with Bell's palsy, compression and/or demyelination of the nerve by tumor, infection or multiple sclerosis (MS), or as an idiopathic disorder. *Blepharospasm* consists of involuntary recurrent spasms of both eyelids, usually occurring in the elderly and sometimes with associated facial spasm; may subside spontaneously.

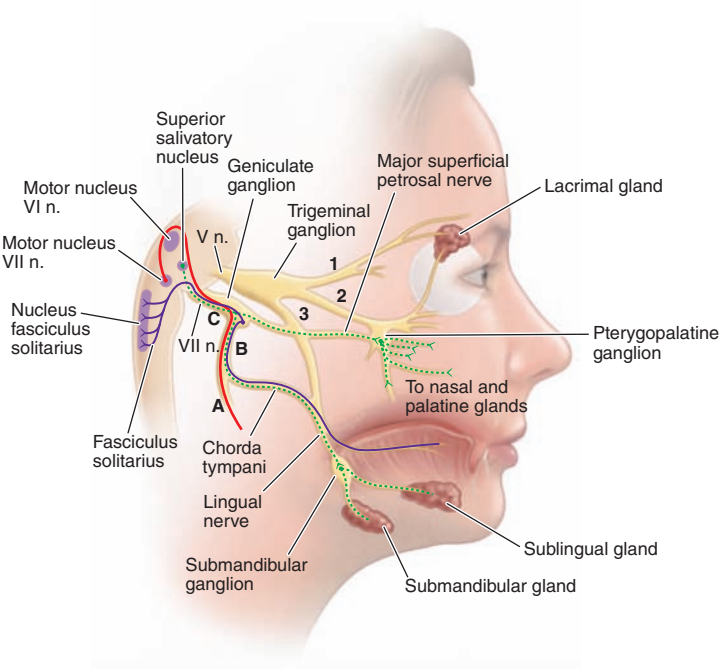


FIGURE 187-2 The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). *(Adapted from MB Carpenter: Core Text of Neuroanatomy, 2nd ed. Baltimore, Williams & Wilkins, 1978.)*

Hemifacial spasm or blepharospasm can be treated by injection of botulinum toxin into the orbicularis oculi.

OTHER CRANIAL NERVE DISORDERS

Disorders of the Sense of Smell

Olfactory nerve (I) disorders are due to interference with access of the odorant to the olfactory neuroepithelium (transport loss), injury to receptor region (sensory loss), or damage to central olfactory pathways (neural loss). The causes of olfactory disorders are summarized in Table 187-2); most common other than aging are severe upper respiratory infections, head trauma, and chronic rhinosinusitis. Although more than half of people between 65 and 80 years of age suffer from olfactory dysfunction that is idiopathic (*presbyosmia*), it is increasingly recognized that a number of neurodegenerative disorders are accompanied by olfactory impairment. Pts often present with a complaint of loss of the sense of taste even though their taste thresholds may be within normal limits.

TREATMENT DISORDERS OF THE SENSE OF SMELL

- Therapy for allergic rhinitis, bacterial rhinitis and sinusitis, polyps, neoplasms, and structural abnormalities of the nasal cavities is usually successful in restoring the sense of smell.

TABLE 187-2 DISORDERS AND CONDITIONS ASSOCIATED WITH COMPROMISED OLFACTORY FUNCTION, AS MEASURED BY OLFACTORY TESTING

22q11 deletion syndrome
AIDS/HIV infection
Adenoid hypertrophy
Adrenal cortical insufficiency
Age
Alcoholism
Allergies
Alzheimer's disease
ALS
Anorexia nervosa
Asperger's syndrome
Ataxias
Attention deficit/hyperactivity disorder
Bardet-Biedl syndrome
Chagas' disease
Chemical exposure
Chronic obstructive pulmonary disease
Congenital
Cushing's syndrome
Cystic fibrosis
Degenerative ataxias
Diabetes
Down's syndrome
Epilepsy
Facial paralysis
Frontotemporal lobe degeneration
Gonadal dysgenesis (Turner's syndrome)
Guamanian ALS/PD/dementia syndrome
Head trauma
Herpes simplex encephalitis
Hypothyroidism
Huntington's disease
Iatrogenesis
Kallmann's syndrome
Korsakoff's psychosis
Leprosy
Liver disease
Lubag disease
Medications
Migraine
Multiple sclerosis
Multi-infarct dementia
Myasthenia gravis
Narcolepsy with cataplexy
Neoplasms, cranial/nasal
Nutritional deficiencies
Obesity
Obsessive compulsive disorder
Obstructive pulmonary disease
Orthostatic tremor
Panic disorder
PD
Pick's disease
Posttraumatic stress disorder
Pregnancy
Pseudohypoparathyroidism
Psychopathy
Radiation (therapeutic, cranial)
Refsum's disease
REM behavior disorder
Renal failure/end-stage kidney disease
Restless leg syndrome
Rhinosinusitis/polyposis
Schizophrenia
Seasonal affective disorder
Sjögren's syndrome
Stroke
Tobacco smoking
Toxic chemical exposure
Upper respiratory infections
Usher syndrome
Vitamin B_{12} deficiency

Abbreviations: ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; REM, rapid eye movement.

- There is no proven treatment for sensorineural olfactory losses; fortunately, spontaneous recovery can occur.
- Cases due to exposure to cigarette smoke and other airborne toxic chemicals can recover if the insult is discontinued.
- A nonblinded study reported that pts with hyposmia may benefit from smelling strong odors before going to bed and upon awakening over the course of several months.

Glossopharyngeal Neuralgia

This neuralgia involves the ninth (glossopharyngeal) and sometimes portions of the tenth (vagus) cranial nerves. Presents with paroxysmal, intense pain in tonsillar fossa of throat that may be precipitated by swallowing. There is no objective sensory or motor deficit. Other diseases affecting this nerve include herpes zoster, MS, or compressive neuropathy due to tumor or aneurysm in region of jugular foramen (when associated with vagus and accessory nerve palsies).

TREATMENT GLOSSOPHARYNGEAL NEURALGIA

- Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice.
- If drug therapy is unsuccessful, surgical procedures (including microvascular decompression if vascular compression is evident, or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb) are frequently successful.

Dysphagia and Dysphonia

Lesions of the vagus nerve (X) may be responsible. Unilateral lesions produce drooping of soft palate, loss of gag reflex, and "curtain movement" of lateral wall of pharynx with hoarse, nasal voice. Etiologies include neoplastic and infectious processes of the meninges, tumors and vascular lesions in the medulla, motor neuron disease (e.g., ALS), or compression of the recurrent laryngeal nerve by intrathoracic processes. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders. A substantial number of cases of recurrent laryngeal palsy remain idiopathic.

With laryngeal palsy, first determine the site of the lesion. If intramedullary, there are usually other brainstem or cerebellar signs. If extramedullary, the glossopharyngeal (IX) and spinal accessory (XI) nerves are frequently involved (jugular foramen syndrome). If extracranial in the posterior laterocondylar or retroparotid space, there may be combinations of ninth, tenth, eleventh, and twelfth cranial nerve palsies and a Horner's syndrome. If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

Neck Weakness

Isolated involvement of the accessory (XI) nerve can occur anywhere along its route, resulting in paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull. An idiopathic form of accessory neuropathy, similar to Bell's palsy, has been described; most pts recover but it may recur.

Tongue Paralysis

The hypoglossal (XII) nerve supplies the ipsilateral muscles of the tongue. The nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

MULTIPLE CRANIAL NERVE PALSIES

APPROACH TO THE PATIENT: Multiple Cranial Nerve Palsies

First determine whether the process is within the brainstem or outside it. Lesions on the surface of the brainstem tend to involve adjacent cranial nerves in succession with only late and slight involvement of long sensory and motor pathways. The opposite is true of processes within the brainstem. Involvement of multiple cranial nerves outside the brainstem may be due to trauma, localized infections including varicella zoster virus, infectious and noninfectious (especially carcinomatous) causes of meningitis; granulomatous diseases such as granulomatosis with polyangiitis, Behçet's disease, vascular disorders including those associated with diabetes, enlarging aneurysms, or locally infiltrating tumors. A purely motor disorder without atrophy raises the question of myasthenia gravis. *Facial diplegia* is common in Guillain-Barré syndrome. *Ophthalmoplegia* may occur with Guillain-Barré syndrome (Fisher variant) or Wernicke's encephalopathy.

The *cavernous sinus syndrome* (Fig. 187-3) is frequently life threatening. It often presents as orbital or facial pain; orbital swelling and chemosis; fever;

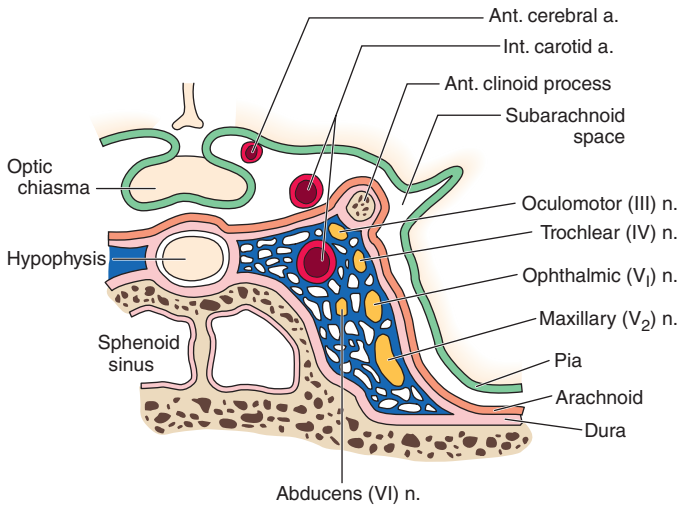


FIGURE 187-3 Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

oculomotor neuropathy; and trigeminal neuropathy affecting the ophthalmic (V_1) and occasionally maxillary (V_2) divisions. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis, a cutaneous source on the face, or sinusitis, is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. Tolosa-Hunt syndrome generally responds to glucocorticoids.

For a more detailed discussion, see Beal MF, Hauser SL: Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders, Chap. 455, p. 2645; Doty RL, Bromley SM: Disorders of Smell and Taste, Chap. 42, p. 211, in HPIM-19.

188 Spinal Cord Diseases

Spinal cord disorders can be devastating, but many are treatable if recognized early (Table 188-1). Knowledge of relevant spinal cord anatomy is often the key to correct diagnosis (Fig. 188-1).

SYMPTOMS AND SIGNS

Sensory symptoms often include paresthesias; may begin in one or both feet and ascend. Sensory level to pin sensation or vibration often correlates well with location of transverse lesions. May have isolated pain/temperature sensation loss over the shoulders ("cape" or "syringomyelic" pattern) or loss of sensation to vibration/position sense on one side of the body and pain/temperature loss on the other (Brown-Séquard hemicord syndrome).

Motor symptoms are caused by disruption of corticospinal tracts that leads to quadriplegia or paraplegia with increased muscle tone, hyperactive deep tendon reflexes, and extensor plantar responses. With acute severe lesions, there may be initial flaccidity and areflexia (spinal shock).

Autonomic dysfunction includes primarily urinary retention; should raise suspicion of spinal cord disease when associated with back or neck pain, weakness, and/or a sensory level.

Interscapular pain may be first sign of midthoracic cord compression; radicular pain may mark site of more laterally placed spinal lesion; pain from lower cord (conus medullaris) lesion may be referred to low back.

SPECIFIC SIGNS BY SPINAL CORD LEVEL

Approximate indicators of level of lesion include the location of a sensory level, a band of hyperalgesia/hyperpathia at the upper end of the sensory disturbance,

TABLE 188-1 TREATABLE SPINAL CORD DISORDERS

Compressive
Epidural, intradural, or intramedullary neoplasm
Epidural abscess
Epidural hemorrhage
Cervical spondylosis
Herniated disk
Posttraumatic compression by fractured or displaced vertebra or hemorrhage
Vascular
Arteriovenous malformation and dural fistula
Antiphospholipid syndrome and other hypercoagulable states
Inflammatory
Multiple sclerosis
Neuromyelitis optica
Transverse myelitis
Sarcoidosis
Sjögren-related myelopathy
Systemic lupus erythematosus-related myelopathy
Vasculitis
Infectious
Viral: VZV, HSV-1 and 2, CMV, HIV, HTLV-1, others
Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others
Mycoplasma pneumoniae
Parasitic: schistosomiasis, toxoplasmosis
Developmental
Syringomyelia
Meningomyelocele
Tethered cord syndrome
Metabolic
Vitamin B_{12} deficiency (subacute combined degeneration)
Copper deficiency

Abbreviation: HTLV, human T-cell lymphotropic virus.

isolated atrophy or fasciculations, or lost tendon reflex at a specific spinal cord segment.

Lesions Near the Foramen Magnum

Weakness of the ipsilateral shoulder and arm, followed by weakness of ipsilateral leg, then contralateral leg, then contralateral arm, often with respiratory paralysis. There is often suboccipital pain spreading to the neck and shoulders.

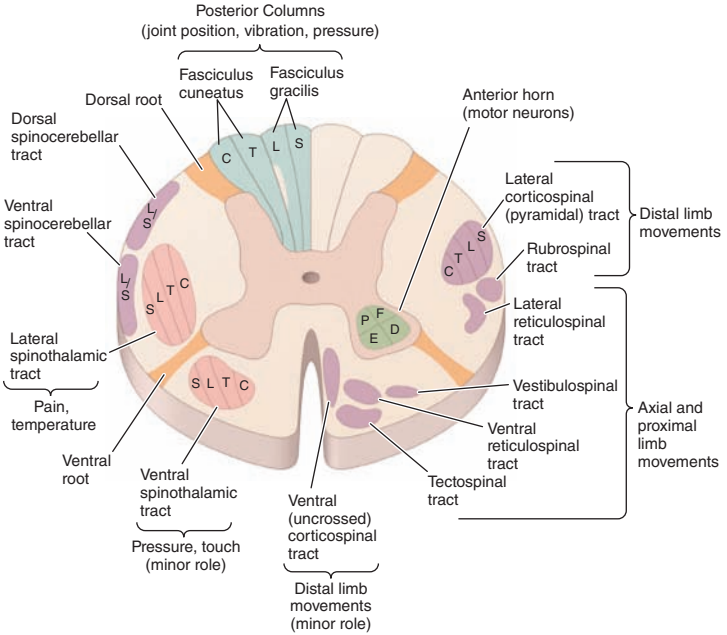


FIGURE 188-1 Transverse section through the spinal cord, composite representation, illustrating the principal ascending *(left)* and descending *(right)* pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.

Cervical Cord

Best localized by noting pattern of motor weakness and areflexia; shoulder (C5), biceps (C5–6), brachioradialis (C6), triceps/finger and wrist extensors (C7), finger and wrist flexors (C8).

Thoracic Cord

Localized by identification of a sensory level on the trunk. Useful markers are the nipples (T4) and umbilicus (T10).

Lumbar Cord

Upper lumbar cord lesions paralyze hip flexion and knee extension and abolish the patella reflex, whereas lower lumbar lesions affect foot and ankle movements, knee flexion, and thigh extension, while abolishing the ankle jerks.

Sacral Cord (Conus Medullaris)

Saddle anesthesia, early bladder/bowel dysfunction, impotence; muscle strength is largely preserved.

Cauda Equina (Cluster of Nerve Roots Derived from Lower Cord)

Lesions below spinal cord termination at the L1 vertebral level produce a flaccid, areflexic, asymmetric paraparesis with possible bladder/bowel dysfunction and sensory loss below L1; pain is common and projected to perineum or thighs.

INTRAMEDULLARY AND EXTRAMEDULLARY SYNDROMES

Spinal cord disorders may be intramedullary (arising from within the substance of the cord) or extramedullary (compressing the cord or its blood supply). Extramedullary lesions often produce radicular pain, early corticospinal signs, and sacral sensory loss. Intramedullary lesions produce poorly localized burning pain, less prominent corticospinal signs, and often spare perineal/sacral sensation.

ACUTE AND SUBACUTE SPINAL CORD DISEASES (SEE CHAP. 20)

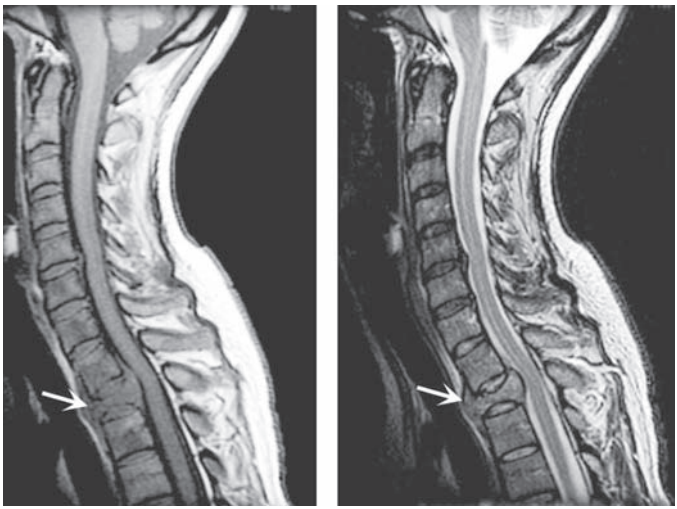
Neoplastic spinal cord compression (Chap. 20): Most are epidural in origin, resulting from metastases to the adjacent spinal bones (Fig. 188-2). Almost any tumor can be responsible: breast, lung, prostate, kidney, lymphoma, and myeloma most frequent. Thoracic cord most commonly involved. Initial symptom is usually back pain, worse when recumbent, with local tenderness preceding other symptoms by many weeks. Spinal cord compression due to metastases is a medical emergency; in general, therapy will not reverse paralysis of >48 h duration.

Spinal epidural abscess: Triad of fever, localized midline dorsal spine or neck pain, and progressive limb weakness; once neurologic signs appear, cord compression rapidly progresses.

Spinal epidural hematoma: Presents as acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder.

Acute disk herniation: Cervical and thoracic disk herniations are less common than lumbar.

Spinal cord infarction: Anterior spinal artery infarction produces paraplegia or quadriplegia, sensory loss affecting pain/temperature but sparing vibration/position sensation (supplied by posterior spinal arteries), and loss of sphincter control. Onset sudden or progressive, evolving over minutes or a few hours. Associated conditions:



A **B**

FIGURE 188-2 Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted **(A)** and T2-weighted **(B)** MRI scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in **A.** signifies replacement by tumor.

aortic atherosclerosis, dissecting aortic aneurysm, vertebral artery occlusion or dissection in the neck, aortic surgery, or profound hypotension. Therapy is directed at the predisposing condition. Lumbar drainage of spinal fluid is sometimes used prophylactically during aortic surgery but has not been studied systematically.

Immune-mediated myelopathies: Acute transverse myelopathy (ATM) occurs in 1% of pts with SLE; associated with antiphospholipid antibodies. Sjögren's and Behçet's syndromes, mixed connective tissue disease, and p-ANCA vasculitis are other causes. Sarcoid can produce ATM with large edematous swelling of the spinal cord. Demyelinating diseases, either neuromyelitis optica (NMO) or multiple sclerosis (MS), also can present as ATM; glucocorticoids, consisting of IV methylprednisolone followed by oral prednisone, are indicated for moderate to severe symptoms and refractory cases may respond to plasma exchange (Chap. 190). Treatment with azathioprine, mycophenolate mofetil, or rituximab may protect against relapses in NMO. Other cases of ATM are idiopathic.

Infectious myelopathies: Herpes zoster is the most common viral agent, but herpes simplex virus types 1 and 2, EBV, CMV, and rabies virus are also well described; in cases of suspected viral myelitis, antivirals may be appropriately started pending laboratory confirmation. A number of enteroviruses and flaviviruses (e.g., West Nile virus) can cause a polio-like syndrome. Bacterial and mycobacterial causes are less common. Schistosomiasis is an important cause worldwide.

CHRONIC MYELOPATHIES

Spondylitic myelopathies: One of the most common causes of gait difficulty in the elderly. Presents as neck and shoulder pain with stiffness, radicular arm pain, and progressive spastic paraparesis with paresthesias and loss of vibration sense; in advanced cases, urinary incontinence may occur. A tendon reflex in the arms is often diminished at some level. Diagnosis is best made by MRI. Treatment is surgical (Chap. 48).

Vascular malformations: An important treatable cause of progressive or episodic myelopathy. May occur at any level; diagnosis is often suggested by contrast-enhanced MRI (Fig. 188-3), but is confirmed by selective spinal angiography. Treatment is embolization or surgery with occlusion of the major feeding vessels.

Retrovirus-associated myelopathies: Infection with human T-cell lymphotropic virus I (HTLV-I) may produce a slowly progressive spastic paraparesis with variable pain, sensory loss, and bladder disturbance; diagnosis is made by demonstration of specific serum antibody. Treatment is symptomatic. A progressive vacuolar myelopathy may also result from HIV infection.

Syringomyelia: Cavitary expansion of the spinal cord resulting in progressive myelopathy; may be an isolated finding or associated with protrusion of cerebellar tonsils into cervical spinal canal (Chiari type 1). Classic presentation is loss of pain/temperature sensation in the neck, shoulders, forearms, or hands with areflexic weakness in the upper limbs and progressive spastic paraparesis; cough headache, facial numbness, or thoracic kyphoscoliosis may occur. Diagnosis is by MRI; treatment is surgical and often unsatisfactory.

Multiple sclerosis: Spinal cord involvement is common and is a major cause of disability especially in progressive forms of MS (Chap. 190).

Subacute combined degeneration (vitamin B_{12} deficiency): Paresthesias in hands and feet, early loss of vibration/position sense, progressive spastic/ataxic weakness, and areflexia due to associated peripheral neuropathy; mental changes and optic atrophy may be present along with a serum macrocytic anemia. Diagnosis is confirmed by a low serum B_{12} level, elevated levels of homocysteine and methylmalonic acid. Treatment is vitamin replacement beginning with 1 mg of IM vitamin B_{12} repeated at regular intervals or by subsequent oral treatment.

Hypocupric myelopathy: Clinically nearly identical to subacute combined degeneration (above) except there is no neuropathy. Low levels of serum copper and usually ceruloplasmin make the diagnosis. Some cases are idiopathic and others follow GI

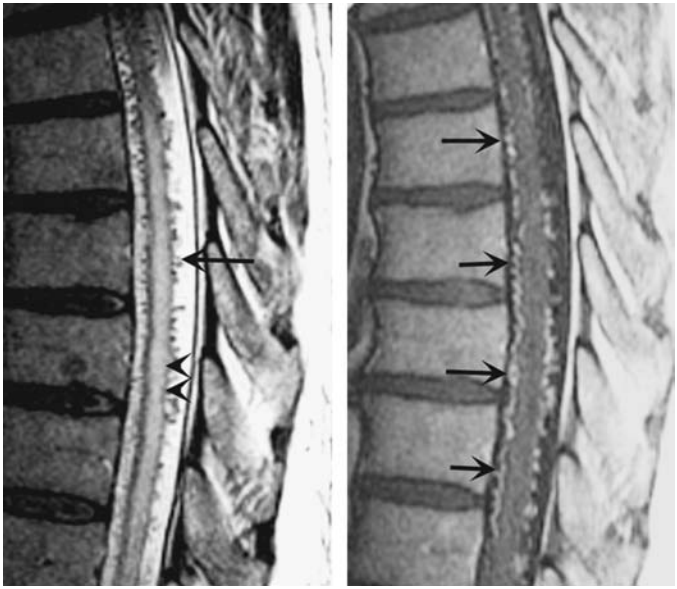


FIGURE 188-3 Arteriovenous malformation. Sagittal MR scans of the thoracic spinal cord: T2 fast spin-echo technique (*left*) and T1 postcontrast image (*right*). On the T2-weighted image (*left*), abnormally high signal intensity is noted in the central aspect of the spinal cord (*arrowheads*). Numerous punctate flow voids indent the dorsal and ventral spinal cord (*arrow*). These represent the abnormally dilated venous plexus supplied by the dural arteriovenous fistula. After contrast administration (*right*), multiple, serpentine, enhancing veins (*arrows*) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This pt was a 54-year-old man with a 4-year history of progressive paraparesis.

procedures that hinder absorption; excess zinc ingestion is another cause. Treatment is oral copper supplementation.

Tabes dorsalis (tertiary syphilis): May present as lancinating pains, gait ataxia, bladder disturbances, and visceral crises. Cardinal signs are areflexia in the legs, impaired vibration/position sense, Romberg sign, and Argyll Robertson pupils which fail to constrict to light but accommodate.

Familial spastic paraplegia: Progressive spasticity and weakness in the legs occurring on a familial basis; may be autosomal dominant, recessive, or X-linked. More than 30 different loci identified.

Adrenomyeloneuropathy: X-linked disorder that is a variant of adrenoleukodystrophy. Usually, affected males have a history of adrenal insufficiency and then develop a progressive spastic paraparesis. Female heterozygotes may develop a slower progressive myelopathy without adrenal insufficiency. Diagnosis made by elevated very long chain fatty acids in plasma and in cultured fibroblasts. No therapy is clearly effective although bone marrow transplantation and nutritional supplements have been tried.

COMPLICATIONS

Bladder dysfunction with risk of urinary tract infection; bowel dysmotility; pressure sores; in high cervical cord lesions, mechanical respiratory failure; paroxysmal

hypertension or hypotension with volume changes; severe hypertension and bradycardia in response to noxious stimuli or bladder or bowel distention; venous thrombosis and pulmonary embolism.

For a more detailed discussion, see Hauser SL, Ropper AH: Diseases of the Spinal Cord, Chap. 456, p. 2650, in HPIM-19.

189 Tumors of the Nervous System

APPROACH TO THE PATIENT: Tumors of the Nervous System

Clinical Presentation: Brain tumors of any type can present with general and/or focal symptoms and signs. General nonspecific symptoms include headache with or without nausea and vomiting, cognitive difficulties, personality change, and gait disorder. The classic headache associated with a brain tumor is most evident in the morning and improves during the day, but this pattern is actually seen in only a minority of pts. Papilledema may suggest elevated intracranial pressure. Focal symptoms and signs include hemiparesis, aphasia, or visual field deficit; these are typically subacute and progressive. Seizures are a common presentation, occurring in about 25% of pts with brain metastases or malignant glioma.

Evaluation: Primary brain tumors, unlike metastases, have no serologic features of malignancy such as an elevated ESR or tumor-specific antigens. Cranial MRI with contrast is the preferred diagnostic test for any pt suspected of having a brain tumor; CT should be reserved for pts unable to undergo MRI. Malignant brain tumors typically enhance with contrast and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas typically do not enhance. Additional testing such as cerebral angiogram, EEG, or lumbar puncture is rarely indicated or helpful.

TREATMENT TUMORS OF THE NERVOUS SYSTEM

SYMPTOMATIC TREATMENT

- Glucocorticoids (dexamethasone 12–16 mg/d in divided doses PO or IV) to temporarily reduce edema
- Anticonvulsants (levetiracetam, topiramate, lamotrigine, valproic acid, or lacosamide) for pts who present with seizures; there is no role for prophylactic anticonvulsant drugs
- Low-dose SC heparin for immobile pts

DEFINITIVE TREATMENT

- Based on the specific tumor types and includes surgery, radiotherapy (RT), and chemotherapy

PRIMARY INTRACRANIAL TUMORS

Astrocytomas

Infiltrative tumors with a presumptive glial cell of origin. Most common primary intracranial neoplasm. Only known risk factors are ionizing radiation and uncommon hereditary syndromes (neurofibromatosis, tuberous sclerosis). Infiltration along white matter pathways often prevents total resection. Imaging studies (Fig. 189-1) fail to indicate full tumor extent. Grade I tumors (pilocytic astrocytomas) are the most common tumor of childhood, typically in the cerebellum; can be cured if completely resected. Grade II astrocytomas usually present with seizures in young adults; if feasible should be surgically resected. RT is helpful and chemotherapeutic agents such as temozolomide are increasingly used. Grade III (anaplastic astrocytoma) and grade IV (glioblastoma) astrocytomas are treated similarly with maximal safe surgical resection followed by RT with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. Median survival in glioblastoma is 12–15 months. Glioblastomas invariably recur, and treatment options include reoperation, carmustine wafer implantation, and chemotherapeutic regimens including bevacizumab. The most important adverse prognostic factors in high-grade astrocytomas are older age, histologic features of glioblastoma, poor performance status, and unresectable tumor.

Oligodendrogliomas

Generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. Usually nonenhancing; often partially calcified. Treated with surgery and, if necessary, RT and chemotherapy. Median survival in excess of 10 years. Chemotherapy response improved when deletions of chromosomes 1p and 19q present.

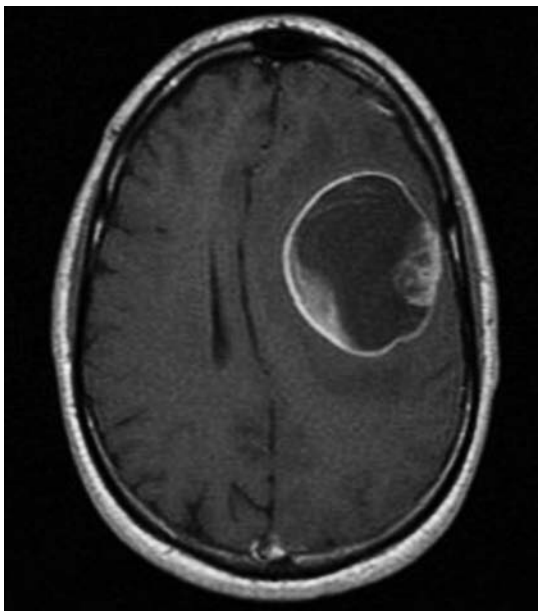


FIGURE 189-1 Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.

Ependymomas

Derived from ependymal cells; highly cellular. Location—spinal canal more than intracranial in adults. If total excision possible, may be curable. Partially resected tumors will recur and require irradiation.

Primary CNS Lymphomas

B-cell malignancy; most occur in immunosuppressed pts (organ transplantation, HIV). May present as a single mass lesion or as multiple mass lesions or meningeal disease. Dramatic, transient responses occur with glucocorticoids; therefore, whenever possible, steroids should be withheld until after biopsy has been obtained. Pts should be tested for HIV and the extent of disease assessed by performing positron emission tomography (PET) or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. In immunocompetent pts, high-dose methotrexate produces median survival up to 50 months, which may be increased with concurrent whole-brain RT and combinations of other chemotherapeutic agents such as cytarabine or rituximab. In immunocompromised pts, prognosis is worse and treatment is with high-dose methotrexate, whole-brain RT, and, in HIV, antiretroviral therapy.

Medulloblastomas

Most common malignant brain tumor of childhood. Half in posterior fossa; highly cellular; derived from neural precursor cells. Treatment with surgery, RT, and chemotherapy. Approximately 70% of pts have long-term survival, but usually at the cost of significant neurocognitive impairment.

Meningiomas

The most common primary brain tumor. Extra-axial mass attached to dura; dense and uniform contrast enhancement is diagnostic (Fig. 189-2). Total surgical resection of large, symptomatic benign meningiomas is curative. With subtotal resection, local RT reduces recurrence. Small, asymptomatic meningiomas may be followed radiologically without surgery. Treat rare aggressive meningiomas with excision and RT.

Schwannomas

Vestibular schwannomas present as progressive, unexplained unilateral hearing loss. MRI reveals dense, uniformly enhancing tumor at the cerebellopontine angle. Surgical excision may preserve hearing.

TUMORS METASTATIC TO THE NERVOUS SYSTEM

Hematogenous spread most common. Skull metastases rarely invade CNS; may compress adjacent brain or cranial nerves or obstruct intracranial venous sinuses. Primary tumors that commonly metastasize to the nervous system are listed in Table 189-1. Brain metastases are well demarcated by MRI and enhance with gadolinium. Ring enhancement is nonspecific; differential diagnosis includes brain abscess, radiation necrosis, toxoplasmosis, granulomas, tuberculosis, sarcoidosis, demyelinating lesions, primary brain tumors, CNS lymphoma, stroke, hemorrhage, and trauma. Screen for occult cancer: examine skin and thyroid gland; blood carcinoembryonic antigen (CEA) and liver function tests; CT of chest, abdomen, and pelvis. In approximately 10% of pts, a systemic cancer may present with brain metastases; biopsy of primary tumor or accessible brain metastasis is needed to plan treatment. Treatment with glucocorticoids, anticonvulsants, RT, or surgery. Whole-brain RT is often given because multiple microscopic tumor deposits are likely throughout the brain; stereotaxic radiosurgery is of benefit in pts with three or fewer metastases demonstrated by MRI. If a single metastasis is found, it may be surgically excised followed by whole-brain RT. Systemic chemotherapy may produce dramatic responses in rare cases of a highly chemosensitive tumor type such

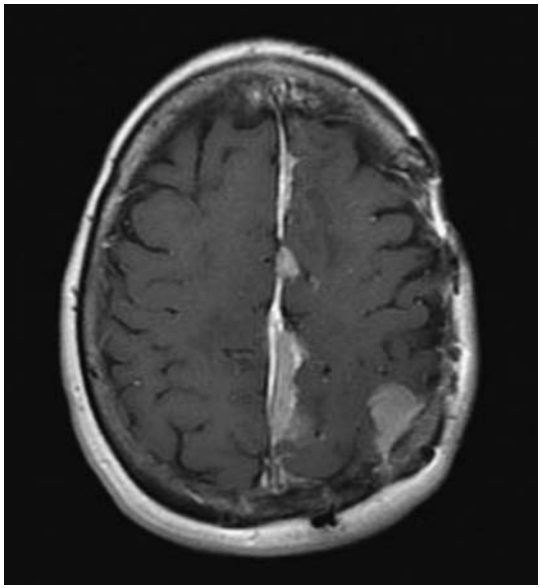


FIGURE 189-2 Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

as germ cell tumors or small-cell lung cancer harboring specific epidermal growth factor receptor (EGFR) mutations that sensitize them to EGFR inhibitors.

Leptomeningeal Metastases

Presents as headache, encephalopathy, cranial nerve, or polyradicular symptoms. Diagnosis by CSF cytology, MRI (nodular meningeal tumor deposits or diffuse meningeal enhancement), or meningeal biopsy. Associated with hydrocephalus due to CSF pathway obstruction. Treatment is palliative, often with RT or chemotherapy (systemic or intrathecal).

TABLE 189-1 FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS

	Brain %	LM %	ESCC %
Lung	41	17	15
Breast	19	57	22
Melanoma	10	12	4
Prostate	1	1	10
GIT	7	—	5
Renal	3	2	7
Lymphoma	<1	10	10
Sarcoma	7	1	9
Other	11	—	18

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.

Spinal Cord Compression from Metastases

(See Chap. 20) Expansion of vertebral body metastasis posteriorly into epidural space compresses cord. Most common primary tumors are breast, lung, prostate, kidney, lymphoma, and myeloma. Back pain (>90%) precedes development of weakness, sensory level, or incontinence. Medical emergency; early recognition of impending spinal cord compression essential to avoid devastating sequelae. Diagnosis is by spine MRI.

COMPLICATIONS OF RADIATION THERAPY

Three patterns of radiation injury after CNS RT:

1. Acute: headache, sleepiness, worse neurologic deficits during or immediately after RT. Rarely seen with current protocols. Can be both prevented and treated with glucocorticoids.
2. Early delayed: somnolence (children), Lhermitte's sign; within weeks to months of RT. Increased T2 signal and sometimes enhancement on MRI that can mimic tumor recurrence ("pseudoprogression"). Self-limited and improves with glucocorticoids; if very symptomatic may require resection.
3. Late delayed: dementia or other progressive neurologic deficits; typically months to years after RT. White matter abnormalities on MRI (leukoencephalopathy) or ring-enhancing mass (radiation necrosis). PET can distinguish delayed necrosis from tumor recurrence as can MR perfusion sequences. Progressive radiation necrosis is best treated palliatively with surgical resection unless it can be managed with glucocorticoids. Radiation injury of large arteries accelerates the development of atherosclerosis, increasing the risk of stroke years after RT. Endocrine dysfunction due to hypothalamus or pituitary gland injury can be due to delayed effects of RT. Development of a second neoplasm after RT also is a risk year after exposure.

For a more detailed discussion, see DeAngelis LM, Wen PY: Primary and Metastatic Tumors of the Nervous System, Chap. 118, p. 598, in HPIM-19.

190 Multiple Sclerosis

Characterized by chronic inflammation and selective destruction of CNS myelin; peripheral nervous system is spared. Pathologically, the multifocal scarred lesions of multiple sclerosis (MS) are termed *plaques*. Etiology is autoimmune, with susceptibility determined by genetic and environmental factors. MS affects >350,000 in the United States and 2.5 million worldwide; onset is often in early to middle adulthood, and women are affected three times as often as men.

CLINICAL FEATURES

Onset may be abrupt or insidious. Some pts have symptoms that are so trivial that they may not seek medical attention for months or years. Recurrent attacks of focal neurologic dysfunction lasting weeks or months and followed by variable

recovery, are typical; some pts initially present with slowly progressive neurologic deterioration. Symptoms often transiently worsen with fatigue, stress, exercise, or heat. Manifestations include weakness and/or sensory symptoms, visual difficulties, abnormalities of gait and coordination, urinary urgency or frequency, and abnormal fatigue. Motor involvement can present as a heavy, stiff, weak, or clumsy limb. Localized tingling, "pins and needles," and "dead" sensations are common. Optic neuritis produces monocular blurring of vision, especially in the central visual field, often with associated retro-orbital pain accentuated by eye movement. Involvement of the brainstem may result in diplopia, nystagmus, vertigo, or facial pain, numbness, weakness, hemispasm, or myokymia (rippling muscular contractions). Ataxia, tremor, and dysarthria may reflect disease of cerebellar pathways. Lhermitte's symptom, a momentary electric shock–like sensation evoked by neck flexion, indicates disease in the cervical spinal cord. Diagnostic criteria are listed in **Table 190-1**; MS mimics are summarized in **Table 190-2**.

PHYSICAL EXAMINATION

Abnormal signs usually more widespread than expected from the history. Check for abnormalities in visual fields, loss of visual acuity, disturbed color perception, optic pallor or papillitis, afferent pupillary defect (paradoxical dilation to direct light following constriction to consensual light), nystagmus, internuclear ophthalmoplegia (slowness or loss of adduction in one eye with nystagmus in the abducting eye on lateral gaze), facial numbness or weakness, dysarthria, weakness and spasticity, hyperreflexia, ankle clonus, upgoing toes, ataxia, sensory abnormalities.

DISEASE COURSE

Three major subtypes:

- *Relapsing-remitting MS* (RRMS) is characterized by recurrent attacks of neurologic dysfunction over days to weeks with or without recovery; between attacks, no progression of neurologic impairment is noted. Accounts for 85% of new-onset MS cases.
- *Secondary progressive MS* (SPMS) always initially presents as RRMS but evolves in many pts into SPMS (~1–2% each year).

TABLE 190-1 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS)

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) *or* • Await a further clinical attack implicating a different CNS site

(*Continued*)

TABLE 190-1 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS) (*CONTINUED*)

Clinical Presentation	Additional Data Needed for MS Diagnosis
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time *or* • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan *or* • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space • ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) *or* • Await a second clinical attack implicating a different CNS site *and* For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time *or* • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan *or* • Await a second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) *plus* 2 out of the 3 following criteria Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Abbreviations: MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis.
Source: From CH Polman et al: Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria." *Ann Neurol* 69:292, 2011.

TABLE 190-2 DISORDERS THAT CAN MIMIC MULTIPLE SCLEROSIS (MS)

Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
CADASIL
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
HIV infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
MELAS
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

Abbreviations: AV, arteriovenous; CADASIL, cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy; HTLV, human T-cell lymphotropic virus; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke.

- *Primary progressive MS* (PPMS) is characterized by gradual progression of disability from onset without discrete attacks; 15% of new-onset MS cases.

Historically, 15 years after diagnosis only 20% of pts have no functional limitation and one-third to one-half have progressed to SPMS and require assistance with ambulation. With the introduction of disease modifying therapies for MS, the long-term course of the disease may have become less disabling.

LABORATORY EVALUATION

MRI reveals multifocal bright areas on T2-weighted sequences in >95% of pts, often in periventricular location; gadolinium enhancement indicates acute lesions with disruption of blood-brain barrier (**Fig. 190-1**). MRI also useful to exclude MS mimics, although findings in MS are not completely specific for the disorder. CSF findings include mild lymphocytic pleocytosis (5–75 cells in 25%), oligoclonal bands (>75% have two or more), elevated IgG (80%), and normal total protein level. Visual, auditory, and somatosensory evoked response tests can identify lesions that are clinically silent; one or more evoked response tests are prolonged in 80–90% of pts. Urodynamic studies aid in management of bladder symptoms.

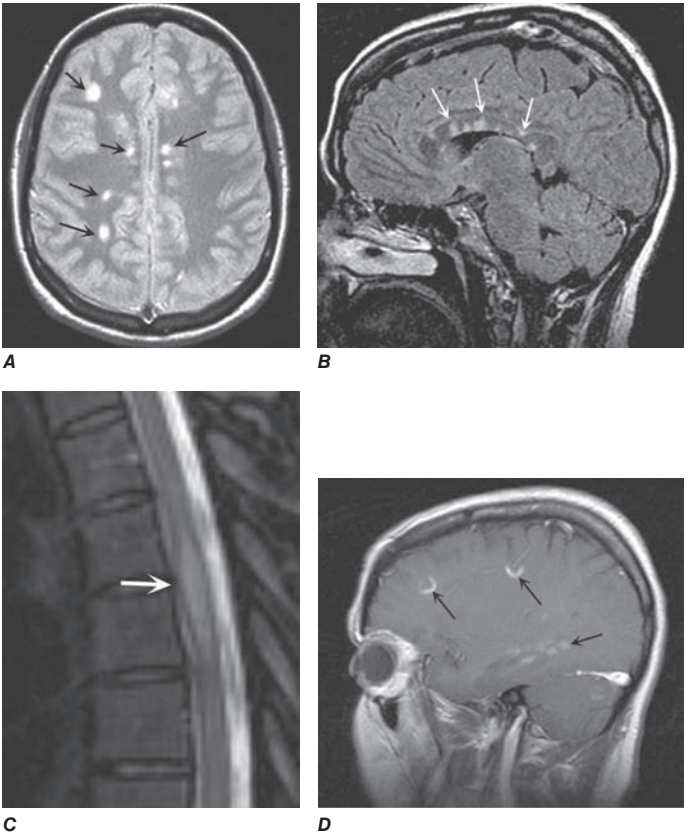
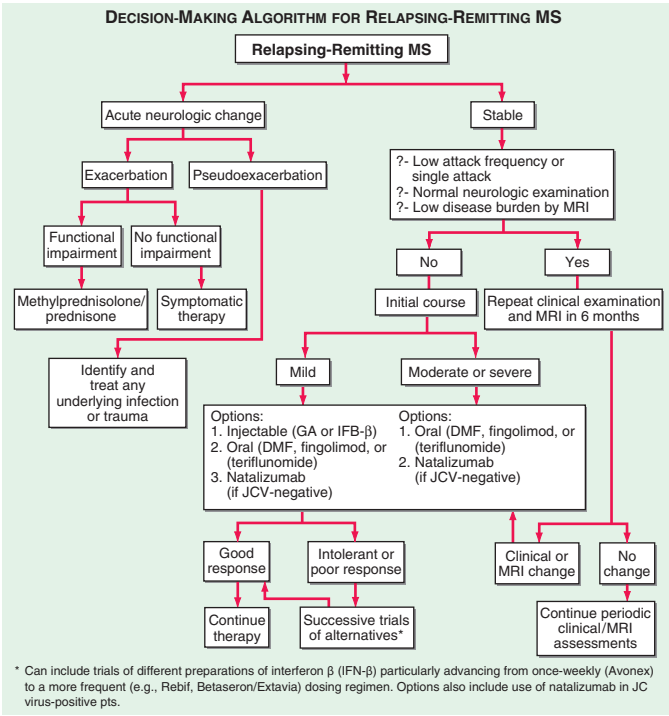


FIGURE 190-1 MRI findings in MS. **A.** Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. **B.** Sagittal T2-weighted fluid-attenuated inversion recovery image (FLAIR) in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (*arrows*). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. **C.** Sagittal T2-weighted fast spin-echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. **D.** Sagittal T1-weighted image obtained after the IV administration of gadolinium reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (*arrows*).

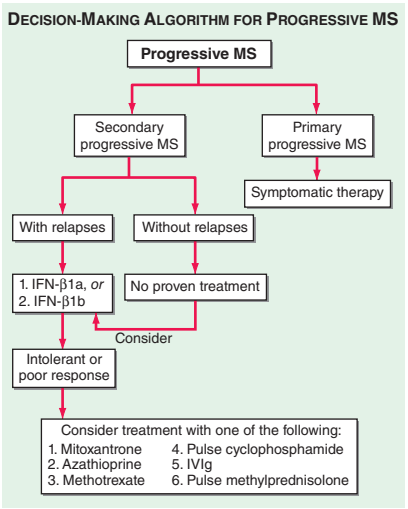
TREATMENT MULTIPLE SCLEROSIS (SEE FIG. 190-2)

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS)

- Ten treatments are available in the United States: interferon (IFN)-β1a (Avonex; 30 μg IM once a week), IFN-β1a (Rebif; 44 μg SC thrice weekly), IFN-β1b (Betaseron; 250 μg SC every other day or Extavia; 0.25 mg SC every other day), glatiramer acetate (Copaxone; 12 mg/d SC), natalizumab (Tysabri; 300 mg IV every 4 weeks), fingolimod (Gilenya; 0.5 mg PO daily), dimethyl fumarate



A



B

FIGURE 190-2 Therapeutic decision-making for MS.

(Tecfidera; 240 mg PO twice daily after initial lower starting dose), teriflunomide (Aubagio; 7–14 mg PO daily), mitoxantrone (Novantrone; 12 mg/m^2 IV every 3 months), and alemtuzumab (Lemtrada; 12 mg IV daily for 5 days followed 12 months later with 12 mg IV daily for 5 days).

- IFN preparations that are given multiple times weekly (e.g., Rebif or Betaseron/Extavia) appear to have slightly greater efficacy compared with once-weekly agents (e.g., Avonex).
- Side effects of IFN include flulike symptoms, injection-site reactions (with SC dosing), and mild abnormalities on laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, severe hepatotoxicity may occur. Side effects of IFN often subside with time. Injection-site reactions also occur with glatiramer acetate but are less severe than with IFN. Approximately 15% of pts receiving glatiramer acetate experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety.
- Fingolimod is generally well tolerated, and oral dosing is convenient for pts. First-degree heart block and bradycardia can occur, necessitating the prolonged (6-h) observation of pts receiving their first dose.
- Dimethyl fumarate has a twice-daily oral dosing schedule that makes it somewhat less convenient for pts. GI side effects are common as treatment is initiated, but usually subside with continued administration.
- Teriflunomide is well-tolerated and convenient for pts given its once daily oral dosing. However, there is less evidence of its superiority to the injectable medications than for the other oral agents A major limitation in women of childbearing age is its possible teratogenicity.
- Natalizumab is the most effective MS agent available; however, because of the development of progressive multifocal leukoencephalopathy (PML) in 0.3% of pts, it is generally used only for pts who have failed other therapies or who have particularly aggressive presentations. A blood test to detect antibodies against the PML (JC) virus can identify individuals who are at highest risk for this complication.
- Most pts with relapsing MS and a mild initial course receive an injectable (IFN-β or glatiramer acetate) or oral (dimethyl fumarate, fingolimod, or teriflunomide) agent as first-line therapy.
- For pts presenting with a moderate or severe initial course, either an oral agent (dimethyl fumarate or fingolimod) or, if the pt is JC virus antibody seronegative, infusion therapy with natalizumab is recommended.
- Regardless of which agent is chosen first, treatment should probably be altered in pts who continue to have frequent attacks (Fig. 190-2).
- Several studies suggest that these agents can improve the long-term outcome of MS. Thus, early treatment with a disease-modifying drug is appropriate for most pts. It may be reasonable to delay initiating treatment in pts with (1) a normal neurologic examination, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI.
- Untreated pts need to be followed closely; the need for therapy is reassessed if there is evidence of ongoing disease.
- Vitamin D deficiency should be corrected in all pts with MS, usually by oral supplementation with vitamin D_3, 4000–5000 IU daily.

ACUTE RELAPSES

- Acute relapses that produce functional impairment may be treated with a short course of IV methylprednisolone (500–1000 mg IV q A.M. × 3–5 days) followed often by oral prednisone (60 mg q A.M. × 4, 40 mg q A.M. × 4, 20 mg q A.M. × 3). This regimen modestly reduces the severity and shortens the duration of attacks.

- Plasma exchange (seven exchanges: 40–60 mL/kg, every other day for 14 days) may benefit pts with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids; cost is high and conclusive evidence of efficacy is lacking.

PROGRESSIVE SYMPTOMS

- For pts with SPMS who continue to experience relapses, treatment with one of the IFNs is reasonable; however, the IFNs are ineffective against purely progressive MS symptoms.
- Mitoxantrone is approved in the United States for treatment of SPMS; however, this is not the population studied in the pivotal trial, evidence for efficacy is relatively weak, and leukemia risk as well as dose-related cardiac toxicity are important concerns.
- Methotrexate (7.5–20 mg PO once each week) or azathioprine (2–3 mg/kg per day PO) is sometimes tried.
- Pulse therapy with cyclophosphamide is employed in some centers for young adults with aggressive forms of MS.
- Other smaller studies have examined monthly pulses of IV immunoglobulin (IVIg) or IV methylprednisolone.
- For pts with PPMS, symptomatic therapy only is recommended, although a preplanned secondary analysis of a negative rituximab trial was promising and a follow-up trial with a related agent (ocrelizumab) is ongoing.

SYMPTOMATIC THERAPY

- Spasticity may respond to physical therapy, baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d).
- Dysesthesia may respond to carbamazepine (100–1000 mg/d in divided doses), phenytoin (300–600 mg/d), gabapentin (300–3600 mg/d), pregabalin (50–300 mg/d), or amitriptyline (25–150 mg/d).
- Treatment of bladder symptoms is based on the underlying pathophysiology investigated with urodynamic testing: bladder hyperreflexia is treated with evening fluid restriction and frequent voiding; if this fails, anticholinergics such as oxybutynin (5–15 mg/d) may be tried; hyporeflexia is treated with the cholinergic drug bethanechol (30–150 mg a day), and dyssynergia due to loss of coordination between bladder wall and sphincter muscles is treated with anticholinergics and intermittent catheterization.
- Depression should be treated aggressively.

CLINICAL VARIANTS OF MS

Neuromyelitis optica (NMO) consists of separate attacks of acute optic neuritis (bilateral or unilateral) and myelitis. In contrast to MS, the brain MRI is typically, but not always, normal. A focal enhancing region of swelling and cavitation, extending over three or more spinal cord segments, is typically seen on spinal MRI. A highly specific autoantibody directed against the water channel aquaporin-4 is present in the sera of two-thirds of pts with a clinical diagnosis of NMO. Acute attacks are usually treated with high-dose glucocorticoids as for MS exacerbations. Plasma exchange has also been used empirically for acute episodes that fail to respond to glucocorticoids. Prophylaxis against relapses can be achieved with mycophenolate mofetil, rituximab, or a combination of glucocorticoids plus azathioprine.

Acute MS (Marburg's variant) is a fulminant demyelinating process that progresses to death within 1–2 years. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

A fulminant, often devastating, demyelinating disease that has a monophasic course and may be associated with antecedent immunization or infection. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). Fever, headache, meningismus, lethargy progressing to coma, and seizures may occur. CSF pleocytosis, generally 200 cells/μL, is common. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord. Initial treatment is with high-dose glucocorticoids. Pts who fail to respond may benefit from a course of plasma exchange or IVIg.

For a more detailed discussion, see Hauser SL, Goodin DS: Multiple Sclerosis and Other Demyelinating Diseases, Chap. 458, p. 2661, in HPIM-19.

191 Acute Meningitis and Encephalitis

Acute infections of the nervous system include bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Key goals: emergently distinguish between these conditions, identify the pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT: Acute Infection of the Nervous System

(Fig. 191-1) First identify whether infection predominantly involves the subarachnoid space (*meningitis*) or brain tissue (termed *encephalitis* when viral, *cerebritis* or *abscess* if bacterial, fungal, or parasitic). Nuchal rigidity is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion.

Principles of management:

- Initiate empirical therapy whenever bacterial meningitis is considered.
- All pts with head trauma, immunocompromised states, known malignancies, or focal neurologic findings (including papilledema or stupor/coma) should undergo a neuroimaging study of the brain prior to LP. If bacterial meningitis is suspected, begin empirical antibiotic therapy prior to neuroimaging and LP.
- Stupor/coma, seizures, or focal neurologic deficits do not occur in viral meningitis; pts with these symptoms should be hospitalized and treated empirically for bacterial and viral meningoencephalitis.
- Immunocompetent pts with a normal level of consciousness, no prior antimicrobial treatment, and a CSF profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be treated as outpatients. Failure of a pt with suspected viral meningitis to improve within 48 h should prompt reevaluation including follow-up examination, repeat imaging, and laboratory studies, often including a second LP.

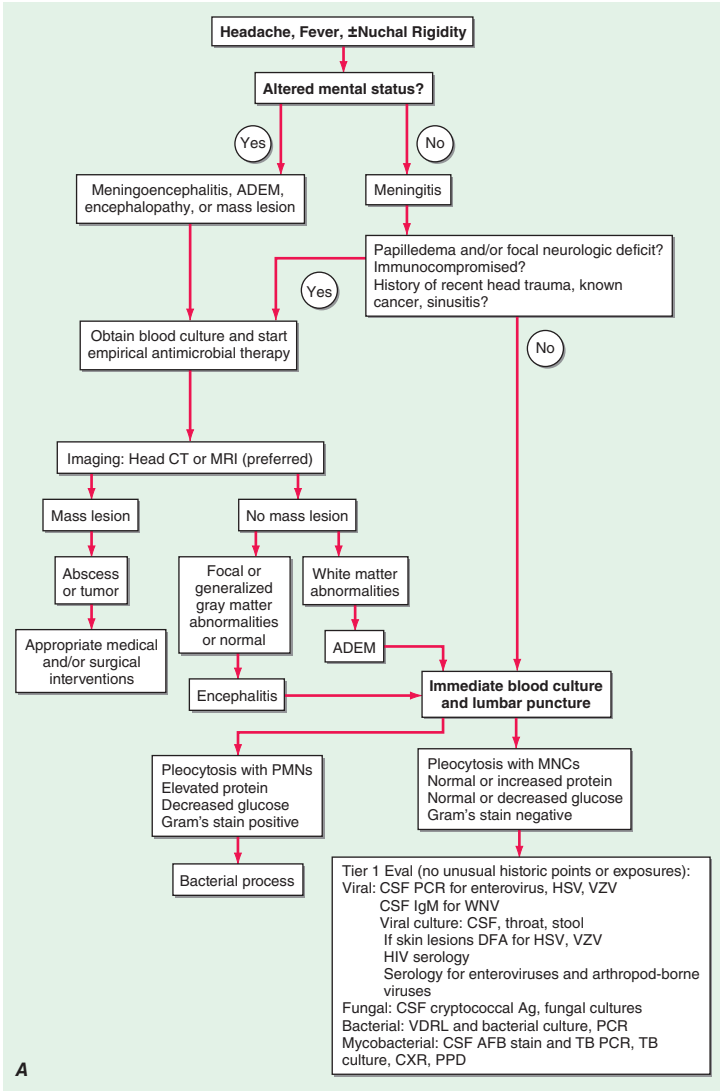


FIGURE 191-1 The management of pts with suspected CNS infection. ADEM, acute disseminated encephalomyelitis; AFB, acid-fast bacillus; Ag, antigen; CTFV, Colorado tick fever virus; DFA, direct fluorescent antibody; HHV, human herpesvirus; LCMV, lymphocytic choriomeningitis virus; MNCs, mononuclear cells; TB, tuberculosis; WNV, West Nile virus.

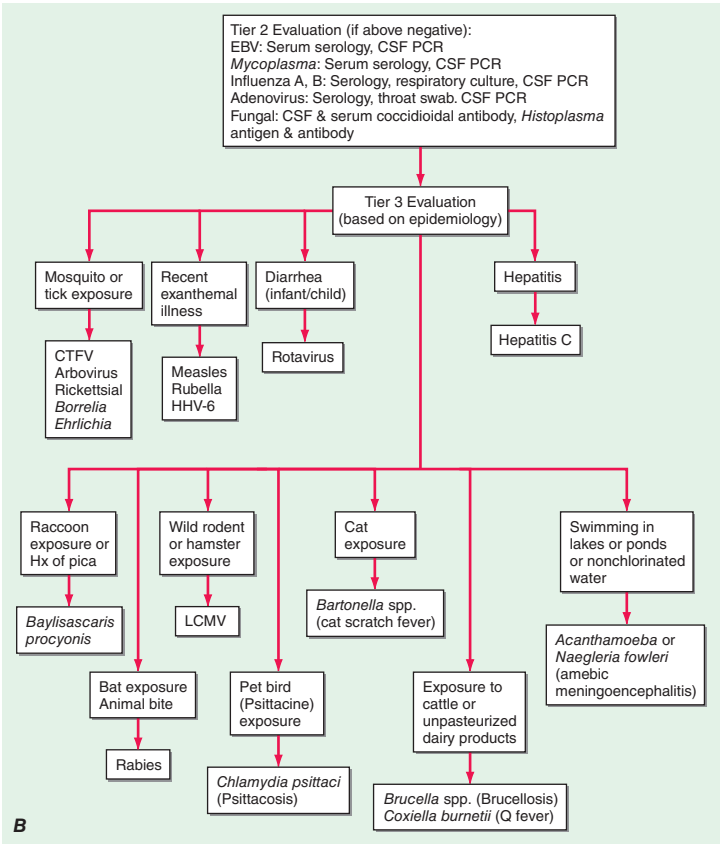


FIGURE 191-1 (*Continued*)

ACUTE BACTERIAL MENINGITIS

Pathogens most frequently involved in immunocompetent adults are *Streptococcus pneumoniae* ("pneumococcus," ~50%) and *Neisseria meningitidis* ("meningococcus," ~25%). Predisposing factors for pneumococcal meningitis include infection (pneumonia, otitis, sinusitis), asplenia, hypogammaglobulinemia, complement deficiency, alcoholism, diabetes, and head trauma with CSF leak. *Listeria monocytogenes* is a consideration in pregnant women, individuals >60 years, alcoholics, and immunocompromised individuals of all ages. Enteric gram-negative bacilli and group B streptococcus are increasingly common causes of meningitis in individuals with chronic medical conditions. *Staphylococcus aureus* and coagulase-negative staphylococci are causes following neurosurgical procedures, especially shunting procedures for hydrocephalus.

Clinical Features

Presents as an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity ("stiff neck"). Mental status

TABLE 191-1 CEREBROSPINAL FLUID ABNORMALITIES IN BACTERIAL MENINGITIS

Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type b, *Escherichia coli*, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

changes occur in >75% of pts and vary from lethargy to coma. Nausea, vomiting, and photophobia are also common. Seizures occur in 20–40% of pts. Raised intracranial pressure (ICP) is the major cause of obtundation and coma. The rash of meningococcemia begins as a diffuse maculopapular rash resembling a viral exanthem but rapidly becomes petechial on trunk and lower extremities, mucous membranes and conjunctiva, and occasionally palms and soles.

Laboratory Evaluation

The CSF profile is shown in Table 191-1. CSF bacterial cultures are positive in >80% of pts, and CSF Gram's stain demonstrates organisms in >60%. A 16S rRNA conserved sequence broad-based bacterial PCR can detect small numbers of viable and nonviable organisms in the CSF and is useful for diagnosis in pts pretreated with antibiotics and when Gram's stain and CSF cultures are negative. When positive, more specific PCR tests for individual organisms can be obtained. The latex agglutination (LA) test for detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *Haemophilus influenzae* type b, group B streptococcus, and *Escherichia coli* K1 strains in the CSF is being replaced by the CSF bacterial PCR assay. The Limulus amebocyte lysate assay rapidly detects gram-negative endotoxin in CSF and thus is useful in diagnosis of gram-negative bacterial meningitis; false-positives may occur but sensitivity approaches 100%. Petechial skin lesions, if present, should be biopsied. Blood cultures should always be obtained.

Differential Diagnosis

Includes viral meningoencephalitis, especially herpes simplex virus (HSV) encephalitis (see below); rickettsial diseases such as Rocky Mountain spotted fever (immunofluorescent staining of skin lesions); focal suppurative CNS infections including subdural and epidural empyema and brain abscess (see below); subarachnoid hemorrhage (Chap. 18); and the demyelinating disease acute disseminated encephalomyelitis (ADEM, Chap. 190).

TABLE 191-2 ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CENTRAL NERVOUS SYSTEM INFECTIONS[a]

Indication	Antibiotic
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

	Total Daily Dose and Dosing Interval	
Antimicrobial Agent	**Child (>1 month)**	**Adult**
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225–300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45–60 (mg/kg)/d, q6h	45–60 (mg/kg)/d, q6–12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.
[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

TREATMENT ACUTE BACTERIAL MENINGITIS

- Recommendations for empirical therapy are summarized in **Table 191-2**. Therapy is then modified based on results of CSF culture (**Table 191-3**).
- In general, the treatment course is 7 days for meningococcus, 14 days for pneumococcus, 21 days for gram-negative meningitis, and at least 21 days for *L. monocytogenes*.
- Adjunctive therapy with dexamethasone (10 mg IV), administered 15–20 min before the first dose of an antimicrobial agent and repeated every 6 h for 4 days,

TABLE 191-3 ANTIMICROBIAL THERAPY OF CENTRAL NERVOUS SYSTEM BACTERIAL INFECTIONS BASED ON PATHOGEN[a]

Organism	Antibiotic
Neisseria meningitides	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumonia	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except *Pseudomonas* spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococci spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 191-2.

improves outcome from bacterial meningitis; benefits most striking in pneumococcal meningitis. Dexamethasone may decrease the penetration of vancomycin into CSF, and thus higher vancomycin doses may be needed.

- In meningococcal meningitis, all close contacts should receive prophylaxis with rifampin [600 mg in adults (10 mg/kg in children >1 year)] every 12 h for 2 days; rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg), or one IM dose of ceftriaxone (250 mg).

Prognosis

Moderate or severe sequelae occur in ~25% of survivors; outcome varies with the infecting organism and can include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

VIRAL MENINGITIS

Presents as fever, headache, and meningeal irritation associated with a CSF lymphocytic pleocytosis. Fever may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. A mild degree of lethargy or drowsiness may occur; however, a more profound alteration in consciousness should prompt consideration of alternative diagnoses, including encephalitis.

TABLE 191-4 VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA

Acute Meningitis	
Common	**Less Common**
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Herpes simplex virus 1
Varicella-zoster virus	Human herpesvirus 6
Herpes simplex virus 2	Cytomegalovirus
Epstein-Barr virus	Lymphocytic choriomeningitis virus
Arthropod-borne viruses	Mumps
HIV	
Acute Encephalitis	
Common	**Less Common**
Herpesviruses	Rabies
Cytomegalovirus[a]	Eastern equine encephalitis virus
Herpes simplex virus 1[b]	Powassan virus
Herpes simplex virus 2	Cytomegalovirus[a]
Human herpesvirus 6	Colorado tick fever virus
Varicella-zoster virus	Mumps
Epstein-Barr virus	
Arthropod-borne viruses	
La Crosse virus	
West Nile virus[c]	
St. Louis encephalitis virus	
Enteroviruses	

[a]Immunocompromised host.
[b]The most common cause of sporadic encephalitis.
[c]The most common cause of epidemic encephalitis.

Etiology

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases. The most important agents are enteroviruses, VZV, HSV type 2, HIV, and arboviruses (Table 191-4). The incidence of enteroviral and arboviral infections is greatly increased during the summer.

Diagnosis

Most important test is examination of the CSF. The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are *not* seen on Gram or acid-fast stained smears or india ink preparations of CSF. Rarely, polymorphonuclear leukocytes (PMN) predominate in the first 48 h of illness, especially with echovirus 9, West Nile virus (WNV), eastern equine encephalitis virus, or mumps. The total CSF cell count in viral meningitis is typically 25–500/μL. As a general rule,

a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, listerial, or tuberculous meningitis or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

CSF PCR testing is the procedure of choice for rapid, sensitive, and specific identification of enteroviruses, HSV, EBV, varicella zoster virus (VZV), human herpes virus 6 (HHV-6), and CMV. Attempts should also be made to culture virus from CSF and other sites and body fluids including blood, throat swabs, stool, and urine, although sensitivity of cultures is generally poor. Serologic studies, including those utilizing paired CSF and serum specimens, may be helpful for retrospective diagnosis; they are particularly important for diagnosis of WNV and other arbovirus etiologies.

Differential Diagnosis

Consider bacterial, fungal, tuberculous, spirochetal, and other infectious causes of meningitis; parameningeal infections; partially treated bacterial meningitis; neoplastic meningitis; noninfectious inflammatory diseases including sarcoid and Behçet's disease.

TREATMENT **VIRAL MENINGITIS**

- Supportive or symptomatic therapy is usually sufficient, and hospitalization is not required.
- The elderly and immunocompromised pts should be hospitalized, as should individuals in whom the diagnosis is uncertain or those with significant alterations in consciousness, seizures, or focal neurologic signs or symptoms.
- Severe cases of meningitis due to HSV, EBV, and VZV can be treated with IV acyclovir (5–10 mg/kg every 8 h), followed by an oral drug (acyclovir (800 mg, five times daily; famciclovir 500 mg tid; or valacyclovir 1000 mg tid) for a total course of 7–14 days; for mildly affected patients, an oral course of antivirals alone may be appropriate.
- Additional supportive therapy can include analgesics and antipyretics.
- Prognosis for full recovery is excellent.
- Vaccination is an effective method of preventing meningitis and other neurologic complications associated with poliovirus, mumps, rubella, measles, and VZV infection.

VIRAL ENCEPHALITIS

An infection of the brain parenchyma commonly associated with meningitis ("meningoencephalitis"). Clinical features are those of viral meningitis plus evidence of brain tissue involvement, commonly including altered consciousness such as behavioral changes and hallucinations; seizures; and focal neurologic findings such as aphasia, hemiparesis, involuntary movements, and cranial nerve deficits.

Etiology

The same organisms responsible for viral meningitis are also responsible for encephalitis, although relative frequencies differ. The most common causes of sporadic encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV) (Table 191-4). HSV encephalitis should be considered when focal findings are present and when involvement of the inferomedial frontotemporal regions of the brain is likely (olfactory hallucinations, anosmia, bizarre behavior, or memory disturbance). Epidemics of encephalitis are usually caused by arboviruses. WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States since 2002. Prominent motor manifestations, including acute poliomyelitis-like paralysis, may occur with WNV.

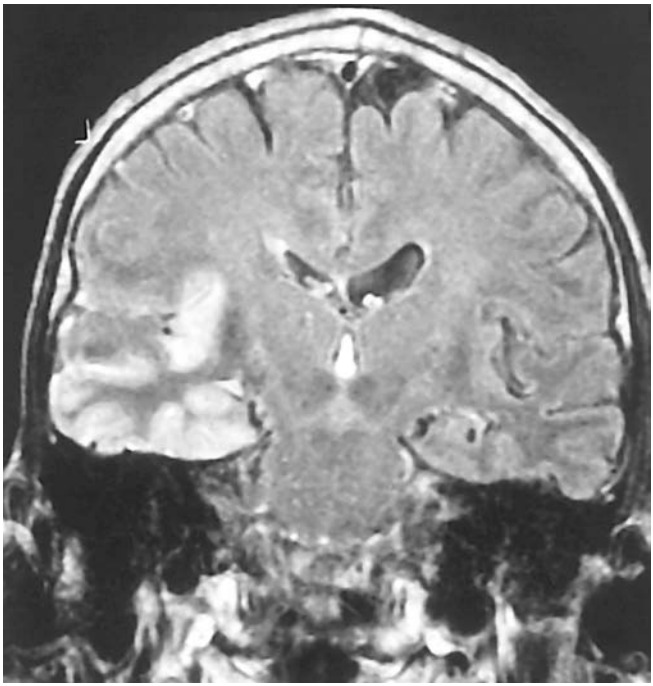


FIGURE 191-2 Coronal FLAIR magnetic resonance image from a pt with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This pt had predominantly unilateral disease; bilateral lesions are more common, but may be quite asymmetric in their intensity.

Diagnosis

CSF studies are essential; typical CSF profile is similar to viral meningitis. CSF PCR tests allow for rapid and reliable diagnosis of HSV, EBV, VZV, CMV, HHV-6, and enteroviruses. CSF virus cultures are generally negative. Serologic studies also have a role for some viruses. Demonstration of WNV IgM antibodies in the CSF is diagnostic of WNV encephalitis.

MRI is the neuroimaging procedure of choice and demonstrates areas of increased T2 signal. Bitemporal and orbitofrontal areas of increased signal are seen in HSV encephalitis, but are not diagnostic (**Fig. 191-2**). The EEG may suggest seizures or show temporally predominant periodic spikes on a slow, low-amplitude background suggestive of HSV encephalitis.

Brain biopsy is now used only when CSF PCR studies fail to identify the cause, focal abnormalities on MRI are present, and progressive clinical deterioration occurs despite treatment with acyclovir and supportive therapy.

Differential Diagnosis

Includes both infectious and noninfectious causes of encephalitis, including vascular diseases; abscess and empyema; fungal (*Cryptococcus* and *Mucor*), spirochetal (*Leptospira*), rickettsial, bacterial (*Listeria*), tuberculous, and mycoplasmal infections; tumors; toxic encephalopathy; SLE; autoimmune or paraneoplastic encephalidities, and acute disseminated encephalomyelitis.

TREATMENT VIRAL ENCEPHALITIS

- All pts with suspected HSV encephalitis should be treated with IV acyclovir (10 mg/kg every 8 h) while awaiting diagnostic studies.
- Pts with a PCR-confirmed diagnosis of HSV encephalitis should receive a 14- to 21-day course of therapy. Consider repeat CSF PCR after completion of acyclovir therapy; pts with a persistently positive CSF PCR for HSV after completing a standard course of acyclovir therapy should receive additional treatment, followed by a repeat CSF PCR test.
- Acyclovir treatment may also be of benefit in severe encephalitis due to EBV and VZV. No therapy currently available for enteroviral, mumps, or measles encephalitis.
- IV ribavirin (15–25 mg/kg per day given in three divided doses) may benefit severe encephalitis due to California encephalitis (LaCrosse) virus.
- CMV encephalitis should be treated with ganciclovir (5 mg/kg every 12 h IV over 1 h, followed by maintenance therapy of 5 mg/kg every day), foscarnet (60 mg/kg every 8 h IV over 1 h, followed by maintenance therapy 60–120 mg/kg per day), or a combination of the two drugs; cidofovir (5 mg/kg IV once weekly for 2 weeks, then biweekly for two or more additional doses, depending on response; prehydrate with normal saline and pretreat with probenecid) may provide an alternative for nonresponders.
- No proven therapy is available for WNV encephalitis; small groups of pts have been treated with interferon, ribavirin, WNV-specific antisense oligonucleotides, IV immunoglobulin preparations of Israeli origin containing high-titer anti-WNV antibody, and humanized monoclonal antibodies directed against the viral envelope glycoprotein. There is optimism that a safe and effective human WNV vaccine can be developed.

Prognosis

In HSV encephalitis treated with acyclovir, 81% survival in one series; neurologic sequelae were mild or absent in 46%, moderate in 12%, and severe in 42%.

BRAIN ABSCESS

A focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is used to describe a nonencapsulated brain abscess. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, head trauma, neurosurgical procedures, and dental infections. Many brain abscesses occur in immunocompromised hosts and are caused less often by bacteria than by fungi and parasites including *Toxoplasma gondii*, *Aspergillus* spp., *Nocardia* spp., *Candida* spp., and *Cryptococcus* neoformans. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and the Far East, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

Clinical Features

Brain abscess typically presents as an expanding intracranial mass lesion, rather than as an infectious process. The classic triad of headache, fever, and a focal neurologic deficit is present in <50% of cases.

Diagnosis

MRI is superior to CT for demonstrating abscesses in the early (cerebritis) stages and also for abscesses in the posterior fossa. A mature brain abscess appears on CT as a focal area of hypodensity surrounded by ring enhancement. The CT and MRI

appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal lesions such as tumors may be facilitated with diffusion-weighted imaging (DWI) sequences in which brain abscesses typically show increased signal due to restricted diffusion.

Microbiologic diagnosis best determined by Gram's stain and culture of abscess material obtained by stereotactic needle aspiration. Up to 10% of pts will also have positive blood cultures. CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

TREATMENT BRAIN ABSCESS

- Optimal therapy involves a combination of high-dose parenteral antibiotics and neurosurgical drainage.
- Empirical therapy of community-acquired brain abscess in an immunocompetent pt typically includes a third or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole (see Table 191-2 for antibiotic dosages).
- In pts with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of resistant staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.
- Aspiration and drainage essential in most cases. Empirical antibiotic coverage is modified based on the results of Gram's stain and culture of the abscess contents.
- Medical therapy alone is reserved for pts whose abscesses are neurosurgically inaccessible and for pts with small (<2–3 cm) or nonencapsulated abscesses (cerebritis).
- All pts should receive a minimum of 6–8 weeks of parenteral antibiotic therapy.
- Pts should receive prophylactic anticonvulsant therapy.
- Glucocorticoids should not be given routinely.
- Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess.

Prognosis

In modern series, the mortality is typically <15%. Significant sequelae including seizures, persisting weakness, aphasia, or mental impairment occur in ≥20% of survivors.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Clinical Features

A progressive disorder due to infection with the JC virus, a human polyoma virus; characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the CNS but sparing the spinal cord and optic nerves. In addition, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Pts often present with visual deficits (45%), typically a homonymous hemianopia, and mental impairment (38%) (dementia, confusion, personality change), weakness, and ataxia. Seizures occur in ~20% of patients. Almost all pts have an underlying immune disorder or are receiving immunosuppressive therapy. More than 80% of currently diagnosed PML cases occur in pts with AIDS; it has been estimated that up to 5% of AIDS pts will develop PML. Immunosuppressant drugs such as natalizumab have also been associated with PML.

Diagnostic Studies

MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased T2 and decreased T1 signal, are generally nonenhancing (rarely they may show ring enhancement), and are not associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JC virus DNA from CSF has become an important diagnostic tool. A positive CSF PCR for JC virus DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML. Pts with negative CSF PCR studies may require brain biopsy for definitive diagnosis as sensitivity of this test is variable; JC virus antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification on tissue. Detection of JC virus antigen or genomic material should be considered diagnostic of PML only if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal pts. Serologic studies are of no utility for diagnosis given high basal seroprevalence level, but are extremely useful for risk stratification in pts contemplating therapy with certain immunomodulatory drugs such as natalizumab.

TREATMENT **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY**

- No effective therapy is available.
- Some pts with HIV-associated PML have shown dramatic clinical gains associated with improvement in immune status following institution of highly active antiretroviral therapy (HAART).

Ps suspected of having PML who are receiving immunomodulatory antibodies should have therapy halted and circulating antibodies cleared by plasma exchange; discontinuation of therapy may lead to transient clinical and radiologic worsening, termed immune reconstitution inflammatory syndrome (IRIS).

For a more detailed discussion, see Roos KL, Tyler KL: Meningitis, Encephalitis, Brain Abscess, and Empyema, Chap. 164, p. 883, in HPIM-19; and HPIM-19 chapters covering specific organisms or infections.

192 Chronic and Recurrent Meningitis

Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The causes are varied. Five categories of disease account for most cases of chronic meningitis:

- Meningeal infections
- Malignancy
- Noninfectious inflammatory disorders

TABLE 192-1 SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

Symptom	Sign
Chronic headache	±Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/incontinence	Myelopathy or radiculopathy
	Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

- Chemical meningitis
- Parameningeal infections

CLINICAL FEATURES

Neurologic manifestations consist of persistent headache with or without stiff neck and hydrocephalus; cranial neuropathies; radiculopathies; and/or cognitive or personality changes (Table 192-1). The diagnosis is usually made when clinical presentation leads the physician to examine CSF for signs of inflammation; on occasion the diagnosis is made when a neuroimaging study shows contrast enhancement of the meninges.

Two clinical forms of chronic meningitis exist. In the first, symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes with complete resolution of meningeal inflammation between episodes without specific therapy. In the latter group, likely etiologies are herpes simplex virus type 2, chemical meningitis due to leakage from a tumor, a primary inflammatory condition, or drug hypersensitivity.

APPROACH TO THE PATIENT: **Chronic Meningitis**

Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (Tables 192-2 and 192-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) examination of meningeal biopsy tissue.

Proper analysis of the CSF is essential; if the possibility of raised intracranial pressure (ICP) exists, a brain imaging study should be performed before LP. In pts with communicating hydrocephalus caused by impaired resorption of CSF, LP is

TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS

Causative Agent	CSF Formula	Helpful Diagnostic Tests	Risk Factors and Systemic Manifestations
Common Bacterial Causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed polymorphonuclear-mononuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) *Borrelia burgdorferi*	Mononuclear cells; elevated protein	Serum Lyme antibody titer; Western blot confirmation; (pts with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) *Treponema pallidum*	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis

(*Continued*)

TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)

Causative Agent	CSF Formula	Helpful Diagnostic Tests	Risk Factors and Systemic Manifestations
Uncommon Bacterial Causes			
Actinomyces	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
Nocardia	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
Brucella	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease *Tropheryma whipplei*	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for *T. whipplei;* brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare Bacterial Causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some pts with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern U.S.; increased virulence in dark-skinned races

Candida sp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post surgery; prolonged IV therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern U.S.; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus sp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
Sporothrix schenckii	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare Fungal Causes			
Xylohypha (formerly *Cladosporium*) *trichoides* and other dark-walled (dematiaceous) fungi such as *Curvularia, Drechslera; Mucor*, and, after water aspiration, *Pseudallescheria boydii,* iatrogenic *Exserohilum rostratum* infection following spinal blocks			
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive pts
Trypanosomiasis *Trypanosoma gambiense*, *T. rhodesiense*	Mononuclear cells, elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder

(*Continued*)

TABLE 192-2 INFECTIOUS CAUSES OF CHRONIC MENINGITIS (*CONTINUED*)

Causative Agent	CSF Formula	Helpful Diagnostic Tests	Risk Factors and Systemic Manifestations
Rare Protozoal Causes			
Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals. *Balamuthia mandrillaris* causing chronic meningoencephalitis in immunocompetent hosts.			
Helminthic Causes			
Cysticercosis (infection with cysts of *Taenia solium*)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Gnathostoma spinigerum	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
Angiostrongylus cantonensis	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign
Baylisascaris procyonis (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis

Rare Helminthic Causes			
Trichinella spiralis (trichinosis); *Fasciola hepatica* (liver fluke), *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord			
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis	Mononuclear cells	Antibody in serum	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis
HIV (acute retroviral syndrome)	Mononuclear cells	p24 antigen in serum and CSF; high level of HIV viremia.	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV
Herpes simplex (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Abbreviations: AFB, acid-fast bacillus; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–*T. pallidum;* PAS, periodic acid–Schiff; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

TABLE 192-3 NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS

Causative Agents	CSF Formula	Helpful Diagnostic Tests	Risk Factors and Systemic Manifestations
Malignancy	Mononuclear cells, elevated protein, low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; meningeal sarcoma; cerebral dysgerminoma; meningeal melanoma or B cell lymphoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs, low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis"	Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary inflammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/meningeal biopsy	CN palsy, especially of CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma
Isolated granulomatous angiitis of the nervous system	Mononuclear cells, elevated protein	Angiography or meningeal biopsy	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus

Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs, elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils	Complete blood count (eosinophilia)	Exposure to nonsteroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure
Granulomatosis with polyangiitis (Wegener's)	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Other: multiple sclerosis, Sjögren's syndrome, monogenic autoinflammatory disorders, and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; PMNs, polymorphonuclear cells.

safe and may lead to temporary improvement. However, if ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then LP carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage of CSF.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy. Cerebral angiography may identify arteritis.

A meningeal biopsy should be considered in pts who are disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT; in one series, biopsies most often identified sarcoid (31%) or metastatic adenocarcinoma (25%). Tuberculosis is the most common condition identified in many reports outside of the United States.

In approximately one-third of cases, the diagnosis is not established despite careful evaluation. A number of the organisms that cause chronic meningitis may take weeks to be identified by culture. It is reasonable to wait until cultures are finalized if symptoms are mild and not progressive. However, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes (most common). It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other cranial nerve palsies, since untreated disease can be fatal within weeks. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time. Important causes of chronic meningitis in HIV pts include infection with *Toxoplasma* (usually presents as intracranial abscesses), *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma.

For a more detailed discussion, see Koroshetz WJ, Nath A: Chronic and Recurrent Meningitis, Chap. 165, p. 906, in HPIM-19.

193 Peripheral Neuropathies, Including Guillain-Barré Syndrome

APPROACH TO THE PATIENT: Peripheral Neuropathy

Peripheral neuropathy (PN) refers to a peripheral nerve disorder of any cause. Nerve involvement may be single (mononeuropathy) or multiple (polyneuropathy); pathology may be axonal or demyelinating. An approach to pts with suspected neuropathy appears in **Fig. 193-1**.

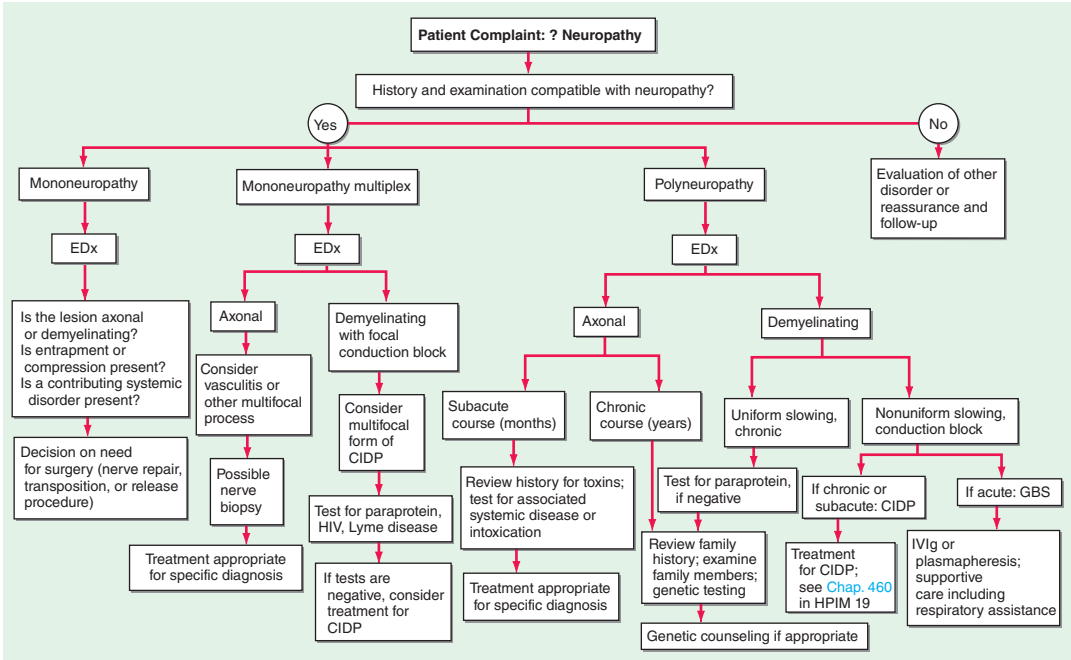


FIGURE 193-1 Approach to evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic studies; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

Seven initial questions:

1. *What systems are involved?* Determine if symptoms and signs are predominantly motor, sensory, autonomic, or a combination of these. If only weakness is present without sensory or autonomic dysfunction, consider a motor neuropathy, neuromuscular junction disorder, or myopathy; myopathies usually have a proximal, symmetric pattern of weakness.
2. *What is the distribution of weakness?* Polyneuropathy involves widespread and often symmetric dysfunction of the peripheral nerves that is usually distal more than proximal; mononeuropathy involves a single nerve, usually due to trauma or compression; multiple mononeuropathies (mononeuropathy multiplex) can be a result of multiple entrapments, vasculitis, or infiltration.
3. *What is the nature of the sensory involvement?* Temperature loss or burning/stabbing pain suggests small fiber involvement. Vibratory or proprioceptive loss implicates large fibers.
4. *Is there evidence of upper motor neuron involvement?* The most common cause is combined system degeneration with B_{12} deficiency, but should also consider copper deficiency, HIV infection, severe hepatic disease, and adrenomyeloneuropathy.
5. *What is the temporal evolution?* Most neuropathies are insidious and slowly progressive. Rapidly evolving neuropathies are often inflammatory, including acute inflammatory demyelinating polyneuropathy (AIDP) or *Guillain-Barré syndrome* (GBS); subacute evolution suggests an inflammatory, toxic, or nutritional cause; chronic neuropathies that are long-standing over years may be hereditary.
6. *Is there evidence for a hereditary neuropathy?* Consider in pts with a slowly progressive distal weakness over many years with few sensory symptoms but significant sensory deficits on clinical examination. Most common is Charcot-Marie-Tooth disease (CMT; look for foot abnormalities such as high or flat arches and hammer toes as well as scoliosis).
7. *Does the pt have other medical conditions?* Inquire about associated medical conditions (e.g., diabetes, systemic lupus erythematosus); preceding or concurrent infections (e.g., diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy); over-the-counter vitamin preparations (B_6); alcohol, dietary habits; and use of dentures (because fixatives contain zinc that can lead to copper deficiency).

Based on the answers to these seven key questions, neuropathic disorders can be classified into several patterns based on the pattern of sensory, motor, and autonomic involvement (**Table 193-1**).

POLYNEUROPATHY

Diagnostic Evaluation

Screening laboratory studies in a distal, symmetric polyneuropathy may include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose, HbA_{1c}, urinalysis, thyroid function tests, B_{12}, folate, ESR, rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixation, and urine for Bence Jones protein. An oral glucose tolerance test is indicated in pts with painful sensory neuropathies even if other screens for diabetes are negative.

Tests to further characterize the neuropathy include nerve conduction studies (NCS), electromyography (EMG), sural nerve biopsy, muscle biopsy, skin biopsies, and quantitative sensory testing. Diagnostic tests are more likely to be informative in pts with asymmetric, motor-predominant, rapid-onset, or demyelinating neuropathies.

TABLE 193-1 PATTERNS OF NEUROPATHIC DISORDERS

Pattern 1: Symmetric proximal and distal weakness with sensory loss
Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP)
Pattern 2: Symmetric distal sensory loss with or without distal weakness
Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, and others
Pattern 3: Asymmetric distal weakness with sensory loss
With involvement of multiple nerves
Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration
With involvement of single nerves/regions
Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy
Pattern 4: Asymmetric proximal and distal weakness with sensory loss
Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, hereditary plexopathy (HNPP, HNA), idiopathic
Pattern 5: Asymmetric distal weakness without sensory loss
With upper motor neuron findings
Consider: motor neuron disease
Without upper motor neuron findings
Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy
Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings
Consider: Vitamin B_{12}, vitamin E, and copper deficiency with combined system degeneration with peripheral neuropathy, hereditary leukodystrophies (e.g., adrenomyeloneuropathy)
Pattern 7: Symmetric weakness without sensory loss
With proximal and distal weakness
Consider: SMA
With distal weakness
Consider: hereditary motor neuropathy ("distal" SMA) or atypical CMT
Pattern 8: Asymmetric proprioceptive sensory loss without weakness
Consider causes of a sensory neuronopathy (ganglionopathy):
Cancer (paraneoplastic)
Sjögren's syndrome
Idiopathic sensory neuronopathy (possible GBS variant)
Cisplatin and other chemotherapeutic agents
Vitamin B_6 toxicity
HIV-related sensory neuronopathy

(*Continued*)

TABLE 193-1 PATTERNS OF NEUROPATHIC DISORDERS (*CONTINUED*)

Pattern 9: Autonomic symptoms and signs
Consider neuropathies associated with prominent autonomic dysfunction:
Hereditary sensory and autonomic neuropathy
Amyloidosis (familial and acquired)
Diabetes mellitus
Idiopathic pandysautonomia (may be a variant of Guillain-Barré syndrome)
Porphyria
HIV-related autonomic neuropathy
Vincristine and other chemotherapeutic agents

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; GBS, Guillain-Barré syndrome; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; SMA, spinal muscular atrophy.

Electrodiagnosis

NCS are carried out by stimulating motor or sensory nerves electrically. Demyelination is characterized by slowing of nerve conduction velocities (NCV), dispersion of evoked compound action potentials, conduction block (decreased amplitude of muscle compound action potentials on proximal, as compared to distal, stimulation of the nerve), and prolongation of distal latencies. In contrast, axonal neuropathies exhibit reduced amplitude of evoked compound action potentials with relative preservation of NCV. EMG records electrical potentials from a needle electrode in muscle, at rest and during voluntary contraction; it is most useful for distinguishing myopathic from neuropathic disorders. Myopathic disorders are marked by small, short-duration, polyphasic muscle action potentials; by contrast, neuropathic disorders are characterized by muscle denervation. Denervation decreases the number of motor units (e.g., an anterior horn cell, its axon, and the motor end plates and muscle fibers it innervates). In long-standing denervation, motor unit potentials become large and polyphasic due to collateral reinnervation of denervated muscle fibers by axonal sprouts from surviving motor axons. Other EMG features of denervation include fibrillations (random, unregulated firing of individual muscle fibers) and fasciculations (random, spontaneous firing of motor units).

TREATMENT POLYNEUROPATHY

- Treatment of the underlying disorder, pain management, and supportive care to protect and rehabilitate damaged tissue all need to be considered.
- Examples of specific therapies include tight glycemic control in diabetic neuropathy, vitamin replacement for B_{12} deficiency, IV immune globulin (IVIg) or plasmapheresis for GBS, and immunosuppression for vasculitis.
- Painful sensory neuropathies can be difficult to treat. Pain management usually begins with tricyclic antidepressants (TCAs), duloxetine hydrochloride, lidocaine patches, or anticonvulsants such as gabapentin or pregabalin (**Table 193-2**). Topical anesthetic agents including EMLA (lidocaine/prilocaine) and capsaicin cream can provide additional relief.

TABLE 193-2 TREATMENT OF PAINFUL SENSORY NEUROPATHIES

Therapy	Route	Dose	Side Effects
First-Line			
Lidoderm 5% patch	Apply to painful area	Up to 3 patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	PO	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	PO	300–1200 mg tid	Cognitive changes, sedation, peripheral edema
Pregabalin	PO	50–100 mg tid	Cognitive changes, sedation, peripheral edema
Duloxetine	PO	30–60 mg qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
Second-Line			
Carbamazepine	PO	200–400 mg q 6–8 h	Cognitive changes, dizziness, leukopenia, liver dysfunction
Phenytoin	PO	200–400 mg qhs	Cognitive changes, dizziness, liver dysfunction
Venlafaxine	PO	37.5–150 mg/d	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence
Tramadol	PO	50 mg qid	Cognitive changes, gastrointestinal upset
Third-Line			
Mexiletine	PO	200–300 mg tid	Arrhythmias
Other Agents			
EMLA cream	Apply cutaneously	qid	Local erythema
2.5% lidocaine			
2.5% prilocaine			
Capsaicin 0.025–0.075% cream	Apply cutaneously	qid	Painful burning skin

Source: Modified from AA Amato, J Russell: *Neuromuscular Disease*. New York, McGraw-Hill, 2008.

- Physical and occupational therapy is important. Proper care of denervated areas prevents skin ulceration, which can lead to poor wound healing, tissue resorption, arthropathy, and ultimately amputation.

Specific Polyneuropathies

AIDP or *GBS* is an ascending, usually demyelinating, motor > sensory polyneuropathy accompanied by areflexia, motor paralysis, and elevated CSF total protein without pleocytosis. Over two-thirds are preceded by an acute respiratory or gastrointestinal infection. Maximum weakness is usually reached within 2 weeks; demyelination by EMG. Most pts are hospitalized; one-third require ventilatory assistance. 85% make a complete or near-complete recovery with supportive care. Variants of GBS include Miller Fisher syndrome (ophthalmoparesis, facial diplegia, ataxia, areflexia; associated with serum antibodies to ganglioside GQ1b) and acute motor axonal neuropathy (more severe course than demyelinating GBS; antibodies to GM_1 in some cases).

- IVIg (2 g/kg divided over 5 days) or plasmapheresis (40–50 mL/kg daily for 4–5 days) significantly shortens the course.
- Glucocorticoids are ineffective.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a slowly progressive or relapsing polyneuropathy characterized by diffuse hyporeflexia or areflexia, diffuse weakness, elevated CSF protein without pleocytosis, and demyelination by EMG.

- Begin treatment when progression is rapid or walking is compromised.
- Initial treatment is usually IVIg; most pts require periodic retreatment at 4- to 6-week intervals.
- Other first-line treatment options include plasmapheresis or glucocorticoids.
- Immunosuppressants (azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab) used in refractory cases.

Diabetic neuropathy typically presents as a distal symmetric, sensorimotor, axonal polyneuropathy. A mixture of demyelination and axonal loss is frequent. Other variants include: isolated sixth or third cranial nerve palsies, asymmetric proximal motor neuropathy in the legs, truncal neuropathy, autonomic neuropathy, and an increased frequency of entrapment neuropathy (see below).

Mononeuropathy multiplex (MM) is defined as involvement of multiple individual peripheral nerves. When an inflammatory disorder is the cause, *mononeuritis multiplex* is the term used. Both systemic (67%) and nonsystemic (33%) vasculitis may present as MM. Immunosuppressive treatment of the underlying disease (usually with glucocorticoids and cyclophosphamide) is indicated. A tissue diagnosis of vasculitis should be obtained before initiating treatment; a positive biopsy helps to justify the necessary long-term treatment with immunosuppressive medications, and pathologic confirmation is difficult after treatment has commenced.

MONONEUROPATHY

Clinical Features

Mononeuropathies are usually caused by trauma, compression, or entrapment. Sensory and motor symptoms are in the distribution of a single nerve—most commonly the ulnar or median nerve in the arm or peroneal (fibular) nerve in the leg. Intrinsic factors making pts more susceptible to entrapment include arthritis, fluid retention (pregnancy), amyloid, hypothyroidism, tumors, and diabetes mellitus. Clinical features favoring conservative management of median neuropathy at the wrist (carpal tunnel syndrome) or ulnar neuropathy at the elbow include sudden onset, no motor deficit, few or no sensory findings (pain or paresthesias may be present), and no evidence of axonal loss by EMG. Surgical decompression is considered for chronic mononeuropathies that are unresponsive to conservative treatment if the site of entrapment is clearly defined. The most common mononeuropathies are summarized in **Table 193-3**.

TABLE 193-3 MONONEUROPATHIES

	Symptoms	Precipitating Activities	Examination	Electro-Diagnosis	Differential Diagnosis	Treatment
Carpal tunnel syndrome	Numbness, pain or paresthesias in fingers	Sleep or repetitive hand activity	Sensory loss in thumb, second, and third fingers Weakness in thenar muscles; inability to make a circle with thumb and index finger Tinel sign, Phalen maneuver	Slowing of sensory and motor conduction across carpal tunnel	C6 radiculopathy	Splint Surgery definitive treatment
Ulnar nerve entrapment (UNE) at the elbow	Numbness or paresthesias in ulnar aspect of hand	Elbow flexion during sleep; elbow resting on desk	Sensory loss in the little finger and ulnar half of ring finger Weakness of the interossei and thumb adductor; claw-hand	Focal slowing of nerve conduction velocity at the elbow	Thoracic outlet syndrome C8–T1 radiculopathy	Elbow pads Avoid further injury Surgery when conservative treatment fails
UNE at the wrist	Numbness or weakness in the ulnar distribution in the hand	Unusual hand activities with tools, bicycling	Like UNE but sensory examination spares dorsum of the hand, and selected hand muscles affected	Prolongation of distal motor latency in the hand	UNE	Avoid precipitating activities

(*Continued*)

TABLE 193-3 MONONEUROPATHIES (*CONTINUED*)

	Symptoms	Precipitating Activities	Examination	Electro-Diagnosis	Differential Diagnosis	Treatment
Radial neuropathy at the spiral groove	Wrist drop	Sleeping on arm after inebriation with alcohol—"Saturday night palsy"	Wrist drop with sparing of elbow extension (triceps sparing); finger and thumb extensors paralyzed; sensory loss in radial region of wrist	Early—conduction block along the spiral groove Late—denervation in radial muscles; reduced radial SNAP	Posterior cord lesion; deltoid also weak Posterior interosseous nerve (PIN); isolated finger drop C7 radiculopathy	Splint Spontaneous recovery provided no ongoing injury
Thoracic outlet syndrome	Numbness, paresthesias in medial arm, forearm, hand, and fingers	Lifting heavy objects with the hand	Sensory loss resembles ulnar nerve and motor loss resembles median nerve	Absent ulnar sensory response and reduced median motor response	UNE	Surgery if correctable lesion present
Femoral neuropathy	Buckling of knee, numbness or tingling in thigh/medial leg	Abdominal hysterectomy; lithotomy position; hematoma, diabetes	Wasting and weakness of quadriceps; absent knee jerk; sensory loss in medial thigh and lower leg	EMG of quadriceps, iliopsoas, paraspinal muscles, adductor muscles	L2–4 radiculopathy Lumbar plexopathy	Physiotherapy to strengthen quadriceps and mobilize hip joint Surgery if needed
Obturator neuropathy	Weakness of the leg, thigh numbness	Stretch during hip surgery; pelvic fracture; childbirth	Weakness of hip adductors; sensory loss in upper medial thigh	EMG—denervation limited to hip adductors sparing the quadriceps	L3–4 radiculopathy Lumbar plexopathy	Conservative management Surgery if needed

Meralgia paresthetica	Pain or numbness in the anterior lateral thigh	Standing or walking Recent weight gain	Sensory loss in the pocket of the pant distribution	Sometimes slowing of sensory response can be demonstrated across the inguinal ligament	L2 radiculopathy	Usually resolves spontaneously
Peroneal nerve entrapment at the fibular head	Footdrop	Usually an acute compressive episode identifiable; weight loss	Weak dorsiflexion, eversion of the foot Sensory loss in the anterolateral leg and dorsum of the foot	Focal slowing of nerve conduction across fibular head Denervation in tibialis anterior and peroneus longus muscles	L5 radiculopathy	Foot brace; remove external source of compression
Sciatic neuropathy	Flail foot and numbness in foot	Injection injury; fracture/dislocation of hip; prolonged pressure on hip (comatose pt)	Weakness of hamstring, plantar and dorsiflexion of foot; sensory loss in tibial and peroneal nerve distribution	NCS—abnormal sural, peroneal, and tibial amplitudes EMG—denervation in sciatic nerve distribution sparing glutei and paraspinal	L5–S1 radiculopathies Common peroneal neuropathy (partial sciatic nerve injury) LS plexopathies	Conservative follow up for partial sciatic nerve injuries Brace and physiotherapy Surgical exploration if needed
Tarsal tunnel syndrome	Pain and paresthesias in the sole of the foot but not in the heel	At the end of the day after standing or walking; nocturnal	Sensory loss in the sole of the foot Tinel sign at tarsal tunnel	Reduced amplitude in sensory or motor components of medial and planter nerves	Polyneuropathy, foot deformity, poor circulation	Surgery if no external cause identified

For a more detailed discussion, see Amato AA, Barohn RJ: Peripheral Neuropathy, Chap. 459, p. 2674; and Hauser SL, Amato AA: Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies, Chap. 460, p. 2694, in HPIM-19.

194 Myasthenia Gravis

An autoimmune neuromuscular disorder resulting in weakness and fatigability of skeletal muscles, usually due to autoantibodies directed against acetylcholine receptors (AChRs) at neuromuscular junctions (NMJs).

CLINICAL FEATURES

May present at any age. Symptoms fluctuate throughout the day and are provoked by exertion. Characteristic distribution: cranial muscles (eyelids, extraocular muscles, facial weakness, "nasal" or slurred speech, dysphagia); in 85%, limb muscles (often proximal and asymmetric) become involved. Reflexes and sensation normal. May be limited to extraocular muscles only. Complications: aspiration pneumonia (weak bulbar muscles), respiratory failure (weak chest wall muscles), exacerbation of myasthenia due to administration of drugs with neuromuscular junction blocking effects (quinolones, macrolides, aminoglycosides, procainamide, propranolol, nondepolarizing muscle relaxants).

PATHOPHYSIOLOGY

Anti-AChR antibodies reduce the number of available AChRs at the NMJ. Postsynaptic folds are flattened or "simplified," with resulting inefficient neuromuscular transmission. During repeated or sustained muscle contraction, decrease in amount of ACh released per nerve impulse ("presynaptic rundown," a normal occurrence), combined with disease-specific decrease in postsynaptic AChRs, results in pathologic fatigue. Thymus is abnormal in 75% of pts (65% hyperplasia, 10% thymoma). Other autoimmune diseases may coexist: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus.

DIFFERENTIAL DIAGNOSIS

Lambert-Eaton syndrome (autoantibodies to calcium channels in presynaptic motor nerve terminals): reduced ACh release; may be associated with malignancy

Neurasthenia: weakness/fatigue without underlying organic disorder

Drug-induced myasthenia: penicillamine may cause myasthenia gravis (MG); resolves weeks to months after discontinuing drug.

Botulism: toxin inhibits presynaptic ACh release; most common form is food-borne.

Diplopia from an intracranial mass lesion: compression of nerves to extraocular muscles or brainstem lesions affecting cranial nerve nuclei

Hyperthyroidism

Progressive external ophthalmoplegia: seen in rare mitochondrial disorders that can be detected with muscle biopsy

LABORATORY EVALUATION

- AChR antibodies: levels do not correlate with disease severity; 85% of all MG pts are positive; only 50% with pure ocular findings are positive; positive antibodies are diagnostic. Muscle-specific kinase (MuSK) antibodies present in 40% of AChR antibody–negative pts with generalized MG.
- Tensilon (edrophonium) test: a short-acting anticholinesterase—look for rapid and transient improvement of strength; false-positive (placebo response, motor neuron

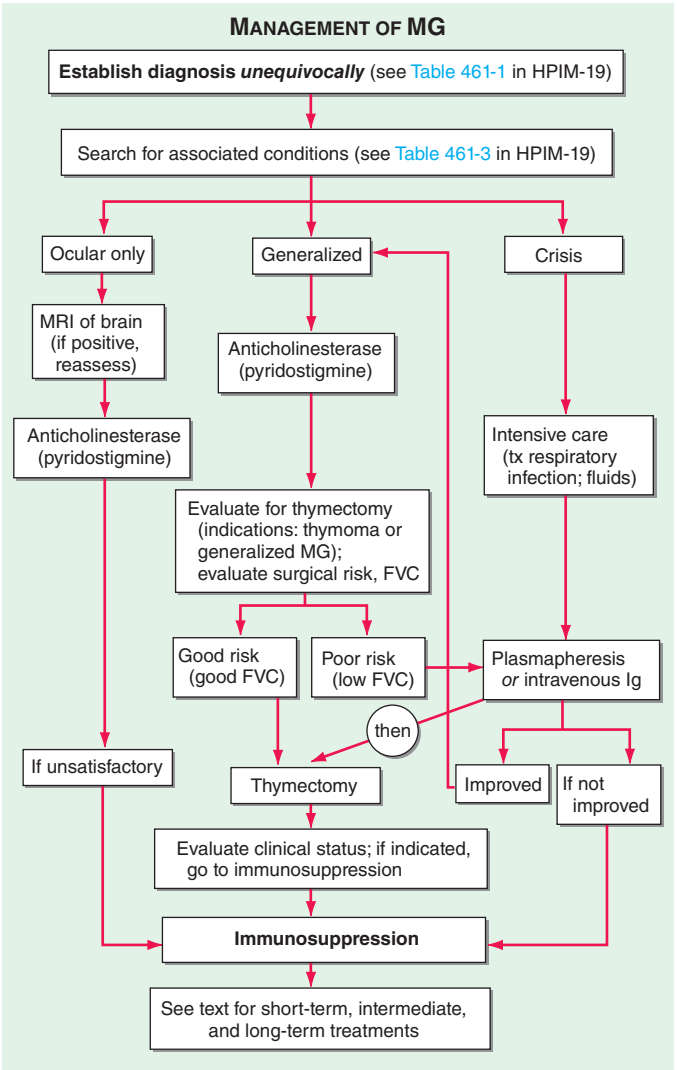


FIGURE 194-1 Algorithm for the management of myasthenia gravis. FVC, forced vital capacity.

disease) and false-negative tests occur. Atropine IV should be on hand if symptoms such as bradycardia occur.
- EMG: low-frequency (2–4 Hz) repetitive stimulation produces rapid decrement in amplitude (>10–15%) of evoked motor responses.
- Chest CT/MRI: search for thymoma.
- Consider thyroid and other studies (e.g., ANA) for associated autoimmune disease.
- Measurements of baseline respiratory function are useful.

TREATMENT MYASTHENIA GRAVIS (SEE FIG. 194-1)

- The anticholinesterase drug pyridostigmine (Mestinon) titrated to assist pt with functional activities (chewing, swallowing, strength during exertion); usual initial dose of 30–60 mg 3–4 times daily; long-acting tablets help at night, but have variable absorption so are not reliable during the day. Muscarinic side effects (diarrhea, abdominal cramps, salivation, nausea) blocked with atropine/diphenoxylate or loperamide if required.

TABLE 194-1 DRUGS WITH INTERACTIONS IN MYASTHENIA GRAVIS (MG)

Drugs That May Exacerbate MG
Antibiotics
Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin
Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin
Macrolides: e.g., erythromycin, azithromycin
Nondepolarizing muscle relaxants for surgery
D-Tubocurarine (curare), pancuronium, vecuronium, atracurium
Beta-blocking agents
Propranolol, atenolol, metoprolol
Local anesthetics and related agents
Procaine, Xylocaine in large amounts
Procainamide (for arrhythmias)
Botulinum toxin
Botox exacerbates weakness
Quinine derivatives
Quinine, quinidine, chloroquine, mefloquine (Lariam)
Magnesium
Decreases acetylcholine release
Penicillamine
May cause MG
Drugs with Important Interactions in MG
Cyclosporine
Broad range of drug interactions, which may raise or lower cyclosporine levels.
Azathioprine
Avoid allopurinol—combination may result in myelosuppression.

- Plasmapheresis or IV immune globulin (IVIg; 400 mg/kg per day for 5 days) provides temporary boost for seriously ill pts; used to improve condition prior to surgery or during myasthenic crisis (see below).
- Thymectomy improves likelihood of long-term remission in adult pts (~85% improve; of these, ~35% achieve drug-free remission); benefit is usually delayed by months to years; unclear if there is benefit in pts with pure ocular disease, children, or those age >55.
- Glucocorticoids are a mainstay of chronic immunosuppressive treatment; begin prednisone at low dose (15–25 mg/d), increase by 5 mg/d every 2–3 days until marked clinical improvement or dose of 50–60 mg/d is reached. Maintain high dose for 1–3 months, then decrease to alternate-day regimen. Immunosuppressive drugs (mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab, and occasionally cyclophosphamide) may spare dose of prednisone required long-term to control symptoms.
- Myasthenic crisis is defined as an exacerbation of weakness, usually with respiratory failure, sufficient to endanger life; expert management in an intensive care setting essential as is prompt treatment with IVIg or plasmapheresis to hasten recovery.
- A number of drugs may exacerbate MG, potentially leading to crisis, and therefore should be avoided (**Table 194-1**).

For a more detailed discussion, see Drachman DB, Amato AA: Myasthenia Gravis and Other Diseases of the Neuromuscular Junction, Chap. 461, p. 2701, in HPIM-19.

195 Muscle Diseases

APPROACH TO THE PATIENT: Muscle Disease

Muscle diseases (*myopathies*) may be intermittent or persistent and usually present with proximal, symmetric weakness with preserved reflexes and sensation. An associated sensory loss suggests injury to peripheral nerve or the central nervous system rather than myopathy; on occasion, disorders affecting the anterior horn cells, the neuromuscular junction, or peripheral nerves can mimic myopathy. Any disorder causing muscle weakness may be accompanied by *fatigue*, referring to an inability to maintain or sustain a force; this must be distinguished from *asthenia*, a type of fatigue caused by excess tiredness or lack of energy. Fatigue without abnormal clinical or laboratory findings almost never indicates a true myopathy.

Muscle disorders are usually painless; however, *myalgias*, or muscle pains, may occur. Myalgias must be distinguished from *muscle cramps*, i.e., painful, involuntary muscle contractions, usually due to neurogenic disorders. A *muscle*

contracture due to an inability to relax after an active muscle contraction is associated with energy failure in glycolytic disorders. *Myotonia* is a condition of prolonged muscle contraction followed by slow muscle relaxation.

CK is the preferred muscle enzyme to measure in the evaluation of suspected myopathies. Electrodiagnostic studies (nerve conduction studies and electromyography, NCS/EMG) are usually necessary to distinguish myopathies from neuropathies and neuromuscular junction disorders. An approach to muscle weakness is presented in **Figs. 195-1** and **195-2**.

MUSCULAR DYSTROPHIES

A varied group of inherited, progressive degenerations of muscle, each with unique phenotypic and genetic features.

DUCHENNE'S MUSCULAR DYSTROPHY

X-linked recessive mutation of the dystrophin gene that affects males almost exclusively. Progressive weakness in hip and shoulder girdle muscles beginning by age 5; by age 12, the majority were nonambulatory in the era prior to the use of glucocorticoids. Survival beyond age 25 is rare. Associated problems include tendon and muscle contractures, progressive kyphoscoliosis, impaired pulmonary function, cardiomyopathy, and intellectual impairment. Palpable enlargement and firmness of some muscles. Becker dystrophy is a less severe form, with a slower course and later age of onset (5–15 years) but similar clinical, laboratory, and genetic features.

Laboratory findings include massive elevations (20–100 × normal) of serum CK, a myopathic pattern on EMG testing, and evidence of groups of necrotic muscle fibers with regeneration, phagocytosis, and fatty replacement of muscle on biopsy. Diagnosis is established by determination of dystrophin deficiency in muscle tissue or mutation analysis in peripheral blood. Testing is available for detecting carriers and prenatal diagnosis. Dystrophin is part of a large complex of muscle membrane glycoproteins, disruption of which weakens the cell membrane.

TREATMENT DUCHENNE'S MUSCULAR DYSTROPHY

- Glucocorticoids [prednisone (0.75 mg/kg)/d] slow progression of disease for up to 3 years; some pts cannot tolerate this therapy due to weight gain and increased risk of fractures.

LIMB-GIRDLE DYSTROPHY

A constellation of diseases with proximal weakness involving the pelvic and shoulder girdle musculature. Age of onset, rate of progression, severity of manifestations, inheritance pattern (autosomal dominant or autosomal recessive), and associated complications (e.g., cardiac, respiratory) vary with the specific subtype of disease.

MYOTONIC DYSTROPHY

Type 1 is an autosomal dominant disorder with genetic anticipation. Weakness typically becomes obvious in the second to third decade and initially involves the muscles of the face, neck, and distal extremities. This results in a distinctive facial appearance ("hatchet-faced") with ptosis, temporal wasting, drooping of the lower lip, and sagging of the jaw. Myotonia manifests as an inability to relax muscles rapidly following a strong exertion (e.g., after tight hand grip) usually by the age of 5, and by sustained contraction of muscles following percussion (e.g., of tongue or thenar eminence).

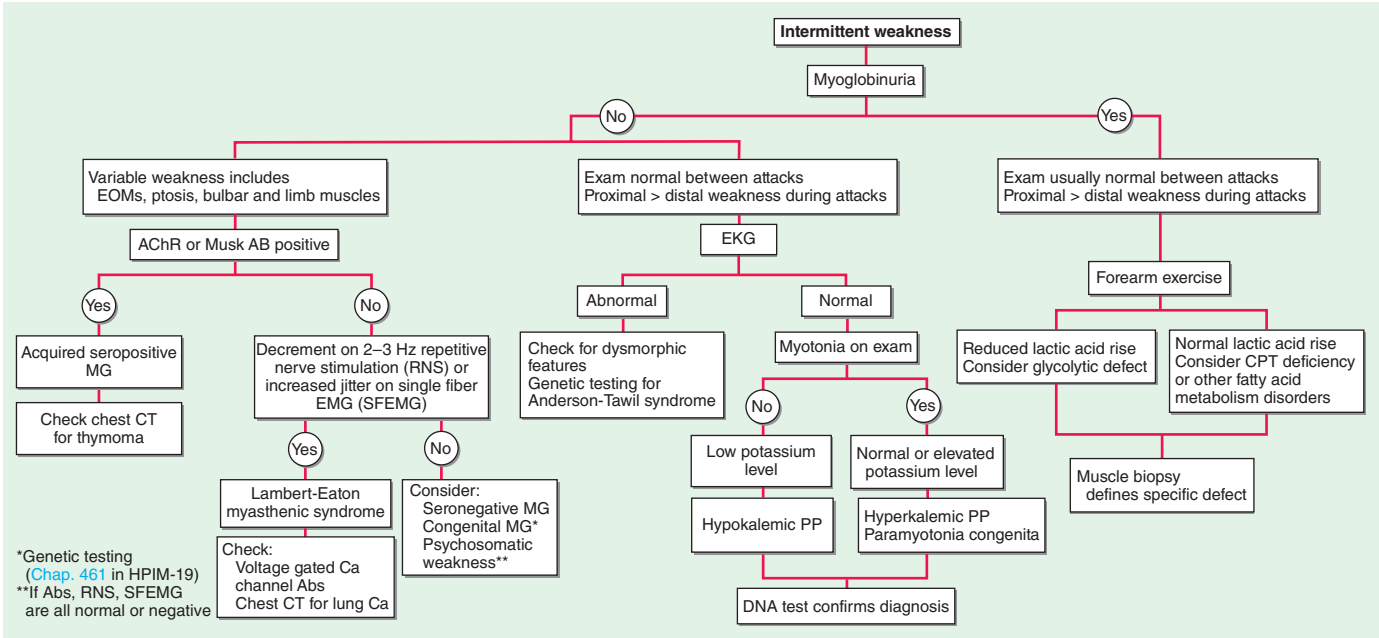


FIGURE 195-1 Diagnostic evaluation of intermittent weakness. AChR AB, acetylcholine receptor antibody; CPT, carnitine palmitoyltransferase; EOMs, extraocular muscles; MG, myasthenia gravis; PP, periodic paralysis.

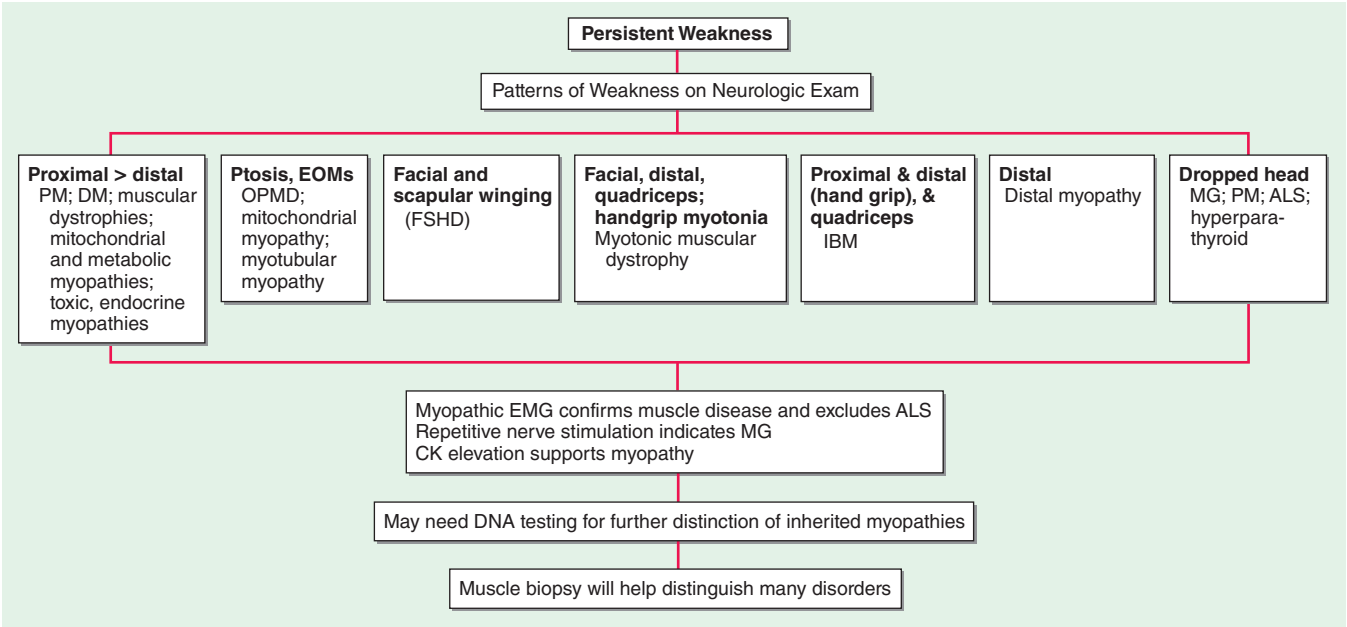


FIGURE 195-2 Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern or weakness in combination with the laboratory evaluation leads to a diagnosis. CK, creatinine kinase; DM, dermatomyositis; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PM, polymyositis.

Associated findings can include frontal baldness, posterior subcapsular cataracts, gonadal atrophy, respiratory and cardiac problems, endocrine abnormalities, intellectual impairment, and hypersomnia. Cardiac disturbances, including complete heart block, may be life-threatening. Respiratory function should be carefully followed, as chronic hypoxia may lead to cor pulmonale.

Laboratory studies show normal or mildly elevated CK, characteristic myotonia and myopathic features on EMG, and a typical pattern of muscle fiber injury on biopsy, including selective type 1 fiber atrophy in 50% of cases. Myotonic dystrophy type 1 is caused by an unstable expansion of a CTG trinucleotide repeat in a protein kinase gene (named *DMPK*) on chromosome 19q13.3. Genetic testing for early detection and prenatal diagnosis is possible.

TREATMENT MYOTONIC DYSTROPHY

- Phenytoin or mexiletine may help alleviate myotonia, although pts are rarely bothered by this symptom.
- Pacemaker insertion may be required for syncope or heart block.
- Orthoses may control foot drop, stabilize the ankle, and decrease falls.
- Excessive daytime somnolence with or without sleep apnea is not uncommon; sleep studies, noninvasive respiratory support (BiPAP), and treatment with modafinil may be beneficial.

FACIOSCAPULOHUMERAL (FSH) DYSTROPHY

An autosomal dominant, slowly progressive disorder with onset in childhood or young adulthood. Weakness involves facial (usually the initial manifestation), shoulder girdle, and proximal arm muscles and can result in atrophy of biceps, triceps, and scapular winging. Facial weakness results in inability to smile, whistle, or fully close the eyes. Foot drop and leg weakness may cause falls and progressive difficulty with ambulation.

Laboratory studies reveal normal or slightly elevated CK and usually myopathic features on EMG and muscle biopsy. Type 1 FSD is caused by deletions at chromosome 4q35 leading to toic expression of the *DUX4* gene. Genetic testing is available for carrier detection and prenatal diagnosis.

TREATMENT FACIOSCAPULOHUMERAL DYSTROPHY

- Ankle-foot orthoses are helpful for foot drop.
- Scapular stabilization procedures may help scapular winging but may not improve function.

OCULOPHARYNGEAL DYSTROPHY

Onset in the fourth to sixth decade of ptosis, limitation of extraocular movements, and facial and cricopharyngeal weakness. One of several disorders characterized by progressive external ophthalmoplegia. Dysphagia may be life-threatening. Most pts are of French-Canadian or Spanish-American descent. Mutation in a poly-RNA binding protein responsible.

INFLAMMATORY MYOPATHIES

The most common group of acquired and potentially treatable skeletal muscle disorders. Three major forms: dermatomyositis (DM), inclusion body myositis (IBM), and polymyositis (PM). Usually present as progressive and symmetric muscle weakness; extraocular muscles spared but pharyngeal weakness (dysphagia) and head

drop from neck muscle weakness are common. Respiratory muscles may be affected in advanced cases. IBM is characterized by early involvement of quadriceps (leading to falls) and distal muscles; IBM may have an asymmetric pattern. Progression is over weeks or months in PM and DM, but typically over years in IBM. Skin involvement in DM may consist of a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, or erythema over knuckles (*Gottron's sign*). A variety of cancers are associated with DM. Features of each disorder are summarized in Table 195-1.

TABLE 195-1 FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES

Characteristic	Polymyositis	Dermatomyositis	Inclusion Body Myositis
Age at onset	>18 years	Adulthood and childhood	>50 years
Familial association	No	No	Yes, in some rare cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-1 (human T cell lymphotropic virus type 1).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), statins (necrotizing, toxic, or autoimmune myositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

TREATMENT **INFLAMMATORY MYOPATHIES**

Often effective for PM and DM but not for IBM.

- Step 1: Glucocorticoids (prednisone, 1 mg/kg per day for 3–4 weeks, then tapered very gradually)
- Step 2: Approximately 75% of pts require additional therapy with other immunosuppressive drugs. Azathioprine (up to 3 mg/kg per day), methotrexate (7.5 mg/week gradually increasing to 25 mg/week), or mycophenolate mofetil (up to 2.5–3 g/day in 2 divided doses) commonly used.
- Step 3: IV immunoglobulin (2 g/kg divided over 2–5 days)
- Step 4: A trial of one of the following agents: rituximab, cyclosporine, cyclophosphamide, or tacrolimus.

DISORDERS OF MUSCLE ENERGY METABOLISM

The two principal sources of energy for skeletal muscle are fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy. Diagnosis usually requires biochemical-enzymatic studies of biopsied muscle.

Progressive muscle weakness usually beginning in the third or fourth decade can be due to the adult form of *acid maltase deficiency (Pompe's disease)*. Respiratory failure is often the initial manifestation; treatment with enzyme replacement may be of benefit. Progressive weakness beginning after puberty occurs with *debranching enzyme deficiency*. Glycolytic defects, including *myophosphorylase deficiency* (McArdle's disease) or *phosphofructokinase deficiency*, present as exercise intolerance with myalgias. Disorders of fatty acid metabolism present with a similar picture. In adults, the most common cause is *carnitine palmitoyltransferase deficiency*. Exercise-induced cramps and myoglobinuria are common; strength is normal between attacks. Dietary approaches (frequent meals and a low-fat high-carbohydrate diet, or a diet rich in medium-chain triglycerides) are of uncertain value.

MITOCHONDRIAL MYOPATHIES

More accurately referred to as *mitochondrial cytopathies* because multiple tissues are usually affected, these disorders result from defects in mitochondrial DNA. Clinical presentations vary greatly: muscle symptoms may include weakness, ophthalmoparesis, pain or stiffness, or they may even be absent; age of onset ranges from infancy to adulthood; associated clinical presentations include ataxia, encephalopathy, seizures, stroke-like episodes, and recurrent vomiting. Three groups: chronic progressive external ophthalmoplegia (CPEO); skeletal muscle–central nervous system syndromes; and pure myopathy syndromes simulating muscular dystrophy. The characteristic finding on muscle biopsy is "ragged red fibers," which are muscle fibers with accumulations of abnormal mitochondria. Affected families often have a maternal pattern of inheritance because mitochondrial genes are inherited almost exclusively from the oocyte.

PERIODIC PARALYSES

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. Onset is usually in childhood or adolescence. Episodes typically occur after rest or sleep, often following earlier exercise. May be due to genetic disorders of calcium (hypokalemic periodic paralysis [hypoKPP]), sodium (hyperkalemic periodic paralysis), chloride, or potassium channels.

- Attacks of hypoKPP are treated with potassium chloride (usually oral). Prophylaxis with acetazolamide (125–1000 mg/d in divided doses) is usually effective in hypoKPP type 1.
- Attacks of thyrotoxic periodic paralysis (usually in Asian men) resemble those of hypoKPP; attacks abate with treatment of the underlying thyroid condition.

ENDOCRINE AND METABOLIC MYOPATHIES

Abnormalities of thyroid function can cause a wide array of muscle disorders. Hypothyroidism is associated with muscle cramps, pain, and stiffness, and proximal muscle weakness occurs in one-third of pts; the relaxation phase of muscle stretch reflexes is prolonged, and serum CK is often elevated (up to 10 times normal).

TABLE 195-2 DRUG-INDUCED MYOPATHIES

Drugs	Major Toxic Reaction
Lipid-lowering agents Fibric acid derivatives HMG-CoA reductase inhibitors Niacin (nicotinic acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Nondepolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers
Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine	All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune toxic myopathy D-Penicillamine	Use of this drug may cause polymyositis and myasthenia gravis.
Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs Colchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows autophagic vacuoles.

Hyperthyroidism can produce proximal muscle weakness and atrophy; bulbar, respiratory, and even esophageal muscles are occasionally involved, causing dysphagia, dysphonia, and aspiration. Other neuromuscular disorders associated with hyperthyroidism include hypoKPP, myasthenia gravis, and a progressive ocular myopathy associated with proptosis (*Graves' ophthalmopathy*).

Parathyroid, adrenal, and pituitary disorders, as well as diabetes mellitus, can also produce myopathy. Deficiencies of vitamins D and E are additional causes of muscle weakness.

DRUG-INDUCED MYOPATHIES

Drugs (including glucocorticoids and lipid-lowering agents) and toxins (e.g., alcohol) are associated with myopathies (**Table 195-2**). In most cases, weakness is symmetric and involves proximal limb girdle muscles; myalgia and cramps may also occur. An elevated CK is often found. Diagnosis often depends on resolution of signs and symptoms with removal of offending agent.



For a more detailed discussion, see Amato AA, Brown RH Jr.: Muscular Dystrophies and Other Muscle Diseases, Chap. 462e; Dalakas MC: Polymyositis, Dermatomyositis, and Inclusion Body Myositis, Chap. 388, p. 2194, in HPIM-19.

This page intentionally left blank

196 Psychiatric Disorders

Mental disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is ~30%, but only one-third of those individuals are currently receiving treatment.

Disorders of mood, thinking, and behavior may be due to a primary psychiatric diagnosis or a personality disorder or may be secondary to metabolic abnormalities, drug toxicities, focal cerebral lesions, seizure disorders, or degenerative neurologic disease. Any pt presenting with new onset of psychiatric symptoms must be evaluated for underlying psychoactive substance abuse and/or medical or neurologic illness. Psychiatric medications are discussed in Chap. 197.

MAJOR PSYCHIATRIC DISORDERS (AXIS I DIAGNOSES)

MOOD DISORDERS (MAJOR AFFECTIVE DISORDERS)

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect; subdivided into (1) depressive disorders, (2) bipolar disorders (depression plus manic or hypomanic episodes), and (3) depression in association with medical illness or alcohol and substance abuse (see Chaps. 199 and 200).

Major Depression

Clinical Features Affects 15% of the general population at some point in life; 6–8% of all outpatients in primary care settings satisfy diagnostic criteria. Diagnosis is made when five (or more) of the following symptoms have been present for 2 weeks (at least one of the symptoms must be #1 or #2 below):

1. Depressed mood
2. Loss of interest or pleasure
3. Change in appetite or weight
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt
8. Decreased ability to concentrate and make decisions
9. Recurrent thoughts of death or suicide

A small number of pts with major depression will have psychotic symptoms (hallucinations and delusions) with their depressed mood. Negative life events can precipitate depression, but genetic factors influence the sensitivity to these events.

Onset of a first depressive episode is typically in early adulthood, although major depression can occur at any age. Untreated episodes generally resolve spontaneously in a few months to a year; however, a sizable number of pts suffer from chronic, unremitting depression, or from a partial treatment response. Half of all pts experiencing a first depressive episode will go on to a recurrent course. Untreated or partially treated episodes put the pt at risk for future problems with mood disorders. Within an individual, the nature of episodes may be similar over time. A family history of mood disorder is common and tends to predict a recurrent course. Major depression can also be the initial presentation of bipolar disorder (manic depressive illness).

Suicide Approximately 4–5% of all depressed pts will commit suicide, and most will have sought help from a physician within 1 month of their death. Physicians must always inquire about suicide when evaluating a pt with depression.

Depression with Medical Illness Virtually every class of medication can potentially induce or worsen depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Among the antihypertensive agents, β-adrenergic blockers and, to a lesser extent, calcium channel blockers are most likely to cause depressed mood. Iatrogenic depression should also be considered in pts receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants.

Between 20–30% of cardiac pts manifest a depressive disorder. Tricyclic antidepressants (TCAs) are contraindicated in pts with bundle branch block, and TCA-induced tachycardia is an additional concern in pts with congestive heart failure. Selective serotonin reuptake inhibitors (SSRIs) appear not to induce ECG changes or adverse cardiac events, and thus, are reasonable first-line drugs for pts at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In *cancer*, the prevalence of depression is 25%, but it occurs in 40–50% of pts with cancers of the pancreas or oropharynx. Extreme cachexia from cancer may be misinterpreted as depression. Antidepressant medications in cancer pts improve quality of life as well as mood.

Diabetes mellitus is another consideration; the severity of the mood state correlates with the level of hyperglycemia and the presence of diabetic complications. Monoamine oxidase inhibitors (MAOIs) can induce hypoglycemia and weight gain. TCAs can produce hyperglycemia and carbohydrate craving. SSRIs, like MAOIs, may reduce fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Depression may also occur with *hypothyroidism* or *hyperthyroidism*, in *neurologic disorders*, in *HIV*-positive individuals, and in *chronic hepatitis C infection* (depression worsens with interferon treatment). Some chronic disorders of uncertain etiology, such as *chronic fatigue syndrome* and *fibromyalgia*, are strongly associated with depression.

TREATMENT MAJOR DEPRESSION

- Pts with suicidal ideation require treatment by a psychiatrist and may require hospitalization.
- Most other pts with an uncomplicated unipolar major depression (a major depression that is not part of a cyclical mood disorder, such as a bipolar disorder) can be successfully treated by a nonpsychiatric physician.
- Vigorous intervention and successful treatment appear to decrease the risk of future relapse.
- Pts who do not respond fully to standard treatment should be referred to a psychiatrist.
- Antidepressant medications are the mainstay of treatment, although combined treatment with psychotherapy improves outcome. Symptoms are ameliorated after 6–8 weeks at a therapeutic dose in 60–70% of pts.
- A guideline for the medical management of depression is shown in **Fig. 196-1**.
- Once remission is achieved, antidepressants should be continued for 6–9 months. Pts must be monitored carefully after termination of treatment since relapse is common.
- Pts with two or more episodes of depression should be considered for indefinite maintenance treatment.

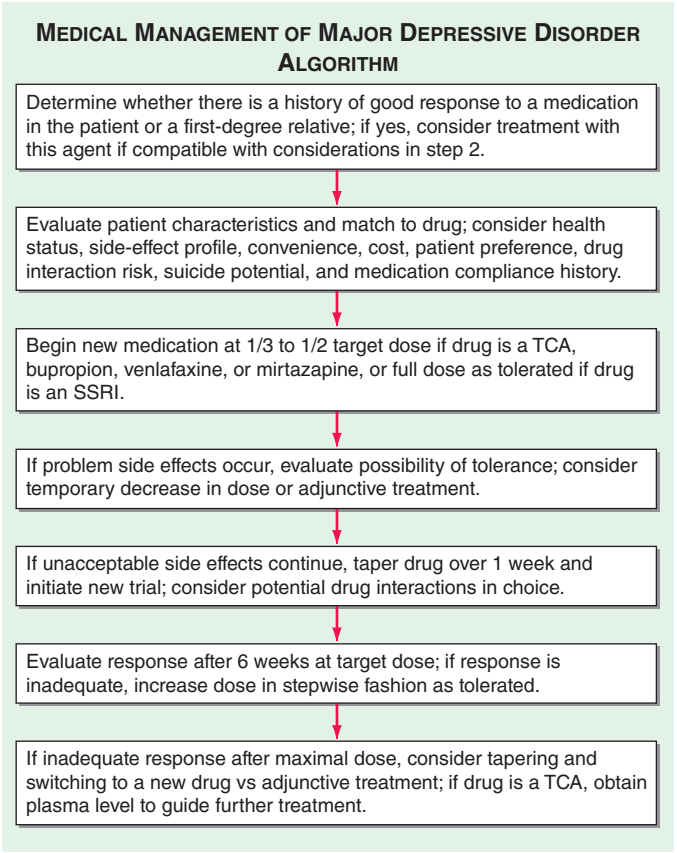


FIGURE 196-1 A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

- Electroconvulsive therapy is generally reserved for treatment-resistant depression unresponsive to medication or for pts in whom the use of antidepressants is medically contraindicated.
- Transcranial magnetic stimulation (TMS) is approved for treatment-resistant depression.
- Vagus nerve stimulation (VNS) has been approved for treatment-resistant depression as well, but its degree of efficacy is controversial.

Bipolar Disorder (Manic Depressive Illness)

Clinical Features A cyclical mood disorder in which episodes of major depression are interspersed with episodes of mania or hypomania; 1.5% of the population is affected. Most pts initially present with a manic episode in adolescence or young adulthood. Antidepressant therapy may provoke a manic episode; pts with a major depressive episode and a prior history of "highs" (mania or hypomania—which

can be pleasant/euphoric or irritable/impulsive) and/or a family history of bipolar disorder should not be treated with antidepressants, but instead referred promptly to a psychiatrist.

With mania, an elevated, expansive mood, irritability, angry outbursts, and impulsivity are characteristic. Specific symptoms include (1) unusual talkativeness, (2) flight of ideas and racing thoughts, (3) inflated self-esteem that can become delusional, (4) decreased need for sleep (often the first feature of an incipient manic episode), (5) increase in goal-directed activity or psychomotor agitation, (6) distractibility, and (7) excessive involvement in risky activities (buying sprees, sexual indiscretions). Pts with full-blown mania can become psychotic. Hypomania is characterized by attenuated manic symptoms and is greatly underdiagnosed, as are "mixed episodes," where both depressive and manic or hypomanic symptoms coexist simultaneously.

Untreated, a manic or depressive episode typically lasts for several weeks but can last for 8–12 months. Variants of bipolar disorder include rapid and ultrarapid cycling (manic and depressed episodes occurring at cycles of weeks, days, or hours). In many pts, especially females, antidepressants trigger rapid cycling and worsen the course of illness. Bipolar disorder has a strong genetic component; the concordance rate for monozygotic twins approaches 80%.

TREATMENT BIPOLAR DISORDER

- Bipolar disorder is a serious, chronic illness that requires lifelong monitoring by a psychiatrist.
- Acutely manic pts often require hospitalization to reduce environmental stimulation and to protect themselves and others from the consequences of their reckless behavior.
- The recurrent nature of bipolar disorder necessitates maintenance treatment.
- Mood stabilizers (lithium, valproic acid, second-generation antipsychotic drugs, carbamazepine) are effective for the resolution of acute episodes and for prophylaxis of future episodes.

SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

Schizophrenia

Clinical Features Characterized by perturbations of language, perception, thinking, social activity, affect, and volition. Occurs in 0.85% of the population worldwide; lifetime prevalence is ~1–1.5%. Pts usually present in late adolescence, often after an insidious premorbid course of subtle psychosocial difficulties. Core psychotic features last ≥6 months and include positive symptoms (such as conceptual disorganization, delusions, or hallucinations) and negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement). Negative symptoms predominate in one-third and are associated with a poor long-term outcome and poor response to treatment.

Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic pts commit suicide. Comorbid substance abuse is common.

TREATMENT SCHIZOPHRENIA

- Hospitalization is required for acutely psychotic pts who may be dangerous to themselves or others.
- Conventional antipsychotic medications are effective against hallucinations, delusions, and thought disorder.

- The novel antipsychotic medications—risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, and clozapine—are helpful in pts unresponsive to conventional neuroleptics and may also be more useful for negative and cognitive symptoms.
- Drug treatment by itself is insufficient, and educational efforts directed toward families and relevant community resources are necessary to maintain stability and optimize outcomes.

ANXIETY DISORDERS

Characterized by severe, persistent anxiety or sense of dread or foreboding. Most prevalent group of psychiatric illnesses seen in the community; present in 15–20% of medical clinic pts.

Panic Disorder

Occurs in 2–3% of the population; familial aggregation may occur. Onset in late adolescence or early adulthood. Initial presentation is almost always to a nonpsychiatric physician, frequently in the ER, as a possible heart attack or serious respiratory problem. The disorder is often initially unrecognized or misdiagnosed. Three-quarters of pts with panic disorder will also satisfy criteria for major depression at some point.

Clinical Features Characterized by panic attacks, which are sudden, unexpected, overwhelming paroxysms of terror and apprehension with multiple associated somatic symptoms. Attacks usually reach a peak within 10 min, then slowly resolve spontaneously, occurring in an unexpected fashion. Diagnostic criteria for panic disorder include recurrent panic attacks and at least 1 month of concern or worry about the attacks or a change in behavior related to them. Panic attacks are accompanied by palpitations, sweating, trembling, dyspnea, chest pain, dizziness, and a fear of impending doom or death.

When the disorder goes unrecognized and untreated, pts often experience significant morbidity: they become afraid of leaving home and may develop anticipatory anxiety, agoraphobia, and other spreading phobias; many turn to self-medication with alcohol or benzodiazepines.

Panic disorder must be differentiated from cardiovascular and respiratory disorders. Other conditions that may mimic or worsen panic attacks include hyperthyroidism, pheochromocytoma, hypoglycemia, drug ingestions (amphetamines, cocaine, caffeine, sympathomimetic nasal decongestants), and drug withdrawal (alcohol, barbiturates, opiates, minor tranquilizers).

TREATMENT PANIC DISORDER

- The cornerstone of drug therapy is antidepressant medication.
- SSRIs benefit the majority of pts and do not have the adverse effects of the TCAs.
- Benzodiazepines may be used in the short term while waiting for antidepressants to take effect.
- Early psychotherapeutic intervention and education aimed at symptom control enhances the effectiveness of drug treatment.
- Psychotherapy (identifying and aborting panic attacks through relaxation and breathing techniques) can be effective.

Generalized Anxiety Disorder (GAD)

Characterized by persistent, chronic anxiety; occurs in 5–6% of the population.

Clinical Features Pts experience persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling "on edge" or restless, and insomnia. Pts worry excessively over minor matters, with life-disrupting effects; unlike panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare. Secondary depression is common, as is social phobia and comorbid substance abuse.

TREATMENT GENERALIZED ANXIETY DISORDER

- A combination of pharmacologic and psychotherapeutic interventions is most effective; complete symptom relief is rare.
- Benzodiazepines are the initial agents of choice when generalized anxiety is severe and acute enough to warrant drug therapy; physicians must be alert to psychological and physical dependence on benzodiazepines.
- A subgroup of pts respond to buspirone, a nonbenzodiazepine anxiolytic.
- Some SSRIs also are effective at doses comparable to their efficacy in major depression.
- Anticonvulsants with GABAergic properties (gabapentin, oxcarbazepine, tiagabine, pregabalin, divalproex) may also be effective against anxiety.

Obsessive-Compulsive Disorder (OCD)

A severe disorder present in 2–3% of the population and characterized by recurrent obsessions (persistent intrusive thoughts) and compulsions (repetitive behaviors) that impair everyday functioning. Pts are often ashamed of their symptoms; physicians must ask specific questions to screen for this disorder including asking about recurrent thoughts and behaviors.

Clinical Features Common obsessive thoughts and compulsive behaviors include fears of germs or contamination, handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked.

Onset is usually in early adulthood (childhood onset is not rare); more common in males and first-born children. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. The course of OCD is usually episodic with periods of incomplete remission; some cases may show a steady deterioration in psychosocial functioning.

TREATMENT OBSESSIVE-COMPULSIVE DISORDER

- Clomipramine and the SSRIs (fluoxetine, fluvoxamine, sertraline) are effective, but only 50–60% of pts show adequate improvement with pharmacotherapy alone.
- A combination of drug therapy and cognitive-behavioral psychotherapy is most effective for the majority of pts.

Posttraumatic Stress Disorder (PTSD)

Occurs in some individuals exposed to a severe life-threatening trauma. If the reaction occurs shortly after the event, it is termed *acute stress disorder*, but if the reaction is delayed and subject to recurrence, PTSD is diagnosed. Predisposing factors include a past psychiatric history and personality characteristics of extroversion and high neuroticism.

Clinical Features Individuals experience associated symptoms of detachment and loss of emotional responsivity. The pt may feel depersonalized and unable to recall specific events of the trauma, although it is reexperienced through intrusions in thought, dreams, or flashbacks. Comorbid substance abuse and other mood and anxiety disorders are common. This disorder is extremely debilitating; most pts require referral to a psychiatrist for ongoing care.

TREATMENT **POSTTRAUMATIC STRESS DISORDER**

- SSRIs, venlafaxine, and topiramate all are somewhat effective.
- Propranolol and opiates such as morphine given during the acute stress period may prevent the development of PTSD.
- Adjunctive naltrexone can be effective when comorbid alcoholism is present.
- Trazodone is frequently used at night to help with insomnia.
- Psychotherapeutic strategies help the pt overcome avoidance behaviors and master fear of recurrence of the trauma.

Phobic Disorders

Clinical Features Recurring, irrational fears of specific objects, activities, or situations, with subsequent avoidance behavior of the phobic stimulus. Diagnosis is made only when the avoidance behavior interferes with social or occupational functioning. Affects ~10% of the population. Common phobias include fear of closed places, (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others (e.g., having to converse at a party, use of public restrooms, meeting strangers).

TREATMENT **PHOBIC DISORDERS**

- Agoraphobia is treated as for panic disorder.
- Beta blockers (e.g., propranolol, 20–40 mg PO 2 h before the event) are particularly effective in the treatment of "performance anxiety."
- SSRIs and MAOIs are very helpful in treating social phobias. Social and simple phobias respond well to behaviorally focused psychotherapy.

Somatic Symptom Disorder

Clinical Features Pts with multiple somatic complaints that cannot be explained by a known medical condition or by the effects of substances; seen commonly in primary care practice (prevalence of 5–7%). Pts may present with multiple physical complaints referable to different organ systems; pts with somatic symptom disorder can be impulsive and demanding. In *conversion disorder*, the symptoms involve voluntary motor or sensory function In *factitious illnesses*, the pt consciously and voluntarily produces physical symptoms; the sick role is gratifying. *Munchausen's syndrome* refers to individuals with dramatic, chronic, or severe factitious illness. A variety of signs, symptoms, and diseases have been simulated in factitious illnesses; most common are chronic diarrhea, fever of unknown origin, intestinal bleeding, hematuria, seizures, hypoglycemia. In *malingering*, the fabrication of illness derives from a desire for an external reward (narcotics, disability).

TREATMENT **SOMATIC SYMPTOM DISORDER**

- Pts with somatic symptom disorder are usually subjected to multiple diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. This approach is doomed to failure.
- Successful treatment is achieved through behavior modification, in which access to the physician is adjusted to provide a consistent, sustained, and predictable level of support that is not contingent on the pt's level of presenting symptoms or distress.
- Visits are brief, supportive, and structured and are not associated with a need for diagnostic or treatment action.
- Pts may benefit from antidepressant treatment.
- Consultation with a psychiatrist is essential.

PERSONALITY DISORDERS

Characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. Individuals with personality disorders are often regarded as "difficult pts."

Three major categories of personality disorders; pts usually present with a combination of features.

CLUSTER A PERSONALITY DISORDERS

Includes individuals who are odd and eccentric and who maintain an emotional distance from others. The *paranoid* personality has pervasive mistrust and suspiciousness of others. The *schizoid* personality is interpersonally isolated, cold, and indifferent, while the *schizotypal* personality is eccentric and superstitious, with magical thinking and unusual perceptual experiences.

CLUSTER B PERSONALITY DISORDERS

Describe individuals whose behavior is impulsive, excessively emotional, and erratic. The *borderline* personality is impulsive and manipulative, with unpredictable and fluctuating intense moods and unstable relationships, a fear of abandonment, and occasional rage episodes. The *histrionic* pt is dramatic, engaging, seductive, and attention seeking. The *narcissistic* pt is self-centered and has an inflated sense of self-importance combined with a tendency to devalue or de-mean others, while pts with *antisocial* personality disorder use other people to achieve their own ends and engage in exploitative and manipulative behavior with no sense of remorse.

CLUSTER C PERSONALITY DISORDERS

Enduring traits are anxiety and fear. The *dependent* pt fears separation, tries to engage others to assume responsibility, and often has a help-rejecting style. Pts with obsessive-*compulsive* personality disorder are meticulous and perfectionistic but also inflexible and indecisive. *Avoidant* pts are anxious about social contact and have difficulty assuming responsibility for their isolation.

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

197 Psychiatric Medications

Four major classes are commonly used in adults: (1) antidepressants (ADs), (2) anxiolytics, (3) antipsychotics, and (4) mood-stabilizing agents. Nonpsychiatric physicians should become familiar with one or two drugs in each of the first three classes so that the indications, dose range, efficacy, potential side effects, and interactions with other medications are well known.

GENERAL PRINCIPLES OF USE

1. Most treatment failures are due to undermedication and impatience. For a proper medication trial to take place, an effective dose must be taken for an adequate amount of time. For ADs, antipsychotics, and mood stabilizers, full effects may take weeks or months to occur.
2. History of a positive response to a medication usually indicates that a response to the same drug will occur again. A family history of a positive response to a specific medication is also useful.
3. Pts who fail to respond to one drug will often respond to another in the same class; one should attempt another trial with a drug that has a different mechanism of action or a different chemical structure. Treatment failures should be referred to a psychiatrist, as should all pts with psychotic symptoms or who require mood stabilizers.
4. Avoid polypharmacy; a pt who is not responding to standard monotherapy requires referral to a psychiatrist.
5. Pharmacokinetics may be altered in the elderly, with smaller volumes of distribution, reduced renal and hepatic clearance, longer biologic half-lives, and greater potential for CNS toxicity. The rule with elderly pts is to "start low and go slow."
6. Never stop treatment abruptly, especially true for ADs and anxiolytics. In general, medications should be slowly tapered and discontinued over 2–4 weeks.
7. Review possible side effects each time a drug is prescribed; educate pts and family members about side effects and need for patience in awaiting a response.

ANTIDEPRESSANTS

Useful to group according to known actions on CNS monoaminergic systems (Table 197-1). The selective serotonin reuptake inhibitors (SSRIs) have predominant effects on serotonergic neurotransmission, also reflected in side-effect profile. The TCAs, or tricyclic ADs, affect noradrenergic and, to a lesser extent, serotonergic neurotransmission but also have anticholinergic and antihistaminic effects. Venlafaxine, desvenlafaxine, duloxetine, mirtazapine, vilazodone, vortioxetine, and levomilnacipran have mixed noradrenergic and serotonergic effects. Bupropion is a novel antidepressant that enhances noradrenergic function. Trazodone and amoxapine have mixed effects on serotonin receptors and on other neurotransmitter systems. The monoamine oxidase inhibitors (MAOIs) inhibit monoamine oxidase, the primary enzyme responsible for the degradation of monoamines in the synaptic cleft.

ADs are effective against major depression, particularly when neurovegetative symptoms and signs are present. Despite the widespread use of SSRIs, there is no convincing evidence that they are more efficacious than TCAs, although their safety profile in overdose is more favorable than that of the TCAs. ADs are also useful in treatment of panic disorder, posttraumatic stress disorder, chronic pain syndromes, and generalized anxiety disorder. The TCA clomipramine and the SSRIs successfully treat obsessive-compulsive disorder.

TABLE 197-1 ANTIDEPRESSANTS

Name	Usual Daily Dose, mg	Side Effects	Comments
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare	Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
Escitalopram (Lexapro)	10–30		
TCAs			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly FDA approved for OCD
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300		
Clomipramine (Anafranil)	150–300		
Mixed Norepinephrine/SNRI and Receptor Blockers			
Venlafaxine (Effexor)	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid-tid dosing (extended release available); lower potential for drug interactions than SSRIs; contraindicated with MAOIs
Desvenlafaxine (Pristiq)	50–400	Nausea, dizziness, insomnia	Primary metabolite of venlafaxine; no increased efficacy with higher dosing
Duloxetine (Cymbalta)	40–60	Nausea, dizziness, headache, insomnia, constipation	May have utility in treatment of neuropathic pain and stress incontinence

Mirtazapine (Remeron)	15–45	Somnolence, weight gain; neutropenia rare	Once a day dosing
Vilazodone (Viibryd)	40	Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator	Also 5-HT_{1a} receptor partial agonist
Vortioxetine (Brintellix)	5–20	Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain	No specific p450 effects; 5-HT_{3a} and 5-HT_{7} receptor antagonist, 5-HT_{1b} partial agonist, and 5-HT_{1a} agonist
Levomilnacipran (Fetzima)	40–120	Nausea, constipation, sweating; rare increase in blood pressure/pulse	Most noradrenergic of SNRIs
Mixed-Action Drugs			
Bupropion (Wellbutrin)	250–450	Jitteriness; flushing; seizures in at-risk pts; anorexia; tachycardia; psychosis	Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation, dry mouth, ventricular irritability, postural hypotension, priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects
Trazodone extended release (Oleptro)	150–375	Daytime somnolence, dizziness, nausea	
Amoxapine (Asendin)	200–600	Sexual dysfunction	Lethality in overdose; EPS possible
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs; narcotics	May be more effective in pts with atypical features or treatment-refractory depression
Tranylcypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		Less weight gain and hypotension than phenelzine
Transdermal selegiline (Emsam)	6–12	Local skin reaction hypertension	No dietary restrictions with 6-mg dose

Abbreviations: ADD, attention deficit disorder; EPS, extrapyramidal symptoms; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; SNRI, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

All ADs require at least 2 weeks at a therapeutic dose before clinical improvement is observed. All ADs also have the potential to trigger a manic episode or rapid cycling when given to a pt with bipolar disorder. The MAOIs must not be prescribed concurrently with other ADs or with narcotics, as potentially fatal reactions may occur. "Withdrawal syndromes" usually consisting of malaise can occur when ADs are stopped abruptly.

ANXIOLYTICS

Benzodiazepines bind to sites on the γ-aminobutyric acid receptor and are cross-tolerant with alcohol and with barbiturates. Four clinical properties: (1) sedative, (2) anxiolytic, (3) skeletal muscle relaxant, and (4) antiepileptic. Individual drugs differ in terms of potency, onset of action, duration of action (related to half-life and presence of active metabolites), and metabolism (Table 197-2). Benzodiazepines have additive effects with alcohol; like alcohol, they can produce tolerance and physiologic dependence, with serious withdrawal syndromes (tremors, seizures, delirium, and autonomic hyperactivity) if discontinued too quickly, especially for those with short half-lives.

Buspirone is a nonbenzodiazepine anxiolytic that is nonsedating, is not cross-tolerant with alcohol, and does not induce tolerance or dependence. It requires at least 2 weeks at therapeutic doses to achieve full effects.

ANTIPSYCHOTIC MEDICATIONS

These include the first-generation (typical) neuroleptics, which act by blocking dopamine D_2 receptors, and the second-generation (atypical) neuroleptics, which act on dopamine, serotonin, and other neurotransmitter systems. Some antipsychotic effect may occur within hours or days of initiating treatment, but full effects usually require 6 weeks to several months of daily, therapeutic dosing.

FIRST-GENERATION ANTIPSYCHOTICS

Useful to group into high-, mid-, and low-potency neuroleptics (Table 197-3). High-potency neuroleptics are least sedating, have almost no anticholinergic side effects, and have a strong tendency to induce extrapyramidal side effects (EPSEs). The EPSEs occur within several hours to several weeks of beginning treatment and include acute dystonias, akathisia, and pseudo-parkinsonism. Extrapyramidal symptoms respond well to trihexyphenidyl, 2 mg twice daily, or benztropine mesylate, 1–2 mg twice daily. Akathisia may respond to beta blockers. Low-potency neuroleptics are very sedating, may cause orthostatic hypotension, are anticholinergic, and tend not to induce EPSEs frequently.

Up to 20% of pts treated with conventional antipsychotic agents for >1 year develop tardive dyskinesia (probably due to dopamine receptor supersensitivity), an abnormal involuntary movement disorder most often observed in the face and distal extremities. Treatment includes gradual withdrawal of the neuroleptic, with possible switch to a novel neuroleptic; anticholinergic agents can worsen the disorder.

Rarely, pts exposed to neuroleptics develop neuroleptic malignant syndrome (NMS), a life-threatening complication with a mortality rate as high as 25%; hyperpyrexia, autonomic hyperactivity, muscle rigidity, obtundation, and agitation are characteristics associated with increased WBC, increased creatine phosphokinase, and myoglobinuria. Treatment involves immediate discontinuation of neuroleptics, supportive care, and use of dantrolene and bromocriptine.

SECOND-GENERATION ANTIPSYCHOTICS

A class of agents that has become the first line of treatment (Table 197-3); efficacious in treatment-resistant pts, tend not to induce EPSEs or tardive dyskinesia,

TABLE 197-2 ANXIOLYTICS

Name	Equivalent PO Dose, mg	Onset of Action	Half-Life, h	Comments
Benzodiazepines				
Diazepam (Valium)	5	Fast	20–70	Active metabolites; quite sedating
Flurazepam (Dalmane)	15	Fast	30–100	Flurazepam is a prodrug; metabolites are active; quite sedating
Triazolam (Halcion)	0.25	Intermediate	1.5–5	No active metabolites; can induce confusion and delirium, especially in elderly
Lorazepam (Ativan)	1	Intermediate	10–20	No active metabolites, direct hepatic glucuronide conjugation, quite sedating, FDA approved for anxiety with depression
Alprazolam (Xanax)	0.5	Intermediate	12–15	Active metabolites,; not too sedating, FDA approved for panic disorder and anxiety with depression, tolerance and dependence develop easily, difficult to withdraw
Chlordiazepoxide (Librium)	10	Intermediate	5–30	Active metabolites, moderately sedating
Oxazepam (Serax)	15	Slow	5–15	No active metabolites, direct glucuronide conjugation, not too sedating
Temazepam (Restoril)	15	Slow	9–12	No active metabolites, moderately sedating
Clonazepam (Klonopin)	0.5	Slow	18–50	No active metabolites, moderately sedating, FDA approved for panic disorder
Clorazepate (Tranxene)	15	Fast	40–200	Low sedation, unreliable absorption
Nonbenzodiazepines				
Buspirone (BuSpar)	7.5	2 weeks	2–3	Active metabolites, tid dosing—usual daily dose 10–20 mg tid, nonsedating; no additive effects with alcohol, useful for controlling agitation in demented or brain-injured pts

TABLE 197-3 ANTIPSYCHOTIC AGENTS

Name	Usual PO Daily Dose, mg	Side Effects	Sedation	Comments
First-Generation Antipsychotics				
Low potency				
Chlorpromazine (Thorazine)	100–1000	Anticholinergic effects, orthostasis, photosensitivity, cholestasis, QT prolongation	+++	EPSEs usually not prominent; can cause anticholinergic delirium in elderly pts
Thioridazine (Mellaril)	100–600			
Midpotency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects	++	Well tolerated by most pts
Perphenazine (Trilafon)	4–64	Fewer EPSEs than with higher potency agents	++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	++	
Molindone (Moban)	30–100	Frequent EPSEs	0	Little weight gain
High potency				
Haloperidol (Haldol)	5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	

Second-Generation Antipsychotics				
Clozapine (Clozaril)	150–600	Agranulocytosis (1%), weight gain, seizures, drooling, hyperthermia	+ +	Requires weekly WBC count for first 6 months, then biweekly if stable
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	++	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation, weight gain, anxiety	+++	Bid dosing
Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+/++	Minimal weight gain, increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist
Paliperidone (Invega)	3–12	Restlessness, EPSEs, increased prolactin, headache	+	Active metabolite of risperidone
Iloperidone (Fanapt)	12–24	Dizziness, hypotension	0/+	Requires dose titration, long-acting injectable available
Asenapine (Saphris)	10–20	Dizziness, anxiety, EPSEs, minimal weight gain	++	Sublingual tablets; bid dosing
Lurasidone (Latuda)	40–80	Nausea, EPSEs	++	Uses CYP3A4

Abbreviations: EPSEs, extrapyramidal side effects.

and appear to have uniquely beneficial properties on negative symptoms and cognitive dysfunction. Main problem is side effect of weight gain (most prominent with clozapine and in olanzapine; can induce diabetes). The CATIE study, a large-scale investigation of antipsychotic agents in the "real world," revealed a high rate of discontinuation of all medications over 18 months; olanzapine was modestly more effective than other agents but with a higher discontinuation rate due to side effects.

MOOD-STABILIZING AGENTS

Four mood stabilizers in common use: lithium, valproic acid, carbamazepine/oxcarbazepine, and lamotrigine (Table 197-4). Lithium is the gold standard and the best studied, and along with carbamazepine and valproic acid, is used for treatment of acute manic episodes; 1–2 weeks to reach full effect. As prophylaxis, the mood stabilizers reduce frequency and severity of both manic and depressed episodes in cyclical mood disorders. In refractory bipolar disorder, combinations of mood stabilizers may be beneficial.

TABLE 197-4 CLINICAL PHARMACOLOGY OF MOOD STABILIZERS

Agent and Dosing	Side Effects and Other Effects
Lithium	**Common side effects**
Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L	Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism
	Blood level is increased by thiazides, tetracyclines, and NSAIDs
	Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors
	Rare side effects: Neurotoxicity, renal toxicity, hypercalcemia, ECG changes
Valproic acid	**Common side effects**
Starting dose: 250 mg tid Therapeutic blood level: 50–125 µg/mL	Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia
	Inhibits hepatic metabolism of other medications
	Rare side effects: Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome
Carbamazepine/ Oxcarbazepine	**Common side effects**
Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine	Nausea/anorexia, sedation, rash, dizziness/ataxia
Therapeutic blood level: 4–12 µg/mL for carbamazepine	Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications
	Rare side effects: Hyponatremia, agranulocytosis, Stevens-Johnson syndrome
Lamotrigine	**Common side effects**
Starting dose: 25 mg/d	Rash, dizziness, headache, tremor, sedation, nausea
	Rare side effect: Stevens-Johnson syndrome

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

198 Eating Disorders

DEFINITIONS AND EPIDEMIOLOGY

Eating disorders constitute a group of conditions in which there is persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. *Anorexia nervosa* is characterized by restriction of caloric intake to a degree that body weight deviates significantly from age, gender, health, and developmental norms accompanied by a fear of gaining weight and an associated disturbance in body image. *Bulimia nervosa* is characterized by recurrent episodes of binge eating followed by abnormal compensatory behaviors, such as self-induced vomiting, laxative abuse, or excessive exercise; weight is in the normal range or above. *Binge eating disorder* is similar to bulimia nervosa but lacks the compensatory behavior element.

Both anorexia nervosa and bulimia nervosa occur primarily among previously healthy young women who become overly concerned with body shape and weight. Binge eating and purging behavior may be present in both conditions, with the critical distinction between the two resting on the weight of the individual. In women, the lifetime prevalence of anorexia nervosa is up to 4% and of bulimia nervosa approximately 2%. There is at least a 10:1 female-to-male ratio for both conditions. Typically, the onset of anorexia is mid-adolescence and bulimia early adulthood. Both can occur later, but onset is uncommon after age 40.

These disorders are most common in postindustrialized and urbanized countries. Affected pts frequently exhibit perfectionist and obsessional tendencies and often have comorbid anxiety disorders. Pursuit of activities that emphasize thinness (ballet, modeling, distance running) is prevalent, as is a drive for high scholastic achievement. Risk factors are a family history of mood disturbance, childhood obesity, and psychological or physical abuse during childhood.

CLINICAL FEATURES

Anorexia Nervosa

- General: feeling cold
- Skin, hair, nails: alopecia, lanugo hair, acrocyanosis, edema
- Cardiovascular: bradycardia, hypotension
- Gastrointestinal: salivary gland enlargement, slow gastric emptying, constipation, elevated liver enzymes
- Hematopoietic: normochromic, normocytic anemia; leukopenia
- Fluid/electrolyte: increased blood urea nitrogen, increased creatinine, hyponatremia, hypokalemia. Hypokalemia can become life threatening.
- Endocrine: low luteinizing hormone and follicle-stimulating hormone with secondary amenorrhea, hypoglycemia, normal thyroid-stimulating hormone with low normal thyroxine, increased plasma cortisol, osteopenia

Bulimia Nervosa

- Gastrointestinal: salivary gland enlargement, dental erosion from gastric acid exposure
- Fluid/electrolyte: hypokalemia, hypochloremia, alkalosis (from vomiting), or acidosis (from laxative abuse)
- Other: callus or scar on dorsum of hand (from repeated scraping against teeth during induced vomiting)

TREATMENT EATING DISORDERS

ANOREXIA NERVOSA

Maudsley family-based therapy is effective in younger individuals, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain should be undertaken gradually with a goal of 0.5–1 lb per week to prevent complications from rapid refeeding (fluid retention, congestive heart failure, acute gastric dilatation). Most individuals are able to achieve remission within 5 years of the original diagnosis.

BULIMIA NERVOSA

Effective treatment approaches include selective serotonin reuptake inhibitors (SSRIs) antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies.

PROGNOSIS

The prognosis of anorexia nervosa is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated mortality is 5.1/1000 annually, the highest among psychiatric conditions. Bulimia nervosa has a more benign outcome but 10–15% will transition to anorexia.

For a more detailed discussion, see Reus VI: Mental Disorders, Chap. 466, p. 2708, in HPIM-19.

199 Alcohol Use Disorder

Alcohol use disorder is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period (Table 199-1). Severity is based on the number of items endorsed: mild is two or three items, moderate is four or five, and severe is six or more.

TABLE 199-1 *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS*, FIFTH EDITION, CLASSIFICATION OF ALCOHOL USE DISORDER (AUD)

Criteria
Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an AUD[a]:
Drinking resulting in recurrent failure to fulfill role obligations
Recurrent drinking in hazardous situations
Continued drinking despite alcohol-related social or interpersonal problems
Tolerance
Withdrawal, or substance use for relief/avoidance of withdrawal
Drinking in larger amounts or for longer than intended
Persistent desire/unsuccessful attempts to stop or reduce drinking
Great deal of time spent obtaining, using, or recovering from alcohol
Important activities given up/reduced because of drinking
Continued drinking despite knowledge of physical or psychological problems caused by alcohol
Alcohol craving

[a]*Mild AUD*: 2–3 criteria required; *moderate AUD*: 4–5 items endorsed; *severe AUD:* 6 or more items endorsed.

CLINICAL FEATURES

Lifetime risk for alcohol use disorder is 10–15% for men and 5–8% for women. Typically, the first major life problem from excessive alcohol use appears in early adulthood, followed by periods of exacerbation and remission. The course is not hopeless; following treatment, between half and two-thirds of pts maintain abstinence for years and often permanently. If the alcoholic continues to drink, life span is shortened by an average of 10 years due to increased risk of death from heart disease, cancer, accidents, or suicide.

Screening for alcoholism is important given its high prevalence. Standardized questionnaires can be helpful in busy clinical practices including the 10-item Alcohol Use Disorders Identification Test (AUDIT) (Table 199-2).

Routine medical care requires attention to potential alcohol-related illness and to alcoholism itself:

1. Neurologic: blackouts, seizures, delirium tremens (DTs), cerebellar degeneration, neuropathy, myopathy
2. GI: esophagitis, gastritis, pancreatitis, hepatitis, cirrhosis, GI hemorrhage
3. Cardiovascular: hypertension, cardiomyopathy
4. Hematologic: macrocytosis, folate deficiency, thrombocytopenia, leukopenia
5. Endocrine: gynecomastia, testicular atrophy, amenorrhea, infertility
6. Skeletal: fractures, osteonecrosis
7. Cancer: breast cancer, oral and esophageal cancers, rectal cancers

Alcohol Intoxication

Alcohol is a CNS depressant that acts on receptors for γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the nervous system. Behavioral, cognitive, and psychomotor changes can occur at blood alcohol levels as low as 0.02–0.03 g/dL, a level achieved after the ingestion of one or two typical drinks. "Legal intoxication" in most states requires a blood alcohol concentration of 0.08 g/dL; levels twice this can

TABLE 199-2 THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)[a]

Item	5-Point Scale (Least to Most)
1. How often do you have a drink containing alcohol?	Never (0) to 4+ per week (4)
2. How many drinks containing alcohol do you have on a typical day?	1 or 2 (0) to 10+ (4)
3. How often do you have six or more drinks on one occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

[a]The AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥8 may indicate harmful alcohol use.

lead to deep but disturbed sleep. Incoordination, tremor, ataxia, confusion, stupor, coma, and even death occur at progressively higher blood alcohol levels.

Alcohol Withdrawal

Chronic alcohol use produces CNS dependence, and the earliest sign of alcohol withdrawal is tremulousness ("shakes" or "jitters"), occurring 5–10 h after decreasing ethanol intake. This may be followed by generalized seizures in the first 24–48 h; these do not require initiation of antiseizure medications. With severe withdrawal, autonomic hyperactivity ensues (sweating, hypertension, tachycardia, tachypnea, fever), accompanied by insomnia, nightmares, anxiety, and GI symptoms.

Delirium Tremens (DTs)

A very severe withdrawal syndrome characterized by profound autonomic hyperactivity, extreme confusion, agitation, vivid delusions, and hallucinations (often visual and tactile) that begins 3–5 days after the last drink. Mortality is 5–15%.

Wernicke's Encephalopathy

An alcohol-related syndrome characterized by ataxia, ophthalmoplegia, and confusion, often with associated nystagmus, peripheral neuropathy, cerebellar signs, and

hypotension; there is impaired short-term memory, inattention, and emotional lability. Wernicke-Korsakoff's syndrome follows, characterized by anterograde and retrograde amnesia and confabulation. Wernicke-Korsakoff's syndrome is caused by chronic thiamine deficiency, resulting in damage to thalamic nuclei, mammillary bodies, and brainstem and cerebellar structures.

LABORATORY FINDINGS

Include mild anemia with macrocytosis, folate deficiency, thrombocytopenia, granulocytopenia, abnormal liver function tests, hyperuricemia, and elevated triglycerides. Two blood tests with ≥60% sensitivity and specificity are γ-glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient transferrin (CDT) (>20 U/L or >2.6%); the combination of the two is likely to be more accurate than either alone. A variety of diagnostic studies may show evidence of alcohol-related organ dysfunction.

TREATMENT ALCOHOLISM

ACUTE WITHDRAWAL

- Acute alcohol withdrawal is treated with multiple B vitamins including thiamine (50–100 mg IV or PO daily for ≥1 week) to replenish depleted stores; use the IV route if Wernicke-Korsakoff's syndrome is suspected since intestinal absorption is unreliable in alcoholics.
- CNS depressant drugs are used when seizures or autonomic hyperactivity is present to halt the rapid state of withdrawal in the CNS and allow for a slower, more controlled reduction of the substance. Low-potency benzodiazepines with long half-lives are preferred (e.g., diazepam 10 mg PO q4–6h, chlordiazepoxide 25–50 mg PO q4–6h) because they produce fairly steady blood levels of drug within a wide dose range. Risks include overmedication and oversedation, which occur less commonly with shorter-acting agents (e.g., oxazepam, lorazepam).
- In severe withdrawal or DTs, high doses of benzodiazepines are usually required. Fluid and electrolyte status and blood glucose levels should be closely followed. Cardiovascular and hemodynamic monitoring is crucial, as hemodynamic collapse and cardiac arrhythmia are not uncommon.
- Generalized withdrawal seizures rarely require aggressive pharmacologic intervention beyond that given to the usual pt undergoing withdrawal, i.e., adequate doses of benzodiazepines.

RECOVERY AND SOBRIETY

Counseling, Education, and Cognitive Approaches

- First, attempts should be made to help the alcoholic achieve and maintain a high level of motivation toward abstinence. These include education about alcoholism and instructing family and/or friends to stop protecting the person from the problems caused by alcohol.
- A second goal is to help the pt to readjust to life without alcohol and to reestablish a functional lifestyle through counseling, vocational rehabilitation, and self-help groups such as alcoholics anonymous (AA).
- A third component, called *relapse prevention*, helps the pt to identify situations in which a return to drinking is likely, formulate ways of managing these risks, and develop coping strategies that increase the chances of a return to abstinence if a slip occurs.
- There is no convincing evidence that inpatient rehabilitation is more effective than outpatient care.

Drug Therapy

Several medications may be useful in alcoholic rehabilitation; usually medications are continued for 6 months if a positive response is seen.

- The opioid-antagonist drug naltrexone (50–150 mg/d PO or monthly 380-mg injection) decreases the probability of a return to drinking and shortens periods of relapse.
- A second medication, acamprosate (2 g/d divided into three oral doses), an *N*-methyl-D-aspartate receptor inhibitor, may be used; efficacy appears similar to naltrexone.
- A combination of naltrexone and acamprosate may be superior to either drug alone, although not all studies agree.
- Disulfiram (250 mg/d), an aldehyde dehydrogenase inhibitor, produces an unpleasant and potentially dangerous reaction in the presence of alcohol.

For a more detailed discussion, see Schuckit MA: Alcohol and Alcoholism, Chap. 467, p. 2723, in HPIM-19.

200 Narcotic Abuse

Narcotics, or opiates, bind to specific opioid receptors in the CNS and elsewhere in the body. These receptors mediate the opiate effects of analgesia, euphoria, respiratory depression, and constipation. Endogenous opiate peptides (enkephalins and endorphins) are natural ligands for the opioid receptors and play a role in analgesia, memory, learning, reward, mood regulation, and stress tolerance.

The prototypic opiates, morphine and codeine, are derived from the juice of the opium poppy. The semisynthetic drugs produced from morphine include hydromorphone (Dilaudid), diacetylmorphine (heroin), and oxycodone (OxyContin). The purely synthetic opioids and their cousins include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, tramadol, methadone, and pentazocine. All produce analgesia and euphoria as well as physical dependence when taken in high enough doses for prolonged periods of time.

CLINICAL FEATURES

The 0.1% annual prevalence of heroin dependence in the United States is only about one-third the rate of prescription opiate abuse and is substantially lower than the 2% rate of morphine dependence in parts of Asia. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially abuse.

Acute Effects

All opiates have the following CNS effects: sedation, euphoria, decreased pain perception, decreased respiratory drive, and vomiting. In larger doses, markedly decreased respirations, bradycardia, pupillary miosis, stupor, and coma ensue. Additionally, the adulterants used to "cut" street drugs (quinine, phenacetin, strychnine, antipyrine, caffeine, powdered milk) can produce permanent neurologic damage, including peripheral neuropathy, amblyopia, myelopathy, and leukoencephalopathy; adulterants can also produce an "allergic-like" reaction characterized by decreased alertness, frothy pulmonary edema, and an elevation in blood eosinophil count.

Chronic Effects

Tolerance and withdrawal commonly occur with chronic daily use after 6–8 weeks depending on the dose and frequency; the ever-increasing amounts of drug needed to sustain euphoriant effects and avoid discomfort of withdrawal strongly reinforce dependence once started.

Withdrawal

Withdrawal produces nausea and diarrhea, coughing, lacrimation, mydriasis, rhinorrhea, diaphoresis, twitching muscles, piloerection, fever, tachypnea, hypertension, diffuse body pain, insomnia, and yawning.

With shorter-acting opiates such as heroin, morphine, or oxycodone, withdrawal signs begin 8–16 h after the last dose, peak at 36–72 h, and subside over 5–8 days. With longer-acting opiates such as methadone, withdrawal begins several days after the last dose, peaks at 7–10 days, and lasts several weeks.

TREATMENT NARCOTIC ABUSE

OVERDOSE

- High doses of opiates, whether taken in a suicide attempt or accidentally when potency is misjudged, are potentially lethal. Toxicity occurs immediately after IV administration and with a variable delay after oral ingestion. Symptoms include miosis, shallow respirations, bradycardia, hypothermia, and stupor or coma.
- Managing overdose requires support of vital functions, including intubation if needed.
- The opiate antagonist naloxone is given at 0.4–2 mg IV or IM with an expected response within 1–2 min; repeated doses, often in the form of an IV drip, may be needed for 24–72 h depending on the opiate used in overdose

WITHDRAWAL

- Long-acting opiates such as methadone or buprenorphine can be used to treat withdrawal and achieve detoxification by slowly tapering the dose over weeks to months. Buprenorphine produces fewer withdrawal symptoms compared with methadone but does not appear to result in better outcomes.
- Several α_2-adrenergic agonists have relieved opioid withdrawal and achieved detoxification by suppressing central noradrenergic activity. Clonidine and lofexidine are commonly used orally in three to four doses per day.
- Rapid opiate detoxification can be accomplished with naltrexone combined with an α_2-adrenergic agonist. Completion rates are high. Ultrarapid opiate detoxification using anesthetics is an extension of this approach but is highly controversial due to medical risks including mortality.

OPIOID MAINTENANCE

- Methadone maintenance is widely used in management of opiate addiction. Methadone is a long-acting opioid optimally dosed at 80–150 mg/d (gradually increased over time).
- The partial agonist buprenorphine can also be used; it has several advantages, including low risk of overdose, potentially easier detoxification than with methadone, and a probable ceiling effect in which higher doses do not increase euphoria. In the United States, primary care physicians can prescribe buprenorphine; this may improve access and quality of treatment.

OPIATE ANTAGONISTS FOR OPIOID DEPENDENCE

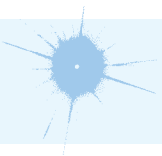
- Rationale is that blocking the action of self-administered opioids should eventually extinguish the habit; poorly accepted by many pts.
- Naltrexone can be given three times a week (100- to 150-mg dose); a depot form for monthly injection is available and improves adherence, retention, and decreases opioid use.

DRUG-FREE PROGRAMS

- Medication-free treatments in inpatient, residential, or outpatient settings have poor 1- to 5-year outcomes compared with pharmacotherapy; exceptions are residential programs lasting 6–18 months, which require full immersion in a regimented system.

PREVENTION

Preventing opiate abuse is a critically important challenge for physicians. In the United States, sources of opiates for adolescents are most commonly family members, not drug dealers or the Internet. Except for the terminally ill, physicians should carefully monitor opioid drug use in pts, keeping doses as low as is practical and administering them over as short a period as the level of pain requires. Pts must dispose of any remaining opiates after treatment. Physicians must be vigilant regarding their own risk for opioid abuse and dependence, never prescribing these drugs for themselves.



For a more detailed discussion, see Kosten TR, Haile CN: Opioid-Related Disorders, Chap. 468e, in HPIM-19.

201 Routine Disease Screening

A primary goal of health care is to prevent disease or to detect it early enough that interventions will be more effective. In general, screening is most effective when applied to relatively common disorders that carry a large disease burden and have a long latency period. Early detection of disease has the potential to reduce both morbidity and mortality; however, screening asymptomatic individuals carries some risk. False-positive results can lead to unnecessary laboratory tests and invasive procedures and can increase pt anxiety. Several measurements have been derived to better assess the potential gain from screening and prevention interventions:

- Number of subjects needed to be screened to alter the outcome in one individual
- Absolute impact of screening on disease (e.g., lives saved per thousand screened)
- Relative impact of screening on disease outcome (e.g., the % reduction in deaths)
- The cost per year of life saved
- The increase in average life expectancy for a population

As part of a routine health care examination, history should include medication use, allergies, vaccination history, dietary history, use of alcohol and tobacco, sexual practices, safety practices (seat belt and helmet use, gun possession), and a thorough family history. Routine measurements should include assessments of height, weight, body-mass index, and blood pressure. Screening should also be considered for domestic violence and depression.

Counseling by health care providers should be performed at health care visits. Tobacco and alcohol use, diet, and exercise represent the vast majority of factors that influence preventable deaths. While behavioral changes are frequently difficult to achieve, it should be emphasized that studies show even brief (<5 min) tobacco counseling by physicians results in a significant rate of long-term smoking cessation. Instruction about self-examination (e.g., skin, breast, testicular) should also be provided during preventative visits.

The top causes of age-specific mortality and corresponding preventative strategies are listed in Table 201-1. Formal recommendations from the U.S. Preventive Services Task Force are listed in Table 201-2.

In addition to the general recommendations applicable to all persons, screening for specific diseases and preventive measures need to be individualized based on family history, travel history, or occupational history. For example, when there is a significant family history of breast, colon, or prostate cancer, it is prudent to initiate screening about 10 years before the age at which the youngest family member developed cancer.

Specific recommendations for disease prevention can also be found in subsequent chapters on "Cardiovascular Disease Prevention" (Chap. 202), "Prevention and Early Detection of Cancer" (Chap. 203), "Smoking Cessation" (Chap. 204), and "Women's Health" (Chap. 205).

TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS

Age Group	Leading Causes of Age-Specific Mortality	Screening Prevention Interventions to Consider for Each Specific Population
15–24	1. Accident 2. Homicide 3. Suicide 4. Malignancy 5. Heart disease	• Counseling on routine seat belt use, bicycle/motorcycle/all terrain vehicle helmets (1) • Counseling on diet and exercise (5) • Discuss dangers of alcohol use while driving, swimming, boating (1) • Ask about vaccination status (tetanus, diphtheria, pertussis, hepatitis B, MMR, varicella, meningitis, HPV) • Ask about gun use and/or gun possession (2,3) • Assess for substance abuse history including alcohol (2,3) • Screen for domestic violence (2,3) • Screen for depression and/or suicidal/homicidal ideation (2,3) • Pap smear for cervical cancer screening, discuss STD prevention (4) • Recommend skin, breast, and testicular self-exams (4) • Recommend UV light avoidance and regular sun screen use (4) • Measurement of blood pressure, height, weight and body mass index (5) • Discuss health risks of tobacco use, consider emphasis of cosmetic and economic issues to improve quit rates for younger smokers (4,5) • *Chlamydia* screening and contraceptive counseling for sexually active females • HIV, hepatitis B, gonorrhea, and syphilis testing if there is high-risk sexual behavior(s) or any prior history of sexually transmitted disease

(*Continued*)

TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS

Age Group	Leading Causes of Age-Specific Mortality	Screening Prevention Interventions to Consider for Each Specific Population
25–44	1. Accident 2. Malignancy 3. Heart disease 4. Suicide 5. Homicide 6. HIV	*As above plus consider the following*: • Readdress smoking status, encourage cessation at every visit (2,3) • Obtain detailed family history of malignancies and begin early screening/prevention program if pt is at significant increased risk (2) • Assess all cardiac risk factors (including screening for diabetes and hyperlipidemia) and consider primary prevention with aspirin for pts at >3% 5-year risk of a vascular event (3) • Assess for chronic alcohol abuse, risk factors for viral hepatitis, or other risks for development of chronic liver disease • Begin breast cancer screening with mammography at age 40 (2)
45–64	1. Malignancy 2. Heart disease 3. Accident 4. Diabetes mellitus 5. Cerebrovascular disease 6. Chronic lower respiratory disease 7. Chronic liver disease and cirrhosis 8. Suicide	• Consider prostate cancer screen with annual PSA and digital rectal examination at age 50 (or possibly earlier in African Americans or pts with family history) (1) • Begin mammography screening by age 50 (1) • Begin colorectal cancer screening at age 50 with either fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy (1) • Reassess vaccination status at age 50 and give special consideration to vaccines against *Streptococcus pneumoniae*, influenza, tetanus, and viral hepatitis • Zoster vaccination at age 60 • Consider screening for coronary disease in higher risk pts (2,5)

(*Continued*)

TABLE 201-1 AGE-SPECIFIC CAUSES OF MORTALITY AND CORRESPONDING PREVENTATIVE OPTIONS

Age Group	Leading Causes of Age-Specific Mortality	Screening Prevention Interventions to Consider for Each Specific Population
≥65	1. Heart disease 2. Malignancy 3. Cerebrovascular disease 4. Chronic lower respiratory disease 5. Alzheimer's disease 6. Influenza and pneumonia 7. Diabetes mellitus 8. Kidney disease 9. Accidents 10. Septicemia	*As above plus consider the following:* • Readdress smoking status, encourage cessation at every visit (1,2,3) • One-time ultrasound for AAA in men 65–75 who have ever smoked • Consider pulmonary function testing for all long-term smokers to assess for development of chronic obstructive pulmonary disease (4,6) • Vaccinate all smokers against influenza and *S. pneumoniae* at age 50 (6) • Screen all postmenopausal women (and all men with risk factors) for osteoporosis • Reassess vaccination status at age 65, emphasis on influenza and *S. pneumoniae* (4,6) • Screen for dementia and depression (5) • Screen for visual and hearing problems, home safety issues, and elder abuse (9)

Note: The numbers in parentheses refer to areas of risk in the mortality column affected by the specified intervention.
Abbreviations: AAA, abdominal aortic aneurysm; HPV, human papilloma virus; MMR, measles-mumps-rubella; PSA, prostate-specific antigen; STD, sexually transmitted disease.

TABLE 201-2 CLINICAL PREVENTIVE SERVICES FOR NORMAL-RISK ADULTS RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE

Test or Disorder	Population,[a] Years	Frequency
Abdominal aortic aneurysm (ultrasound)	Men 65–75 who have ever smoked	Once
Adult immunization		
Human papillomavirus (HPV)	Up to age 26	If not done prior
Influenza	>50	Yearly
Measles, mumps, rubella (MMR)	Women, childbearing age	One dose
Pneumococcal	>65	One dose
Tetanus-diphtheria (Td)	>18	Every 10 years
Varicella (VZV)	Susceptibles only, >18	Two doses
Zoster	>60	One dose

(*Continued*)

TABLE 201-2 CLINICAL PREVENTIVE SERVICES FOR NORMAL-RISK ADULTS RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE (*CONTINUED*)

Test or Disorder	Population,[a] Years	Frequency
Alcohol use	>18	Periodically
Blood pressure, height and weight	>18	Periodically
Breast cancer (mammography and clinical breast examination)[a]	Women 50–75	Every 2 years
Cervical cancer[c]	Women 21–65	Every 3 years
Pap smear	Women 30–65	Every 5 years if HPV negative
Pap smear and HPV testing		
Chlamydia/Gonorrhea	Sexually active women <25	Unknown
Cholesterol	Men >35	Every 5 years
	Women >45	Every 5 years
Colorectal cancer[a]	50–75	
fecal occult blood and/or		Every year
sigmoidoscopy or		Every 5 years
colonoscopy		Every 10 years
Depression	All adults	Periodically[b]
Diabetes	>45 or earlier, if there are additional risk factors	Every 3 years
Hepatitis C	Adults born between 1945–1965	Once
HIV	15–65	Once
Intimate partner violence	Women of childbearing age	Unknown
Obesity (BMI)	All adults	Unknown
Osteoporosis	Women >65; >60 at risk	Unknown
Vision, hearing	>65	Periodically

[a]Screening is performed earlier and more frequently when there is a strong family history. Randomized, controlled trials have documented that fecal occult blood testing (FOBT) confers a 15–30% reduction in colon cancer mortality. Although randomized trials have not been performed for sigmoidoscopy or colonoscopy, well-designed case-control studies suggest similar or greater efficacy relative to FOBT.
[b]If staff support is available.
[c]In the future, Pap smear frequency may be influenced by HPV testing and the HPV vaccine.
Note: Prostate-specific antigen (PSA) testing is capable of enhancing the detection of early-stage prostate cancer, but evidence is inconclusive that it improves health outcomes. PSA testing is recommended by several professional organizations and is widely used in clinical practice, but it is not currently recommended by the U.S. Preventive Services Task Force.
Source: Adapted from the U.S. Preventive Services Task Force, *Guide to Clinical Prevention Services*, 2010–2011. *www.ahrq.gov/clinic/pocketgd.htm*.



For a more detailed discussion, see Armstrong K, Martin GJ: Screening and Prevention of Disease, Chap. 4, p. 26, in HPIM-19.

202 Cardiovascular Disease Prevention

Cardiovascular disease is now the leading cause of death worldwide; prevention is targeted at modifiable atherosclerosis risk factors (Table 202-1). Identification and control of these attributes reduce subsequent cardiovascular event rates.

ESTABLISHED RISK FACTORS

Cigarette Smoking

Cigarette smoking increases the incidence of, and mortality associated with, coronary heart disease (CHD). Observational studies show that smoking cessation reduces excess risk of coronary events within months; after 3–5 years, the risk falls to that of individuals who never smoked. Pts should be asked regularly about tobacco use, followed by counseling and, as needed, antismoking pharmacologic therapy to assist cessation.

Lipid Disorders

(See Chap. 178) Both elevated LDL and low HDL cholesterol are associated with cardiovascular events. Each 1-mg/dL increase in serum LDL correlates with a 2–3% rise in CHD risk; each 1-mg/dL decrease in HDL heightens risk by 3–4%. Fasting screening lipid profile in adults should include total cholesterol, triglycerides, HDL, and LDL (calculated or directly measured). Recommended dietary and/or pharmacologic approach depends on presence or risk of coronary artery disease (CAD); treatment should be most aggressive in pts with established CAD and in those with "equivalent risk" (e.g., presence of diabetes mellitus). Current guidelines by American Heart Association/American College of Cardiology recommend statin therapy for four specific groups of pts at highest risk (Table 202-2). In pts with isolated low HDL, encourage beneficial lifestyle measures: smoking cessation, weight loss, and increased physical activity (see Chap. 178).

Hypertension

(See Chap. 117) Systolic or diastolic bp > "optimal" level of 115/75 mmHg is associated with increased risk of cardiovascular disease; each augmentation of 20 mmHg systolic, or 10 mmHg diastolic, above this value doubles the risk. Treatment of elevated blood pressure reduces the rate of stroke, congestive heart failure, and CHD events, with general goal of bp <140/85 mmHg. Cardiovascular event rates in elderly

TABLE 202-1 ESTABLISHED ATHEROSCLEROTIC RISK FACTORS

Modifiable Risk Factors
Cigarette smoking
Dyslipidemias (↑LDL or ↓HDL)
Hypertension
Diabetes mellitus
Obesity
Sedentary lifestyle
Unmodifiable Risk Factors
Premature coronary heart disease in first-degree relatives (age <55 in men, <65 in women)
Age (men ≥45 years; women ≥55 years)
Male sex

pts with isolated systolic hypertension (systolic ≥140 but diastolic <90) are also reduced by antihypertensive therapy.

See Chap. 117 for antihypertensive treatment recommendations. Pts with "prehypertension" (systolic bp 120–139 mmHg or diastolic bp 80–89 mmHg) should receive counseling about beneficial lifestyle modifications such as those listed below (e.g., low-fat diet replete with vegetables and fruit, weight loss if overweight, increased physical activity, reduction of excessive alcohol consumption).

Diabetes Mellitus/Insulin Resistance/Metabolic Syndrome

(See Chaps. 118 and 173) Pts with diabetes most often succumb to cardiovascular disease. LDL levels are typically near average in diabetic pts, but LDL particles are smaller, denser, and more atherogenic; low HDL and elevated triglyceride levels are common. Tight control of serum glucose in type 2 diabetics reduces microvascular diabetic complications (retinopathy, renal disease), but has less impact on macrovascular events (CAD, stroke). However, successful management of associated risk factors in diabetics (e.g., dyslipidemia and hypertension) *does* significantly reduce cardiovascular events and should be vigorously pursued. Statin therapy should be used to lower vascular risk in diabetics (Table 202-2), even if pt has no symptoms of CAD.

Individuals without overt diabetes but who have "metabolic syndrome" (constellation of insulin resistance, central obesity, hypertension, hypertriglyceridemia, low HDL—see Chap. 118) are also at high risk of cardiovascular events. Dietary counseling, weight loss, and increased physical activity are important in reducing the prevalence of this syndrome.

Male Sex/Postmenopausal State

Coronary risk is greater in men compared to that of premenopausal women of same age, but female risk accelerates after menopause. Estrogen-replacement therapy lowers LDL and raises HDL in postmenopausal women and in observational studies has been associated with reduced coronary events. However, prospective clinical trials do not support such a benefit and hormone-replacement therapy should not be prescribed for the purpose of cardiovascular risk reduction, especially in older women.

TABLE 202-2 GROUPS RECOMMENDED FOR STATIN THERAPY

Group	Recommendation
Clinical atherosclerotic disease (ASCVD)	High-intensity statin[a]
LDL cholesterol ≥190 mg/dL	High-intensity statin[a]
Diabetics (age 40–75, LDL 70–189 mg/dL) with	
10 year cardiac risk[c] ≥7.5%	High-intensity statin[a]
10 year cardiac risk[c] <7.5% without established ASCVD	Moderate-intensity statin[b]
Nondiabetics (age 40–75, LDL 70–189 mg/dL) with	
10 year cardiac risk[c] ≥7.5%	Moderate-to-high intensity statin[a,b]

[a]Atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily; for age ≥75, or if at risk of statin adverse effect, consider moderate intensity statin.

[b]Atorvastatin 10–20 mg daily, rosuvastatin 5–10 mg daily, or simvastatin 20–40 mg daily.

[c]10 year ASCVD risk can be estimated using the online calculator: http://my.americanheart.org/cvriskcalculator.

EMERGING RISK FACTORS

May be assessed selectively in pts without above traditional risk factors who have premature vascular disease or strong family history of premature vascular disease.

Homocysteine

There is a graded correlation between serum homocysteine levels and risk of cardiovascular events and stroke. Supplemental folic acid and other B vitamins lower serum levels, but prospective clinical trials have not shown that such therapy reduces cardiac events.

Inflammation

Inflammatory serum markers, such as high-sensitivity C-reactive protein (CRP), correlate with the risk of coronary events. CRP prospectively predicts risk of MI and outcomes after acute coronary syndromes; its usefulness and role in prevention as an independent risk factor is currently being defined.

Potential benefits of assessing other emerging risk factors [e.g., lipoprotein(a), fibrinogen] remain unproven and controversial.

PREVENTION

Antithrombotic Therapy in Primary Prevention

Thrombosis at the site of disrupted atherosclerotic plaque is the most common cause of acute coronary events. In primary prevention trials, chronic low-dose aspirin therapy has reduced the risk of a first MI in men and the risk of stroke in women. The American Heart Association recommends aspirin (75–160 mg daily) for men and women who are at high cardiovascular risk (i.e., by Framingham Study criteria, for men with ≥10% 10-year risk, or women with ≥20% 10-year risk).

Lifestyle Modifications

Encourage beneficial exercise habits (>30 min moderate intensity physical activity daily) and sensible diet (low in saturated and trans fat; 2–3 servings of fish/week to ensure adequate intake of omega-3 fatty acids; balance caloric consumption with energy expenditure). Advise moderation in ethanol intake (no more than 1–2 drinks/day).

For a more detailed discussion, see Libby P: The Pathogenesis, Prevention, and Treatment of Atherosclerosis, Chap. 291e; Gaziano TA, Gaziano JM: Epidemiology of Cardiovascular Disease, Chap. 266e; and Armstrong K, Martin GJ: Screening and Prevention of Disease, Chap. 4, p. 26; in HPIM-19.

203 Prevention and Early Detection of Cancer

One of the most important functions of medical care is to prevent disease or discover it early enough that treatment might be more effective. All risk factors for cancer have not yet been defined. However, a substantial number of factors that elevate risk are within a person's control. Some of these factors are listed in Table 203-1. Every physician visit is an opportunity to teach and reinforce the elements of a

TABLE 203-1 LIFESTYLE FACTORS THAT REDUCE CANCER RISK

Do not use any tobacco products
Maintain a healthy weight; eat a well-balanced diet[a]; maintain caloric balance
Exercise at least 3 times a week
Prevent sun exposure
Avoid excessive alcohol intake
Practice safe sex; use condoms

[a]Not precisely defined, but current recommendations include five servings of fruits and vegetables per day, 25 g fiber, and <30% of calories coming from fat.

healthy lifestyle. Cancer screening in the asymptomatic population at average risk is a complex issue. To be of value, screening must detect disease at a stage that is more readily curable than disease that is treated after symptoms appear. For cervix cancer and colon cancer, screening has been shown to save lives. For other tumors, benefit is less clear. Screening can cause harm; complications may ensue from the screening test or the tests done to validate a positive screening test or from treatments for the underlying disease. Furthermore, quality of life can be adversely affected by false-positive tests. Evaluation of screening tools can be biased and needs to rely on prospective randomized studies. *Lead-time bias* occurs when the natural history of disease is unaffected by the diagnosis, but the pt is diagnosed earlier in the course of disease than normal; thus, the pt spends more of his/her life span knowing the diagnosis. *Length bias* occurs when slow-growing cancers that might never have come to medical attention are detected during screening. *Overdiagnosis* is a form of length bias in which a cancer is detected when it is not growing and is not an influence on length of survival. *Selection bias* is the term for the fact that people who volunteer for screening trials may be different from the general population. Volunteers might have family history concerns that actually elevate their risk, or they may be generally more health-conscious, which can affect outcome.

The various groups that evaluate and recommend screening practice guidelines have used varying criteria to make their recommendations (Table 203-2). The absence of data on survival for a number of diseases has led to a lack of consensus. In particular, four areas are worth noting.

1. *Prostate cancer:* Prostate-specific antigen (PSA) levels are elevated in prostate cancer, but a substantial number of the cancers detected appear to be non-life-threatening. PSA screening has not been shown to improve survival. Efforts are underway to develop better tests (predominantly using bound vs. free and rate of increase of PSA) to distinguish lethal and nonlethal cancers. Genetic profiling has not yet provided useful distinctions.
2. *Breast cancer:* The data on annual mammography support its use in women age >50 years. However, the benefit for women age 40–49 years is quite small. One study shows some advantage for women who are screened starting at age 40 that appears 15 years later; however, it is unclear if this benefit would not have also been derived by starting screening at age 50 years. Women age 40–49 years have a much lower incidence of breast cancer and a higher false-positive rate on mammography. Nearly half of women screened during their forties will have a false-positive test. Refined methods of screening are in development.
3. *Colon cancer:* Annual fecal occult blood testing after age 50 years is felt to be useful. Colonoscopy is the gold standard in colorectal cancer detection, but it is expensive and has not been shown to be cost-effective in asymptomatic people.
4. *Lung cancer:* Chest radiographs and sputum cytology in smokers appear to identify more early-stage tumors, but paradoxically, the screened pts do not have improved survival. Low-dose spiral CT scanning performed annually for 3 years

TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a]

Cancer Type	Test or Procedure	USPSTF	ACS
Breast	Self-examination	"D"	Women ≥20 years: Breast self-exam is an option
	Clinical examination	Women ≥40 years: "I" (as a stand-alone without mammography)	Women 20–39 years: Perform every 3 years Women ≥40 years: Perform annually
	Mammography	Women 40–49 years: The decision should be an individual one, and take pt context/values into account ("C") Women 50–74 years: Every 2 years ("B") Women ≥75 years: "I"	Women ≥40 years: Screen annually for as long as the woman is in good health
	Magnetic resonance imaging (MRI)	"I"	Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI
Cervical	Pap test (cytology)	Women 21–65 years: Screen every 3 years ("A") Women <21 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D"	Women 21–29 years: Screen every 3 years Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below) Women <21 years: No screening Women >65 years: No screening following adequate negative prior screening
		Women after total hysterectomy for noncancerous causes: "D"	Women after total hysterectomy for noncancerous causes: Do not screen

(*Continued*)

TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)

Cancer Type	Test or Procedure	USPSTF	ACS
	HPV test	Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test, above) ("A") Women <30 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D"	Women 30–65 years: Preferred approach to screen with HPV and cytology cotesting every 5 years (see Pap test above) Women <30 years: Do not use HPV testing Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
Colorectal	Sigmoidoscopy	Adults 50–75 years: every 5 years in combination with high-sensitivity FOBT every 3 years ("A")[b] Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every 5 years
	Fecal occult blood testing (FOBT)	Adults 50–75 years: Annually, for high-sensitivity FOBT ("A") Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every year
	Colonoscopy	Adults 50–75 years: every 10 years ("A") Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every 10 years
	Fecal DNA testing	"I"	Adults ≥50 years: Screen, but interval uncertain
	Fecal immunochemical testing (FIT)	"I"	Adults ≥50 years: Screen every year
	CT colonography	"I"	Adults ≥50 years: Screen every 5 years

(*Continued*)

TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)

Cancer Type	Test or Procedure	USPSTF	ACS
Lung	Low-dose computed tomography (CT) scan	Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years. Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery: "B"	Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists
Ovarian	CA-125 Transvaginal ultrasound	"D" "D"	There is no sufficiently accurate test proven effective in the early detection of ovarian cancer. For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic exam may be offered.
Prostate	Prostate-specific antigen (PSA)	Men, all ages: "D"	Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. How often they are tested will depend on their PSA level.

(*Continued*)

TABLE 203-2 SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (*CONTINUED*)

Cancer Type	Test or Procedure	USPSTF	ACS
	Digital rectal examination (DRE)	No individual recommendation	As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal exam
Skin	Complete skin examination by clinician or pt	"I"	Self-examination monthly; clinical exam as part of routine cancer-related checkup

[a]Summary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition.
[b]USPSTF lettered recommendations are defined as follows: "A": The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; "B": The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; "C": The USPSTF recommends selectively offering or providing this service to individual pts based on professional judgment and pt preferences; there is at least moderate certainty that the net benefit is small; "D": The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; "I": The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.
Abbreviations: ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force.

reduces lung cancer death in older smokers by 20% compared with annual chest x-ray. However, 96% of the positive tests are false-positives and overall survival is improved by only 6.7%.

CANCER PREVENTION IN HIGH-RISK GROUPS

BREAST CANCER

Risk factors include age, early menarche, nulliparity or late first pregnancy, high body-mass index, radiation exposure before age 30 years, hormone-replacement therapy (HRT), alcohol consumption, family history, presence of mutations in *BRCA1* or *BRCA2*, and prior history of breast neoplasia. Models are able to predict a woman's risk level (see *www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional#Section_627*).

Diagnosis

MRI scanning is a more effective screening tool than mammography in women with a familial breast cancer risk.

Interventions

Women whose risk exceeds 1.66% in the next 5 years have been shown to have a 50% reduction in breast cancer from taking tamoxifen or raloxifene. Aromatase inhibitors have generally been superior to tamoxifen in the adjuvant treatment of hormone-sensitive breast cancer, and one of them (exemestane) reduces the risk of breast cancer by 65% in postmenopausal women at increased risk. Women with strong family histories should undergo testing for mutations in *BRCA1* and *BRCA2*. Mutations in these genes carry a lifetime probability of >80% for developing breast cancer. Bilateral prophylactic mastectomy prevents at least 90% of these cancers but is a more radical prevention than the usual treatment for the disease. In addition, bilateral salpingo-oophorectomy reduces ovarian and fallopian tube cancer risk by about 96% in women with *BRCA1* or *BRCA2* mutations.

COLORECTAL CANCER

Risk factors include diets high in saturated fats and low in fruits and vegetables, smoking, and alcohol consumption. Stronger but less prevalent risk factors are the presence of inflammatory bowel disease or genetic disorders such as familial polyposis (autosomal dominant germline mutation in *APC*) and hereditary nonpolyposis colorectal cancer (mutations in DNA mismatch repair genes *hMSH2* and *hMLH1*).

Interventions

Pts with ulcerative colitis and familial polyposis generally undergo total colectomy. In familial polyposis, nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the number and size of polyps. Celecoxib, sulindac, and even aspirin appear to be effective, and celecoxib is approved by the U.S. Food and Drug Administration for this indication. Calcium supplementation can lead to a decrease in the recurrence of adenomas, but it is not yet clear that the risk of colorectal cancer is decreased and survival increased. The Women's Health Study noted a significant reduction in the risk of colorectal cancer in women taking HRT, but the increase in thrombotic events and breast cancers counterbalanced this benefit. Studies are underway to assess NSAIDs with and without inhibitors of the epidermal growth factor (EGF) receptor in other risk groups.

LUNG CANCER

Risk factors include smoking, exposure to radiation, asbestos, radon.

Interventions

Smoking cessation is the only effective prevention (Chap. 204). NSAIDs and EGF receptor inhibitors are being evaluated. Carotenoids, selenium, retinoids, and α-tocopherol do not work.

PROSTATE CANCER

Risk factors include age, family history, and possibly dietary fat intake. African Americans are at increased risk. The disease is highly prevalent, with autopsy studies finding prostate cancer in 70–80% of men over age 70.

Interventions

In a group of men age ≥55 years with normal rectal examinations and PSA levels <3 ng/mL, daily finasteride reduced the incidence of prostate cancer by 25%. Finasteride also prevents the progression of benign prostate hyperplasia. However, some men experience decreased libido as a side effect. The Gleason grade of tumors seen in men taking finasteride prevention was somewhat higher than the controls; however, androgen deprivation alters the morphology of the cells and it is not yet clear that the Gleason grade is a reliable indicator of tumor aggressiveness in the setting of androgen deprivation. Dutasteride, another 5α-reductase inhibitor, had similar effects. The

FDA has reviewed the data and concluded that the reduction in risk is primarily in the group of pts with low-grade tumors whose risk from prostate cancer is unclear. One additional high-grade tumor emerges for every 3–4 low-grade tumors averted. More follow-up is necessary to see if higher-grade tumors emerging on preventive therapy have the same aggressive behavior as those occurring in the absence of preventive hormone blockade.

CERVICAL CANCER

Risk factors include early age at first intercourse, multiple sexual partners, smoking, and infection with human papillomavirus (HPV) types 16, 18, 45, and 56.

Interventions

Regular Pap testing can detect nearly all cases of the premalignant lesion called *cervical intraepithelial neoplasia*. Untreated, the lesion can progress to carcinoma in situ and invasive cervical cancer. Surgical removal, cryotherapy, or laser therapy is used to treat the disease and is effective in 80%. Risk of recurrence is highest in women over age 30, those with prior HPV infection, and those who have had prior treatment for the same condition. A vaccine (Gardasil) containing antigens of strains 6, 11, 16, and 18 has been shown to be 100% effective in preventing HPV infections from those strains. The vaccine is recommended for all females and males age 9–26 years and could prevent up to 70% of all cervical cancer. The vaccine is not effective after infection has been established.

HEAD AND NECK CANCER

Risk factors include smoking, alcohol consumption, and possibly HPV infection.

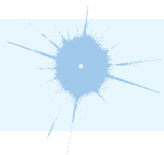
Interventions

Oral leukoplakia, white lesions of the oral mucosa, occur in 1–2 persons in 1000, and 2–3% of these pts go on to develop head and neck cancer. Spontaneous regression of oral leukoplakia is seen in 30–40% of pts. Retinoid treatment (13-*cis* retinoid acid) can increase the regression rate. Vitamin A induces complete remission in ~50% of pts. The use of retinoids in pts who have been diagnosed with head and neck cancer and received definitive local therapy has not produced consistent results. Initial studies claimed that retinoids prevented the development of second primary tumors, a common feature of head and neck cancer. However, large randomized studies did not confirm this benefit. Other studies are underway combining retinoids and NSAIDs with and without EGF receptor inhibitors.

PATIENT EDUCATION IN EARLY DETECTION

Pts can be taught to look for early warning signals. The American Cancer Society has identified seven major warning signs of cancer:

- A change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- A lump in the breast or other parts of the body
- Chronic indigestion or difficulty in swallowing
- Obvious changes in a wart or mole
- Persistent coughing or hoarseness



For a more detailed discussion, see Crosswell JM, Brawley OW, Kramer BS: Prevention and Early Detection of Cancer, Chap. 100, p. 475, in HPIM-19.

204 Smoking Cessation

Over 400,000 individuals die prematurely each year in the United States from cigarette use: one out of every five deaths nationwide. Approximately 40% of smokers will die prematurely unless they are able to quit; major diseases caused by cigarette smoking are listed in Table 204-1.

APPROACH TO THE PATIENT: Nicotine Addiction

All pts should be asked whether they smoke, how much they smoke, how long they have smoked, their past experience with quitting, and whether they are currently interested in quitting; even those who are not interested should be encouraged and motivated to quit. Provide a clear, strong, and personalized message that smoking is an important health concern. A quit date should be negotiated within a few weeks of the visit, and a follow-up contact by office staff around the time of the quit date should be provided. Incorporation of cessation assistance into a practice requires a change of the care delivery infrastructure. Simple changes include:

- Adding questions about smoking and interest in cessation on pt-intake questionnaires
- Asking pts whether they smoke as part of the initial vital sign measurements made by office staff
- Listing smoking as a problem in the medical record
- Automating follow-up contact with the pt on the quit date

TABLE 204-1 RELATIVE RISKS FOR CURRENT SMOKERS OF CIGARETTES

	Current Smokers	
Disease or Condition	**Males**	**Females**
Coronary heart disease		
Age 35–64	2.8	3.1
Age ≥65	1.5	1.6
Cerebrovascular disease		
Age 35–64	3.3	4
Age ≥65	1.6	1.5
Aortic aneurysm	6.2	7.1
Chronic airway obstruction	10.6	13.1
Cancer		
Lung	23.3	12.7
Larynx	14.6	13
Lip, oral cavity, pharynx	10.9	5.1
Esophagus	6.8	7.8
Bladder, other urinary organs	3.3	2.2
Kidney	2.7	1.3
Pancreas	2.3	2.3
Stomach	2	1.4
Liver	1.7	1.7
Colorectal	1.2	1.2
Cervix		1.6
Acute myeloid leukemia	1.4	1.4
Sudden infant death syndrome		2.3
Infant respiratory distress syndrome		1.3
Low birth weight at delivery		1.8

TREATMENT NICOTINE ADDICTION

- Clinical practice guidelines suggest a variety of pharmacologic and nonpharmacologic interventions to aid in smoking cessation (Table 204-2).
- Numerous nicotine-replacement products exist, including over-the-counter nicotine patches, gum, and lozenges, as well as nicotine nasal and oral inhalers available by prescription; these products can be used for 3–6 months with a gradual step-down in dosage with increasing duration of abstinence.
- Prescription medications that have been shown to be effective include antidepressants such as bupropion (300 mg/d in divided doses for up to 6 months) and varenicline, a partial agonist for the nicotinic acetylcholine receptor (initial dose 0.5 mg daily increasing to 1 mg twice daily at day 8; treatment duration up to 6 months). Antidepressants are more effective in pts with a history of depressive symptoms.
- Clonidine or nortriptyline may be useful for pts who have failed first-line therapies.
- Current recommendations are to offer pharmacologic treatment, usually with nicotine replacement therapy or varenicline, to all who will accept it and to provide counseling and other support as a part of the cessation attempt.

PREVENTION

Approximately 85% of individuals who will become cigarette smokers initiate the behavior during adolescence; prevention must begin early, preferably in the elementary school years. Physicians who treat adolescents should be sensitive to the

TABLE 204-2 CLINICAL PRACTICE GUIDELINES

Physician Actions
Ask: Systematically identify all tobacco users at every visit
Advise: Strongly urge all smokers to quit
Identify smokers willing to quit
Assist the patient in quitting
Arrange follow-up contact
Effective Pharmacologic Interventions[a]
First-line therapies
Nicotine gum (1.5)
Nicotine patch (1.9)
Nicotine nasal inhaler (2.7)
Nicotine oral inhaler (2.5)
Nicotine lozenge (2.0)
Bupropion (2.1)
Varenicline (2.7)
Second-line therapies
Clonidine (2.1)
Nortriptyline (3.2)
Other Effective Interventions[a]
Physician or other medical personnel counseling (10 min) (1.3)
Intensive smoking cessation programs (at least 4–7 sessions of 20- to 30-min duration lasting at least 2 and preferably 8 weeks) (2.3)
Clinic-based smoking status identification system (3.1)
Counseling by nonclinicians and social support by family and friends
Telephone counseling (1.2)

[a]Numerical value following the intervention is the multiple for cessation success compared to no intervention.

prevalence of this problem and screen for tobacco use, reinforcing the fact that most adolescents and adults do not smoke, and explaining that all forms of tobacco are both addictive and harmful.

For a more detailed discussion, see Burns DM: Nicotine Addiction, Chap. 470, p. 2729, in HPIM-19.

205 Women's Health

The most common causes of death in both men and women are heart disease and cancer, with lung cancer the top cause of cancer death, despite common misperceptions that breast cancer is the most common cause of death in women. These misconceptions perpetuate inadequate attention to modifiable risk factors in women, such as dyslipidemia, hypertension, and cigarette smoking. Furthermore, since women in the Unites States live on average 5.1 years longer than men, the majority of the disease burden for many age-related disorders (e.g., hypertension, Alzheimer's disease) rests in women.

SEX DIFFERENCES IN HEALTH AND DISEASE

ALZHEIMER'S DISEASE (SEE ALSO CHAP. 182)

Alzheimer's disease (AD) affects approximately twice as many women as men, due to larger numbers of women surviving to older ages and to sex differences in brain size, structure, and functional organization. The impact of postmenopausal hormone therapy on cognitive function and the development of AD is inconclusive, though some studies suggest increased risk.

CORONARY HEART DISEASE (SEE ALSO CHAPS. 119-121)

Coronary heart disease (CHD) presents differently in women, who are usually 10–15 years older than men with CHD and are more likely to have comorbidities, such as hypertension, congestive heart failure, and diabetes. Women more often have atypical symptoms, such as nausea, vomiting, indigestion, and upper back pain, and are less likely to recognize these and call 9-1-1. Physicians are less likely to suspect heart disease in women with chest pain and are less likely to perform diagnostic and therapeutic cardiac procedures in women. The conventional risk factors for CHD are the same in both men and women, though women receive fewer interventions for modifiable risk factors than do men. The prevalence of CHD is increasing in middle-aged women, at a time when the prevalence in men is unchanged or declining. The marked increase in CHD occurring after menopause or oophorectomy suggests that endogenous estrogens are cardioprotective. However, hormone replacement therapy in postmenopausal women was not shown to be cardioprotective in controlled trials such as the Women's Health Initiative and other randomized trials. Therapy with estrogen plus progestin therapy was associated with *increased* cardiovascular events. The discrepancy between endogenous and exogenous estrogen effects is poorly

understood but may be related to deleterious effects of late re-exposure to estrogen after a period of estrogen deficiency.

DIABETES MELLITUS (SEE ALSO CHAP. 173)

The prevalence of type 2 diabetes mellitus (DM) is similar between men and women. Polycystic ovary syndrome and gestational diabetes mellitus are both common conditions in premenopausal women that carry an increased risk for type 2 DM. Premenopausal women with DM have identical rates of CHD to those of males.

HYPERTENSION (SEE ALSO CHAP. 117)

Hypertension, as an age-related disorder, is more common in women than in men after age 60. Antihypertensive drugs appear to be equally effective in women and men; however, women may experience more side effects.

AUTOIMMUNE DISORDERS (SEE ALSO CHAP. 158)

Most autoimmune disorders occur more commonly in women than in men; these include autoimmune thyroid and liver diseases, lupus, rheumatoid arthritis, scleroderma, multiple sclerosis, and idiopathic thrombocytopenic purpura. The mechanism for these sex differences remains obscure.

HIV INFECTION (SEE ALSO CHAP. 105)

Heterosexual contact with an at-risk partner is the fastest-growing transmission category of HIV, and women are more susceptible to HIV infection than men. Women account for about 50% of the 34 million persons infected with HIV-1 worldwide. Women with HIV have more rapid decreases in their CD4 cell counts than men do. Other sexually transmitted diseases, such as chlamydial infection and gonorrhea, are important causes of infertility in women, and papilloma virus infection predisposes to cervical cancer.

OBESITY (SEE ALSO CHAP. 172)

The prevalence of obesity is higher in women than in men, in part due to the unique risk factors of pregnancy and menopause. More than 80% of patients who undergo bariatric surgery are women. The distribution of body fat differs by sex, with a gluteal and femoral (gynoid) pattern in women and a central and upper body (android) pattern in men. The android distribution of fat carries a higher risk for metabolic syndrome, diabetes mellitus, and cardiovascular disease. Obesity increases a woman's risk for postmenopausal breast and endometrial cancer, in part because of adipose tissue aromatization of androgens to estrone.

OSTEOPOROSIS (SEE ALSO CHAP. 177)

Osteoporosis is much more prevalent in postmenopausal women than in age-matched men, since men accumulate more bone mass in their youth and lose bone more slowly than do women, in particular after age 50, when accelerated postmenopausal bone loss occurs in women. In addition, differences in calcium intake, vitamin D, and estrogen levels contribute to sex differences in bone formation and bone loss. Vitamin D insufficiency is present in a large proportion of elderly women living in Northern latitudes. Osteoporotic hip fracture is a major cause of morbidity and an important cause of mortality in elderly women.

PHARMACOLOGY

On average, women have lower body weights, smaller organs, higher percent body fat, and lower total-body water than men do. Gonadal steroids, menstrual cycle phase, and pregnancy can all affect drug metabolism and action. Women also take more medications than men do, including over-the-counter formulations and supplements. The greater use of medications, combined with biologic differences, may account for the reported higher frequency of adverse drug reactions in women.

PSYCHOLOGICAL DISORDERS (SEE ALSO CHAPS. 196 AND 198)

Depression, anxiety, and eating disorders (bulimia and anorexia nervosa) are more common in women than in men. Depression occurs in 10% of women during pregnancy and 10–15% of women during the postpartum period.

SLEEP DISORDERS (SEE ALSO CHAP. 56)

During sleep, women have an increased amount of slow-wave activity, differences in timing of delta activity, and an increase in the number of sleep spindles. They have a decreased prevalence of sleep apnea compared to men, a feature that may be related to lower androgen levels.

SUBSTANCE ABUSE AND TOBACCO (SEE ALSO CHAPS. 199 AND 204)

Substance abuse is more common in men than women. However, women alcoholics are less likely to be diagnosed than men and are less likely to seek help. When they do seek help, it is more likely to be from a physician than from a treatment facility. Alcoholic women drink less than alcoholic men but exhibit the same degree of impairment. Alcohol abuse poses special risks to a woman, adversely affecting fertility and the health of the baby (fetal alcohol syndrome). Even moderate alcohol use increases the risk of breast cancer, hypertension, and stroke in women. More men than women smoke tobacco, but the prevalence of smoking is declining faster in men than women. The effects of smoking on pulmonary disease (COPD and cancer) and osteoporosis are more pronounced in women than in men.

VIOLENCE AGAINST WOMEN

Domestic violence is the most common cause of physical injury in women. More than one in three women in the United States have experienced rape, physical violence, and/or stalking by an intimate partner. Women may present with symptoms of chronic abdominal pain, headaches, substance abuse, and eating disorders, in addition to obvious manifestations such as trauma. Sexual assault is one of the most common crimes against women (reported by one in five women in the United States) and is more likely committed by a spouse, ex-spouse, or acquaintance than by a stranger.



For a more detailed discussion, see Dunaif A: Women's Health, Chap. 6e, HPIM-19.

206 Adverse Drug Reactions

Adverse drug reactions are among the most frequent problems encountered clinically and represent a common cause for hospitalization. They occur most frequently in pts receiving multiple drugs and are caused by:

- Errors in self-administration of prescribed drugs (quite common in the elderly);
- Exaggeration of intended pharmacologic effect (e.g., hypotension in a pt given antihypertensive drugs);
- Concomitant administration of drugs with synergistic effects (e.g., aspirin and warfarin);
- Cytotoxic reactions (e.g., hepatic necrosis due to acetaminophen);
- Immunologic mechanisms (e.g., quinidine-induced thrombocytopenia, hydralazine-induced SLE);
- Genetically determined enzymatic defects (e.g., primaquine-induced hemolytic anemia in G6PD deficiency); or
- Idiosyncratic reactions (e.g., chloramphenicol-induced aplastic anemia).

Recognition

History is of prime importance. Consider the following:

- Nonprescription drugs and topical agents as potential offenders
- Previous reaction to identical drugs
- Temporal association between drug administration and development of clinical manifestations
- Subsidence of manifestations when the agent is discontinued or reduced in dose
- Recurrence of manifestations with cautious readministration (for less hazardous reactions)
- *Rare*: (1) biochemical abnormalities, e.g., red cell G6PD deficiency as cause of drug-induced hemolytic anemia; (2) abnormal serum antibody in pts with agranulocytosis, thrombocytopenia, or hemolytic anemia.

Table 206-1 lists a number of clinical manifestations of adverse effects of drugs. It is not designed to be complete or exhaustive. The table can be accessed via the following link: www.accessmedicine.com.

For a more detailed discussion, see Roden DM: Principles of Clinical Pharmacology, Chap. 5, p. 31, in HPIM-19; Wood AJJ: Adverse Reactions to Drugs, Chap. 71, p. 430, in HPIM-15.

This page intentionally left blank

INDEX

Note: Page numbers followed by *f* or *t* denote figures or tables, respectively.

A
abacavir, for HIV infection, 561*t*, 566
abatacept, for rheumatoid arthritis, 847
abciximab, for thrombotic disorders, 283
abdominal angina, 797
abdominal aortic aneurysm, 693–694, 1090*t*
abdominal infections, actinomycosis, 480
abdominal pain, 154–158
  acute, catastrophic, 157–158
  approach to, 154–157
  causes of, 155*t*
  clinical manifestations of, 156–157
abdominal radiography, 23, 804
abdominal wall disorders, pain in, 155*t*
abdominoperineal resection, for anal cancer, 330
ABG. *See* arterial blood gases
Abiotrophia infections, 439–440
abiraterone, for prostate cancer, 343
abortion, 922
abscess
  brain, 478, 1020, 1029–1030
  epidural. *See* epidural abscess
  intraabdominal, 384–385
  liver, 384–385
  lung, 726, 729–730
  nerve, in leprosy, 491
  Nocardia, 478
  pancreatic, 807
  perinephric, 385
  peritonsillar, 475
  renal, 385
  splenic, 385
  streptococcal, 439
  visceral, 385
absence (petit mal) seizures, 956. *See also* seizures
ABU (asymptomatic bacteriuria), 776, 778
ABVD regimen, for Hodgkin's disease, 304
acamprosate, for alcoholic rehabilitation, 1084
acanthocytes, 202, 265
acarbose, for diabetes mellitus, 908*t*
accelerated idioventricular rhythm (AIVR), 663, 682*t*
accessory nerve (CN XI)
  disorders of, 1000
  examination of, 948
accident prevention, 1088–1090*t*
ACE inhibitors. *See* angiotensin-converting enzyme inhibitors
acetaminophen
  for back pain, 211
  for fever, 128
  for migraine, 217*t*
  for osteoarthritis, 862
  for pain, 37, 38*t*
  for tension-type headache, 218
  toxicity of, 815
acetazolamide, for periodic paralysis, 1060
N-acetylcysteine, for acetaminophen overdose, 815
acetylsalicylic acid. *See* aspirin
achalasia, 164
acid maltase deficiency, 1059
acid-base disorders, 13–22
  metabolic acidosis. *See* metabolic acidosis
  metabolic alkalosis, 20–21, 21*f*
  mixed, 22
  nomogram for, 17*f*
  respiratory acidosis, 21
  respiratory alkalosis, 21–22
acid-fast bacilli, 482
acidosis, 14
Acinetobacter infections, 457
acitretin, for psoriasis, 259
ACMV (assist-control mandatory ventilation), 75*t*
acne, 262–263
acne rosacea, 256*f*, 263
acne vulgaris, 256*f*, 262–263
acoustic neuroma, 227, 997
acrodermatitis chronica atrophicans, 495
acromegaly, 349*t*, 350, 880–881
ACTH. *See* adrenocorticotropic hormone
actinic keratosis, 256*f*
Actinobacillus actinomycetemcomitans infections. *See* HACEK group infection
actinomycetoma, 478, 480*t*
actinomycosis, 479–480, 1034*t*
activated charcoal
  for erythropoietic protoporphyria, 945

activated charcoal (*Cont.*):
for paralytic shellfish poisoning, 122
for toxic and drug-induced hepatitis, 815
acupuncture, for chronic back pain, 211
acute, catastrophic abdominal pain, 157–158
acute coronary syndrome (ACS), 668, 668*f*. *See also* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
acute disseminated encephalomyelitis (ADEM), 1020
acute intermittent porphyria (AIP), 944, 991
acute interstitial nephritis (AIN), 771–772, 771*t*
acute interstitial pneumonia (AIP), 736
acute kidney injury (AKI), 771–772
acute low back pain (ALBP). *See* low back pain
acute lymphoblastic leukemia and lymphoblastic lymphoma (ALL), 295*t*, 296*f*, 299–300
acute myeloid leukemia (AML), 283–287
classification of, 284*t*, 286*f*
clinical manifestations of, 285
incidence of, 285
treatment of, 285–287, 286*f*
acute promyelocytic leukemia, 284*t*, 285
acute renal failure (ARF), 747–751
clinical manifestations of, 749–750
in critically ill patient, 35
definition of, 747
dialysis for, 751
differential diagnosis of, 747–749
etiology of, 747, 747–748*t*
intrinsic, 748–749, 748*t*, 750*t*
laboratory testing in, 749–750
postrenal, 748*t*, 749
prerenal, 747–748, 747*t*, 750*t*
treatment for, 751
acute respiratory distress syndrome (ARDS), 71–73, 72*f*
acute retroviral syndrome, 555, 557, 558*t*
acute stress disorder, 1068
acute uric acid nephropathy, 864
acyclovir
for Bell's palsy, 997
for Epstein-Barr virus infections, 529
for genital HSV infections, 412, 415*t*
for herpes zoster infections, 415*t*
for HSCT patients, 367
for HSV infections, 519, 520–522*t*
for viral encephalitis, 1029
for viral esophagitis, 165
for viral meningitis, 1027
for VZV infections, 524
AD. *See* Alzheimer's disease
adalimumab
for ankylosing spondylitis, 857
for inflammatory bowel disease, 794
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
adaptive immune system, deficiencies of, 841*t*
Addison's disease, 898–899
adefovir, for chronic hepatitis B, 817, 818–819*t*
ADEM (acute disseminated encephalomyelitis), 1020
adenoma
adrenal, 896
colonic, 326
gastric, 325
hepatocellular, 330
pituitary. *See* pituitary adenoma
small-bowel, 325
thyroid, 893–895, 894*f*
adenosine
for arrhythmias, 684*t*
for tachyarrhythmias, 680*t*
for Wolff-Parkinson-White syndrome, 686
adenosine deaminase deficiency, 840
adenovirus infections, 534*t*, 537
adenylate kinase 2 deficiency, 840
ADH (antidiuretic hormone), 883
adnexal mass, 338
ADPKD (autosomal dominant polycystic kidney disease), 773–774
adrenal gland disease, 895–900
Addison's disease, 898–899
adenoma, 896
carcinoma, 896
Cushing's syndrome. *See* Cushing's syndrome
hyperaldosteronism. *See* hyperaldosteronism

hypoaldosteronism, 899–900
incidental masses, 900, 900*f*
adrenal insufficiency
paraneoplastic, 112
primary, 898
secondary, 898
adrenalectomy, for prostate cancer, 343
adrenocorticotropic hormone (ACTH), 878*f*
deficiency of, 882, 883*t*, 898
ectopic hypersecretion of, 348–350, 349*t*, 351
hypersecretion of, 896
for inflammatory bowel disease, 792
production of, 877
adrenomyeloneuropathy, 1007
adult inclusion conjunctivitis (AIC), 514–515
adult T cell leukemia/lymphoma (ATL), 301
advance directives, 49
advanced sleep-wake phase syndrome, 245
adverse drug reactions, 1107. *See also* drug-induced illness
AED (automated external defibrillator), 57
Aeromonas infections, 458
aflatoxin, hepatocellular carcinoma and, 331–332
African tick-bite fever, 501*t*, 504–505
agammaglobulinemia, 843
agglutination, 586
Aggregatibacter actinomycetemcomitans infections, 452, 453*t*
Aggregatibacter aphrophilus infections, 452, 453*t*
aggressive lymphoma, 295*t*, 296, 298–299
agitation, in terminally ill patient, 56*t*
agoraphobia, 1067, 1069
AIC (adult inclusion conjunctivitis), 514–515
AIDS, 554. *See also* HIV infection
AIN (acute interstitial nephritis), 771–772, 771*t*
AION (anterior ischemic optic neuropathy), 230*f*, 231
AIP (acute intermittent porphyria), 944, 991
AIP (acute interstitial pneumonia), 736
airborne precautions, 357
airway obstruction, 142–143
AIVR (accelerated idioventricular rhythm), 663, 682*t*
AKI (acute kidney injury), 771–772
alanine aminotransferase (ALT), 183, 184*t*
albendazole
for ascariasis, 601
for echinococcosis, 609
for enterobiasis, 603
for giardiasis, 391
for hookworm infections, 601
for larva migrans, 600
for lymphatic filariasis, 604
for strongyloidiasis, 602
for taeniasis solium and cysticercosis, 607
for trichinellosis, 599
ALBP (acute low back pain). *See* low back pain
albumin
intravenous, 188, 189
for peritonitis, 382
serum, in liver disease, 184*t*, 185
serum-ascites gradient, 188*f*
urine, 200–201
albuterol
for anaphylaxis, 114
for COPD, 720, 721
for hyperkalemia, 16*t*
alcohol intoxication, 1081–1082
alcohol use disorder, 1080–1084
chronic, 807
clinical manifestations of, 1081–1083
definition of, 1080, 1081*t*
laboratory testing in, 1083
metabolic consequences of, 828
screening for, 1088–1090*t*, 1091*t*
treatment of, 1083–1084
in women, 1106
Alcohol Use Disorders Identification Test (AUDIT), 1082*t*
alcohol withdrawal, 1082, 1083
alcoholic ketoacidosis, 17, 18*t*
alcoholic liver disease, 827–828
alcoholic polyneuropathy, 991
alemtuzumab
for CLL, 297
for multiple sclerosis, 1018
alendronate, for osteoporosis, 934
alkali therapy, for nephrolithiasis, 782*t*
alkaline phosphatase, 183, 184*t*, 804
alkaline-encrusted cystitis, 443

alkalosis, 14
ALL (acute lymphoblastic leukemia and lymphoblastic lymphoma), 295*t*, 296*f*, 299–300
allergic bronchopulmonary aspergillosis, 572, 574*t*
allergy
  anaphylaxis in, 114–115
  to insect sting, 124–125
allodynia, 36, 991
alloimmunization, 46
allopurinol
  for CML, 289
  for gout, 865
  for nephrolithiasis, 781–782*t*
  for tumor lysis syndrome, 113
allylamines, for dermatophyte infections, 262
almotriptan, for migraine, 217*t*, 219*t*
alogliptin, for diabetes mellitus, 908*t*
alosetron, for irritable bowel syndrome, 795, 796*t*
α_1-antitrypsin deficiency, 720
alpha-adrenergic antagonists, for vasospastic disorders, 698
alphavirus infections, 550–551
alprazolam, 1075*t*
alprostadil injection, for erectile dysfunction, 916
ALS. *See* amyotrophic lateral sclerosis
ALT (alanine aminotransferase), 183, 184*t*
alteplase, for thrombotic disorders, 282
aluminum phosphate binders, for hyperphosphatemia, 929
alveolar hemorrhage syndromes, 739
alveolar ventilation, 707
alveolar-arterial oxygen gradient, 707–708
Alzheimer's disease (AD)
  approach to, 968
  clinical manifestations of, 972–973
  differential diagnosis of, 969*t*, 970*t*
  familial, 971
  pathogenesis of, 973
  treatment of, 973–974
  in women, 1104
amantadine
  for influenza, 532, 532*t*
  for Parkinson's disease, 980
amaurosis fugax, 82, 230
AmB. *See* amphotericin B
ambrisentan, for pulmonary hypertension, 702
amebiasis, 396–397
amenorrhea, 917–918, 917*f*
amikacin
  for community-acquired pneumonia, 725*t*
  for enteric GNB infections, 458
  for extraintestinal *E. coli* infections, 454
  for health care–associated pneumonia, 727*t*
  for *Klebsiella* infections, 456
  for nocardiosis, 479
  for nontuberculous mycobacterial infections, 494
  for *P. aeruginosa* infections, 460*t*
  for *Proteus* infections, 457
amiloride
  for diabetes insipidus, 6
  for edema, 153*t*
  for hyperaldosteronism, 898
  for hypertension, 652*t*
  for Liddle's syndrome, 20
aminoglutethimide, for prostate cancer, 343
aminoglycosides
  for *Aeromonas* infections, 458
  for brucellosis, 464
  for enterococcal infections, 440–441
  for HACEK group infections, 453*t*
  for infective endocarditis, 376*t*, 379
  for nontuberculous mycobacterial infections, 494
  for *P. aeruginosa* infections, 460–461*t*
aminophylline, for anaphylaxis, 114
5-aminosalicylic acid (5-ASA), for inflammatory bowel disease, 792
aminotransferases, 183, 184*t*
amiodarone
  for arrhythmias, 684*t*
  for dilated cardiomyopathy, 641
  for hypertrophic cardiomyopathy, 643
  for tachyarrhythmias, 681*t*
  thyrotoxicosis induced by, 892
  for ventricular fibrillation, 59*f*
  for ventricular tachycardia, 662
amitriptyline
  for ciguatera poisoning, 121
  dosage and side effects of, 39*t*, 1072*t*
  for irritable bowel syndrome, 795
  for migraine prevention, 220*t*
  for multiple sclerosis, 1019

for pain, 39*t*
for postherpetic neuralgia, 524
for tension-type headache, 218
AML. *See* acute myeloid leukemia
amlodipine, for pulmonary hypertension, 702
ammonia, blood, in liver disease, 184*t*
amodiaquine, for malaria, 588*t*
amoxapine, 1071, 1073*t*
amoxicillin
for community-acquired pneumonia, 725*t*
for COPD exacerbations, 721
for *H. pylori* eradication, 787*t*
for infective endocarditis prophylaxis, 381*t*
for Lyme borreliosis, 496
for otitis media, 252*t*
for pneumococcal infections, 424
for sinusitis, 249*t*
amoxicillin-clavulanate
for animal bite infections, 116*t*, 415*t*
for community-acquired pneumonia, 725*t*
for *H. influenzae* infections, 449
for *M. catarrhalis*, 452
for nocardiosis, 479
for otitis media, 252*t*
for sinusitis, 249*t*
amphotericin B, 569
for aspergillosis, 574*t*
for blastomycosis, 581
for candidiasis, 571
for coccidioidomycosis, 580
for cryptococcosis, 576
for febrile neutropenia in cancer patient, 113
for fusariosis, 582
for histoplasmosis, 579*t*
for leishmaniasis, 594
for *Malassezia* infections, 581
for mucormycosis, 577
for paracoccidioidomycosis, 582
for penicilliosis, 582
for scedosporiosis, 582
for sepsis/septic shock, 68*t*
for sporotrichosis, 581
ampicillin
for actinomycosis, 481
for bacterial meningitis, 1024*t*, 1025*t*
for clostridial infections, 474*t*
for community-acquired pneumonia, 725*t*
for diverticulitis, 796–797
for enterococcal infections, 440
for Epstein-Barr virus infections, 528
for extraintestinal *E. coli* infections, 454
for *H. influenzae* infections, 449
for HACEK group infections, 453*t*
for infective endocarditis, 376, 377*t*, 378*t*, 379
for infective endocarditis prophylaxis, 381*t*
for listerial infections, 447
for *M. catarrhalis*, 452
for mixed anaerobic infections, 476*t*
for necrotizing fasciitis, 416*t*
for peritonitis, 382
for streptococcal infections, 438
for urinary tract infections, 778
ampicillin-clavulanate, for diverticulitis, 797
ampicillin-sulbactam
for animal bite infections, 116*t*, 415*t*
for cellulitis, 415*t*
for cholecystitis, 801
for epiglottitis, 254
for HACEK group infections, 453*t*
for health care–associated pneumonia, 727*t*
for human bite infections, 116*t*
for infective endocarditis, 378*t*
for myositis/myonecrosis, 418
for snakebite, 117*t*
amylase, serum, 804
amylase-creatinine clearance ratio, urinary, 804
amyloid angiopathy, 84*t*
amyloidosis, 873–875
AA (secondary), 873, 874*f*
AL (primary), 772–773, 773*t*, 873, 874*f*
autonomic involvement in, 991
classification of, 873
clinical manifestations of, 873–874
definition of, 873
diagnosis of, 874, 874*f*
familial, 873
glomerular disease in, 768*t*
treatment of, 875
amyotrophic lateral sclerosis (ALS), 984–988
clinical manifestations of, 985
familial, 984
laboratory testing in, 986
pathophysiology of, 985
treatment of, 987–988

ANA (antinuclear antibodies), 700, 736, 824, 825
anaerobic bacteria, 469
anaerobic infections, 469–477
  bone and joint, 476
  clostridial. *See* clostridial infections
  mixed, 474–477, 476*t*
  of mouth, head, and neck, 475
  pelvic, 475
  skin and soft tissue, 476
anagliptin, for diabetes mellitus, 908*t*
anagrelide, for essential thrombocytosis, 293
anakinra
  for fever of unknown origin, 129
  for gout, 864
  for rheumatoid arthritis, 847
anal cancer, 330, 414
anal condyloma, 798
anal fissure, 798
analgesia, 36
analgesic nephropathy, 772
analgesics, 38–39*t*
anaphylaxis, 114–115, 125
anaplasmosis, 122, 502*t*, 508
anaplastic large cell lymphoma, 294, 296*f*
anastrozole, for breast cancer, 321
ANCA (antineutrophil cytoplasmic autoantibodies), 762, 852
Ancylostoma braziliense infections, 600
Ancylostoma duodenale infections, 601
androgen abuse, 915
androgen deficiency
  approach to, 914*f*
  clinical manifestations of, 913
  etiology of, 912–913
  treatment of, 914–915
androgen deprivation, for prostate cancer, 343
androgen excess, in female, 920
anemia, 194. *See also specific types*
  blood loss and, 269
  in critical illness, 34
  drug-induced, 269, 272*t*
  in hypometabolic states, 270*t*
  hypoproliferative, 194, 267–269, 270*t*
  in inflammation, 270*t*, 271*t*
  microcytic, 268*f*, 269, 271*t*
  in parvovirus infections, 542
  physiologic classification of, 194, 195*f*
  refractory, 269, 292*t*
  in renal failure, 270*t*
  treatment of, 273–274
anemia of chronic disease, 268–269, 273
anesthetics, for delirium, 52*t*
aneurysm
  aortic, 693–694, 1090*t*
  intracranial, 84*t*, 91
  ventricular, 91
angina
  chronic stable. *See* chronic stable angina
  in myocardial ischemia, 138
  Prinzmetal's variant, 676
  recurrent, 667
  unstable. *See* unstable angina/non-ST-elevation myocardial infarction
angiodysplasia, 175, 178, 798
angioedema
  classification of, 836, 836*t*
  diagnosis of, 836–837
  etiology of, 150
  treatment of, 837
angiography, hepatobiliary, 186
angioma, senile, 256*f*
angiotensin receptor blockers (ARBs)
  for diabetic nephropathy, 766
  for dilated cardiomyopathy, 640
  for glomerulonephritis, 764
  for heart failure, 664, 688, 689*t*, 690*t*
  for hypertension, 651, 653*t*, 654*t*, 655*f*
  for slowing renal disease progression, 754
  for STEMI, 662, 667
  for UA/NSTEMI, 671
angiotensin-converting enzyme (ACE) inhibitors
  for aortic regurgitation, 638
  for chronic stable angina, 675
  for diabetic nephropathy, 766
  for dilated cardiomyopathy, 640
  for focal glomerulosclerosis, 765
  for heart failure, 664, 688, 689*t*, 690*t*, 692
  for hypertension, 651, 653*t*, 654*t*, 655*f*
  for membranous glomerulonephritis, 764
  for slowing renal disease progression, 754
  for STEMI, 662, 667
  for systemic sclerosis, 848
  for UA/NSTEMI, 671

anidulafungin, 569
animal bite, 415*t*, 417
anion gap, 15, 18*t*, 19, 22
anisocytosis, 265
anistreplase, for thrombotic disorders, 282
ankle-brachial index, 613, 697
ankylosing spondylitis, 854–857
  clinical manifestations of, 855–856
  definition of, 854–855, 855*t*
  diagnosis of, 856*t*, 857–858
  treatment of, 857
Ann Arbor staging system, for Hodgkin's disease, 304, 305*t*
annular skin lesion, 255
anomia, 239*t*
anorectal disease, 798
anorectal gonorrhea, 405
anorexia, in terminally ill patient, 54*t*
anorexia nervosa, 1079–1080
anosmia, 976
anosognosia, 82
ANS. *See* autonomic nervous system
antacids
  for erosive gastropathies, 788
  for indigestion, 161
  for peptic ulcer disease, 787
  for systemic sclerosis, 848
anterior ischemic optic neuropathy (AION), 230*f*, 231
antiarrhythmics, 683–684*t*
  for dilated cardiomyopathy, 641
  for hypertrophic cardiomyopathy, 643
  for pain, 39*t*, 40
  for tachyarrhythmia, 686
antibacterial therapy
  for acute renal failure, 751
  for bronchiectasis, 729
  for *C. difficile* infections, 398
  for campylobacteriosis, 395
  for cholera, 389
  for COPD, 721
  for cor pulmonale, 693
  for diverticular disease, 796–797
  for epididymitis, 400
  for febrile neutropenic patients, 365–366, 365*f*
  for HSCT patients, 366
  for infective endocarditis, 374, 376–378*t*, 378–380, 381*t*
  for intestinal pseudoobstruction, 797
  for intraabdominal abscess, 384–385
  for irritable bowel syndrome, 795
  for lung abscess, 730
  for peritonitis, 382–384
  resistance to, 361
  for salmonellosis, 394
  for shigellosis, 396
  for transplant recipients, 368
  for typhoid fever, 393
  for urethritis in men, 399–400
anticholinergics
  for asthma, 713–715
  for COPD, 720
  for diverticular disease, 797
  for dystonia, 237
  for irritable bowel syndrome, 795
  for nausea and vomiting, 160
  for Parkinson's disease, 980
  for vertigo, 228*t*
anticholinesterase drugs, for myasthenia gravis, 1052
anticoagulants
  for deep venous thrombosis, 732–733
  for dilated cardiomyopathy, 641
  for pulmonary embolism, 732–733
  for restrictive cardiomyopathy, 642
  for STEMI, 662
  for stroke, 87
  for stroke prevention, 89–90*t*, 90
  for thrombotic disorders, 281–282
  for UA/NSTEMI, 670
  for venous thromboembolism, 732–733
anticonvulsants
  for brain tumor, 1008
  for generalized anxiety disorder, 1068
  for migraine prevention, 220*t*
  for pain, 37, 39*t*, 40
  for polyneuropathy, 1044
  for status epilepticus, 102*f*, 103
  for subarachnoid hemorrhage, 92
antidepressants, 1071, 1074
  for Alzheimer's disease, 973–974
  for bulimia nervosa, 1080
  for chronic fatigue syndrome, 135
  for depression, 1064
  dosage and side effects, 1072–1073*t*
  for fibromyalgia, 868
  for irritable bowel syndrome, 795, 796*t*
  for narcolepsy, 244
  for pain, 37, 39*t*, 40
  for panic disorder, 1067
  for PTSD, 1069
  selective serotonin reuptake inhibitors, 1071, 1072*t*

antidepressants (*Cont.*):
for smoking cessation, 1103
tricyclic. *See* tricyclic antidepressants
withdrawal syndromes, 1074
antidiuretic hormone (ADH), 883
antiepileptic drugs, 961–966*t*, 967*t*
antifungal agents, 569–570
antigenic drift, 530
antigenic shift, 530
anti-glomerular basement membrane disease, 762–763
antihistamines
for allergic rhinitis, 838
for antivenom reaction, 119
for carcinoid tumor, 332
for cough, 148
for erythema multiforme, 263
for hymenoptera sting, 125
for nausea and vomiting, 160
for pityriasis rosea, 259
for scombroid poisoning, 122
for systemic mastocytosis, 839
for urticaria/angioedema, 837
for vertigo, 228*t*
antihypertensives
for aortic dissection, 695
for slowing renal disease progression, 754
antileukotrienes, for asthma, 714
anti-LKM antibodies, 825
antimalarials
for malaria prophylaxis, 590–591*t*
for malaria treatment, 588*t*
for psoriatic arthritis, 859
for SLE, 845
antimonial compounds, for leishmaniasis, 594
antineuronal antibodies, paraneoplastic, 352, 353*t*, 354*t*
antineutrophil cytoplasmic autoantibodies (ANCA), 762, 852
antinuclear antibodies (ANA), 700, 736, 825
antiphospholipid syndrome (APS), 849–850
antiplatelet agents
for membranoproliferative glomerulonephritis, 765
for myocardial infarction, 667
for STEMI, 662
for stroke, 87
for stroke prevention, 89–90
for thrombotic disorders, 283
antiprotozoal agents
for cryptosporidiosis, 393
for cystoisosporiasis, 392
for giardiasis, 391
antipsychotics
for Alzheimer's disease, 974
for bipolar disorder, 1066
dosage and side effects of, 1076–1077*t*
first-generation, 1074, 1076*t*
for schizophrenia, 1066–1067
second-generation, 1074, 1077*t*, 1078
antipyretics, 128
antiretroviral therapy, 559, 566–567
entry inhibitors, 559, 564*t*
initiation of, 557
integrase inhibitors, 559, 564–565*t*
nonnucleoside reverse transcriptase inhibitors, 559, 561–563*t*
nucleoside/nucleotide analogues, 559, 560–561*t*
protease inhibitors, 559, 563*t*
resistance testing for, 557
selection of, 559, 566*t*
antisocial personality disorder, 1070
antithrombotic drugs, for UA/NSTEMI, 670
antithymocyte globulin, for aplastic anemia, 274
antitoxin
botulism, 472
for diphtheria, 442
for tetanus, 470
α_1-antitrypsin deficiency, 720
antitussive agents, 148
antivenom
for snakebite, 119–120
sources of, 119
antiviral agents
for acute viral hepatitis, 814
for HSCT patients, 367–368
for transplant recipients, 368–369
for vasculitis, 854
antrectomy, 788*t*
anuria, 199
anxiety attack, 225
anxiety disorders, 1067–1070
anxiolytics, 1074
for delirium, 52*t*
dosage of, 1075*t*
for dyspnea, 51*t*
pharmacology of, 1075*t*
aorta
abdominal, 696
coarctation of, 630–631, 649
echocardiography of, 624, 626*t*

aortic aneurysm, 693–694
aortic dissection
  chest pain in, 138, 140*f*
  classification of, 694, 695*f*
  clinical manifestations of, 694
  diagnosis of, 694
  etiology of, 694
  treatment of, 695, 696*t*
aortic regurgitation (AR), 616*t*, 624*f*, 637–638
aortic stenosis (AS)
  clinical manifestations of, 636
  echocardiography in, 624*f*, 636
  etiology of, 636
  heart sounds in, 615*f*, 616*t*, 636
  treatment of, 636, 637*f*
aortic valve disease, antithrombotic therapy for, 89*t*
aortography, 694
aphasia, 239–240, 239*t*
aphthous stomatitis, 256*f*
apixaban, for thrombotic disorders, 282
aplastic anemia, 267, 277
aplastic crisis, in parvovirus infections, 542
apnea, 55*t*, 745
apo A-V deficiency, 937*t*
apo B-100, familial defective, 936, 937*t*
apo CII deficiency, 937*t*, 940
apomorphine, for Parkinson's disease, 980*t*
apraxia, 233
apremilast
  for psoriasis, 259
  for psoriatic arthritis, 859
aprepitant, for nausea and vomiting, 51, 160
APS (antiphospholipid antibody syndrome), 849–850
AR (aortic regurgitation), 616*t*, 624*f*, 637–638
arachnoiditis, lumbar adhesive, 210
ARBs. *See* angiotensin receptor blockers
Arcanobacterium haemolyticum infections, 443
ARDS. *See* acute respiratory distress syndrome
ARF. *See* acute renal failure
argatroban
  for heparin-induced thrombocytopenia, 280
  for thrombotic disorders, 282
arginine vasopressin (AVP), 1, 883
aripiprazole
  dosage and side effects of, 1077*t*
  for schizophrenia, 1067
armodafinil, 245
aromatase inhibitors, for breast cancer, 320, 321
arrhythmia
  bradyarrhythmias. *See* bradyarrhythmias
  serum magnesium and, 662
  in STEMI, 662–663
  syncope in, 222, 224*t*
  tachyarrhythmias. *See* tachyarrhythmias
arsenic trioxide, for AML, 287
artemether, for malaria, 588*t*
artemether-lumefantrine, for malaria, 588*t*
artemisinin derivatives, for malaria, 587, 588*t*
arterial blood gases (ABG), 708
  in acid-base disorders, 15, 20
  analysis of, in ICU, 34
arterial embolism, 697
arteriography
  for colonic angiodysplasia, 798
  coronary, 671, 673
  mesenteric, 175
arteriovenous fistula, dural, 84*t*
arteriovenous malformation, 1006, 1007*f*
  intracranial hemorrhage in, 84*t*
  subarachnoid hemorrhage in, 91
artesunate, for malaria, 587, 588–589*t*
arthritis. *See also specific types*
  in alphavirus infections, 550–551
  gonococcal, 406, 419
  infectious, 418–420
  in Lyme disease, 495, 496
  S. aureus, 430
  septic, 427
arthritis mutilans, 858
arthropathy, chronic, 865
arthropod bite/sting, 122–124
arthropod-borne viral diseases
  with arthritis and rash, 550–551
  encephalitis, 550
  with fever and myalgia, 548–550
  microbiology of, 548
  pathogenesis of, 548
  pulmonary, 551
  viral hemorrhagic fever, 551–552
arthroscopic therapy, for osteoarthritis, 862

AS. *See* aortic stenosis
5-ASA (5-aminosalicylic acid), for inflammatory bowel disease, 792
asbestos-related disease, 716
ascariasis, 600–601
ascites, 150, 187–189
  cirrhotic, 188
  complications of, 188–189
  fluid characteristics, 188*f*
  pancreatic, 807
  paracentesis in, 30–31
  primary bacterial peritonitis and, 382
  refractory, 188
  serum-ascites albumin gradient, 188*f*
ASD (atrial septal defect), 627–628
asenapine, 1077*t*
L-asparaginase, for ALL, 300
aspartate aminotransferase (AST), 183, 184*t*, 804
aspergilloma, 572, 574*t*
aspergillosis, 571–573
  clinical manifestations of, 572
  diagnosis of, 572–573
  disseminated, 572
  meningitis in, 1035*t*
  microbiology and epidemiology of, 571–572
  pulmonary, 572
  sinusitis, 572
  treatment of, 573, 574–575*t*
aspiration, of bone marrow, 266
aspirin
  for antiphospholipid antibody syndrome, 850
  for atrial fibrillation, 686
  for cardiovascular disease prevention, 1094
  for chronic stable angina, 675
  for colon cancer prevention, 1100
  for fever, 128
  for migraine, 217*t*
  for pain, 37, 38*t*
  for pericarditis, 645
  Reye's syndrome and, 532
  for rheumatoid arthritis, 846
  for STEMI, 659, 662, 667
  for stroke, 87
  for stroke prevention, 89–90
  for superficial thrombophlebitis, 698
  for tension-type headache, 218
  for thrombotic disorders, 283
  for UA/NSTEMI, 670, 671
assist-control mandatory ventilation (ACMV), 75*t*
assist-control ventilation, 74
assisted reproductive technology, 924
AST (aspartate aminotransferase), 183, 184*t*
asterixis, 238
asthma
  clinical evaluation of, 712
  cough in, 147
  definition and epidemiology of, 711–712
  differential diagnosis of, 713
  dyspnea in, 142
  intrinsic, 711
  occupational, 711, 716–718
  physical examination in, 712
  pulmonary function tests in, 712
  sleep disorders in, 242
  treatment for, 712–714, 714*f*
asthma exacerbations, 714–715
astrocytoma, 1009, 1009*f*
asymptomatic bacteriuria (ABU), 776, 778
asystole, 60, 60*f*
ataxia, 981–984
  approach to, 981, 983
  clinical manifestations of, 981
  diagnosis of, 984
  etiology of, 982*t*
  inherited, 983–984, 983*f*
  treatment of, 984
ataxia-telangiectasia, 842
atazanavir, for HIV infection, 563*t*
atenolol
  for hypertension, 652*t*
  for thyrotoxicosis, 890
atheroembolism, 697–698
atherosclerosis
  C. pneumoniae infections and, 513
  of peripheral arteries, 696–697
  prevention of complications of, 941–942
  risk factors for, 1092–1094, 1092*t*
athetosis, 237
ATL (adult T cell leukemia/lymphoma), 301
atorvastatin
  for dyslipidemia, 938*t*
  for STEMI, 667
  for UA/NSTEMI, 671
atovaquone
  for ANCA-associated glomerulonephritis, 762

for babesiosis, 592
for *Pneumocystis* infections, 584*t*
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
atovaquone-proguanil
for malaria, 588*t*
for malaria prophylaxis, 590*t*
atrial fibrillation
anticoagulants for stroke prevention in, 89*t*, 90
chronic, 686
clinical and ECG features of, 681*t*
atrial flutter, 681*t*
atrial premature beats, 680*t*
atrial septal defect (ASD), 627–628
atrial tachycardia, 680*t*, 681*t*
atrioventricular (AV) block
drug-induced, 678*t*
etiology of, 678*t*
first degree, 677, 679*f*
second degree, 677, 679*f*
in STEMI, 663
third degree (complete), 678, 679*f*
atrophy (skin lesion), 257*t*
atropine
for bradycardia, 60*f*, 659
for inflammatory bowel disease, 792
for tachyarrhythmias, 681–682*t*
atypical parkinsonism, 977, 977*t*
AUDIT (Alcohol Use Disorders Identification Test), 1082*t*
Auer rods, 266
auscultation, 614–615
autoantibody disorders, 48
autoimmune autonomic neuropathy, 991
autoimmune disease
leukopenia in, 276
thrombocytopenia in, 278
in women, 1105
autoimmune hemolysis, 274
autologous transfusion, 46
automated external defibrillator (AED), 57
autonomic dysfunction, paraneoplastic, 354
autonomic nervous system (ANS)
actions of, 988, 990*t*
anatomy of, 989*f*
testing of, 990–991
autonomic nervous system (ANS) disorders, 988–995
approach to, 988, 990–991
classification of, 992–993*t*
clinical manifestations of, 991
drug-induced, 988
treatment of, 994–995, 994*t*
autosomal dominant polycystic kidney disease (ADPKD), 773–774
AV block. *See* atrioventricular block
avascular necrosis (osteonecrosis), 869, 934
avoidant personality disorder, 1070
AVP (arginine vasopressin), 1, 883
5-azacytidine, for myelodysplastic syndromes, 289
azathioprine
for ANCA-associated glomerulonephritis, 762
for autoimmune hepatitis, 825
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for polyneuropathy, 1046
for reactive arthritis, 860
for SLE, 845
for vasculitis, 854
azelastine, for allergic rhinitis, 838
azidothymidine. *See* zidovudine
azithromycin
for adult inclusion conjunctivitis, 515
for babesiosis, 592
for *Bartonella* infections, 467*t*
for *C. pneumoniae* infections, 513
for campylobacteriosis, 395
for chancroid, 413
for cholera, 389
for community-acquired pneumonia, 725*t*
for COPD exacerbation prophylaxis, 721
for donovanosis, 413
for endemic treponematosis, 497
for gonococcal infections, 406*t*
for *H. influenzae* infections, 449
for infective endocarditis prophylaxis, 381*t*
for *Legionella* infections, 512–513
for leptospirosis, 498
for *M. catarrhalis*, 452
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 1025
for nontuberculous mycobacterial infections, 494
for otitis media, 252*t*

azithromycin (*Cont.*):
for pertussis, 451
for pneumococcal infections, 424
for scrub typhus, 507
for shigellosis, 396
for typhoid fever, 393
for urethritis in men, 399
azoles
for candidiasis, 262, 571
pharmacology of, 569
for scedosporiosis, 582
azotemia, 197–199, 198*f*, 198*t*. *See also* acute renal failure
AZT. *See* zidovudine

B
B cell deficiency, 843
B cell receptors, defective rearrangements of, 840
B cells, 189
babesiosis, 122, 592
Babinski sign, 233*t*, 951
bacillary angiomatosis, 415*t*, 467*t*, 468
bacillary peliosis, 467*t*, 468
bacille Calmette-Guérin (BCG), 334, 490
Bacillus cereus infections, 387
back pain. *See also* low back pain
in ankylosing spondylitis, 855
in cancer patient, 111*f*
baclofen
for dystonia, 237
for multiple sclerosis, 1019
bacteremia
clostridial, 473
E. coli, 454
Klebsiella, 456
listerial, 446–447
P. aeruginosa, 459, 460*t*
S. aureus, 427
streptococcal, 437, 439
bacterial food poisoning, 386–389, 388*f*
bacterial infections. *See also specific bacteria and diseases*
chronic meningitis in, 1033–1034*t*
in HSCT patients, 366
lymphadenopathy and, 190*t*
bacterial vaginosis, 401
bacteriuria, asymptomatic, 776, 778
Bacteroides fragilis infections, 474, 475
BAL (bronchoalveolar lavage), 710
Balkan endemic nephropathy (BEN), 772
balloon dilatation, for esophageal disorders, 164
balloon tamponade, for esophageal varices, 832
barbiturate coma, 95*t*
bariatric surgery, 902–903, 903*f*
barium contrast study, 170
barium enema, 328, 330
barium radiography, for GI bleeding, 175
barium swallow, 162, 165, 323
Barmah Forest virus infections, 551
barotrauma, 76
Barrett's esophagus, 161, 322
barrier contraception, 922
Bartonella infections, 466–469, 467*t*
bacillary angiomatosis, 468
bacillary peliosis, 468
Carrión's disease, 468–469
cat-scratch disease, 467–468
endocarditis, 378*t*, 468
trench fever, 468
basal cell carcinoma (BCC), 256*f*, 307
basal energy expenditure (BEE), 40, 41*f*
basic life support (BLS), 57–58, 58*f*, 59*f*, 60*f*
basophilia, 276
basophilic stippling, 265
BCG (bacille Calmette-Guérin), 334, 490
Becker dystrophy, 1054
beclomethasone, for allergic rhinitis, 838
bee sting, 124–125
beer potomania, 2
Behçet's syndrome, 1039*t*
belimumab, for SLE, 845
Bell's palsy, 517, 997
Belsey procedure, 161
BEN (Balkan endemic nephropathy), 772
benign paroxysmal positional vertigo (BPPV), 227, 227*t*, 228*t*, 229
benserazide/levodopa, for Parkinson's disease, 980*t*
bentiromide test, 170
benzathine penicillin
for diphtheria, 442
for endemic treponematosis, 497
for pharyngitis, 253
for rheumatic fever prophylaxis, 632
for streptococcal infections, 436*t*
for syphilis, 411*t*
benzene derivative poisoning, 815
benznidazole, for Chagas' disease, 595

benzodiazepines
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
for fibromyalgia, 868
for generalized anxiety disorder, 1068
for panic disorder, 1067
sleep disorders with, 242
for tetanus, 470
for vertigo, 228*t*
benzonatate, for cough, 148
benzoyl peroxide, for acne, 262
berylliosis, 717
beta agonists
for asthma, 713–715
for COPD, 720, 721
beta blockers
for aortic dissection, 695, 696*t*
for atrial fibrillation, 686
for chronic stable angina, 674
for dilated cardiomyopathy, 640
for esophageal varices, 832
for heart failure, 688, 689*t*, 690, 690*t*, 692
for hypertension, 651, 652*t*, 654*t*
for hypertrophic cardiomyopathy, 643
for migraine prevention, 220*t*
for mitral stenosis, 632
for mitral valve prolapse, 636
for sinus tachycardia, 663
for STEMI, 661–662, 667
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for thyrotoxicosis, 890
for toxic multinodular goiter, 893
for UA/NSTEMI, 670, 671
for Wolff-Parkinson-White syndrome, 686
beta-carotene, for erythropoietic protoporphyria, 945
beta-lactams
for *Corynebacterium* infections, 443
for enterococcal infections, 440
for HACEK group infections, 453*t*
for *P. aeruginosa* infections, 459, 460*t*
for pneumococcal infections, 424
for staphylococcal infections, 430, 431*t*
for urinary tract infections, 777*t*, 778
bethanechol, for bladder hyporeflexia, 1019
bevacizumab
for cervical cancer, 341
for colorectal cancer, 328
for renal cancer, 335
BFM regimen, for Burkitt's lymphoma/leukemia, 301
bicarbonate, renal retention of, 20
bicarbonate therapy
for metabolic acidosis, 20
for renal tubular acidosis, 775
for tumor lysis syndrome, 113
bicuspid aortic valve, congenital, 630
biguanides, for diabetes mellitus, 908*t*
bilastine, for allergic rhinitis, 838
bile ducts, diagnostic evaluation of, 800*t*
bile salt deficiency, 173*t*
biliary colic, 801
bilirubin, serum, 804
conjugated fraction (direct), 179
unconjugated fraction (indirect), 179
binge eating disorder, 1079
Binswanger's disease (diffuse white matter disease), 974, 975*f*
biopsy
bone marrow, 266–267
liver, 186
lung, 737
pleural, 710
prostate, 343, 344*f*
sentinel node, 320
skin, 256
bioterrorism, 361
bipolar disorder, 1065–1066
bisacodyl, for constipation, 50*t*
bismuth subsalicylate, for *H. pylori* eradication, 787*t*
bisoprolol, for heart failure, 690*t*
bisphosphonates
actinomycosis and, 479
for breast cancer, 321
for hypercalcemia, 351
for osteoporosis, 934
for primary biliary cirrhosis, 829
for prostate cancer, 345
bite
arthropod, 122–124
mammalian, 115, 116*t*, 118
snakebite, 117*t*, 118
wound infection from, 116–117*t*
bivalirudin
for STEMI, 662
for UA/NSTEMI, 670

bladder
  cancer, 333–334
  hyper/hyporeflexia in multiple sclerosis, 1019
  pain, 246
Blakemore-Sengstaken tube, for esophageal varices, 832
blastomycosis, 580–582, 1035*t*
bleeding disorders, 277–281
  blood vessel wall defects, 279
  coagulation disorders, 279–280
  platelet disorders, 277–278
  treatment of, 280–281
bleomycin, for testicular cancer, 336
blepharospasm, 997
blood loss
  anemia and, 194
  anemia in, 269
  symptoms of, 174
blood smear, 265–266
  erythrocyte abnormalities, 265
  leukocyte abnormalities, 266
  platelet abnormalities, 266
blood urea nitrogen (BUN), 197
blood vessel wall defects, 279
BLS (basic life support), 57–58, 58*f*, 59*f*, 60*f*
blue toe syndrome, 697
BNP. *See* B-type natriuretic peptide
body louse, 610–611
body mass index (BMI), 41, 901
body temperature, 127
bone density testing, 933, 934*t*
bone disease
  neck pain in, 212
  osteoporosis. *See* osteoporosis
bone infections
  anaerobic, 476
  osteomyelitis. *See* osteomyelitis
  P. aeruginosa, 459, 460*t*
  septic arthritis, 418–420, 427, 430
  in tuberculosis, 484
bone marrow
  cellularity of, 267
  damage causing anemia, 268
  erythroid:granulocytic ratio, 267
  examination of, 194, 266–267
bone marrow aspirate, 266–267
bone marrow failure, 277
bone marrow transplant. *See* hematopoietic stem cell transplant (HSCT)
bone metastasis, osteoblastic, in men, 348
borderline personality disorder, 1070
Bordetella pertussis infections. *See* pertussis
Bornholm disease, 544
Borrelia burgdorferi infections. *See* Lyme borreliosis
Borrelia miyamotoi infections, 499
Borrelia recurrentis infections, 498–499
bortezomib, for multiple myeloma, 302
bosentan
  for pulmonary hypertension, 702
  for systemic sclerosis, 848
botulinum toxin
  for achalasia, 164
  for anal fissures, 798
  for dystonia, 237
  for hemifacial spasm or blepharospasm, 998
botulism, 471–472, 991, 1050
bounding (hyperkinetic) pulse, 613, 614*f*
Bowen's disease, 308
BPPV (benign paroxysmal positional vertigo), 227, 227*t*, 228*t*, 229
brachial neuritis, acute, 212–213
brachial plexus, injury to, 212–213
bradyarrhythmias
  approach to, 60, 60*f*
  in AV block, 677–678, 678*t*
  in sinoatrial node dysfunction, 677
  in STEMI, 663
bradycardia, 677
bradykinesia, 233, 236
brain abscess, 478, 1020, 1029–1030
brain death, 81–82
brain herniation, 94, 94*f*
brain mass, in cancer patients, 364
brain metastasis, 1001*t*, 1010–1011
brain tumor, 971
  approach to, 1008
  headache in, 215*t*
  intracranial, 1009–1010
  metastatic, 84*t*
  treatment of, 1008
brainstem encephalitis, 353
brainstem lesion, 234*t*
BRCA genes, 317, 321, 338, 1100
break-bone fever, 550
breast cancer, 316–321
  in axillary lymph node, 348
  diagnosis of, 317–318, 317*f*
  epidemiology of, 316
  genetic factors in, 317
  incidence of, 316
  infections in, 363*t*

metastatic, 321
oncologic emergencies, 110–111
paraneoplastic syndromes in, 349*t*, 353*t*, 354*t*
prevention of, 321, 1100
prognosis of, 320*t*
risk factors for, 1099
screening for, 1089–1090*t*, 1091*t*, 1095, 1096*t*
staging of, 318–320, 319–320*t*
treatment of, 320–321
breast mass, approach to, 317–318, 317*f*
Brenner tumor, 338
Brill-Zinsser disease, 506
Broca's aphasia, 239*t*, 240
bromocriptine
for acromegaly, 881
for hyperprolactinemia, 880
bronchiectasis, 727–729
bronchitis, hemoptysis in, 148
bronchoalveolar lavage (BAL), 710
bronchodilators
for asthma, 713
for bronchiectasis, 729
for COPD, 720, 721
for cor pulmonale, 693
bronchoscopy, 149, 149*f*, 710
Brown-Séquard syndrome, 235*t*, 1002
brucellosis, 462–464, 463*t*, 1034*t*
Brugada syndrome, 679
Brugia infections. *See* filariasis
Bruton's tyrosine kinase gene, 843
B-type natriuretic peptide (BNP)
in dilated cardiomyopathy, 640
in heart failure, 688
bubonic plague, 465–466
Budd-Chiari syndrome, 188*f*
bulimia nervosa, 1079, 1080
bullae (skin lesion), 257*t*, 416
bumetanide
for edema, 153*t*
for heart failure, 690*t*
for hypertension, 655
BUN (blood urea nitrogen), 197
bundle branch block
left, 619*f*, 621*t*
right, 619*f*
bundled interventions, 358, 359*t*
buprenorphine
abuse, 1084
for opioid maintenance, 1086
bupropion
as antidepressant, 1071
dosage and side effects of, 1073*t*
for smoking cessation, 720, 1103
Burkholderia cepacia infections, 461*t*, 462
Burkholderia mallei infections, 461*t*, 462
Burkholderia pseudomallei infections, 461*t*, 462
Burkitt's lymphoma/leukemia, 294, 296*f*, 300–301, 528
burn patient, neutrophilia in, 274
bursitis, 869
buspirone
as anxiolytic, 1074
dosage and action of, 1075*t*
for generalized anxiety disorder, 1068
butorphanol
for migraine, 218*t*
for pain, 39*t*
byssinosis, 717

C

cabazitaxel, for prostate cancer, 343
cabergoline
for acromegaly, 881
for hyperprolactinemia, 880
CABG (coronary artery bypass grafting), 664, 671, 676, 676*t*
cabozantinib, for renal cancer, 335
CAD (coronary artery disease), 627*f*. *See also* chronic stable angina
caffeine, for migraine, 217*t*
calamine lotion, for insect stings, 125
calcipotriol, for psoriasis, 259
calcitonin, for hypercalcemia, 351, 927*t*
calcitriol
for hypoparathyroidism, 929
for osteomalacia, 935
calcium antagonists, for tetanus, 470
calcium apatite deposition disease, 866–867, 866*t*
calcium carbonate, for hyperphosphatemia, 754
calcium channel blockers
for atrial fibrillation, 686
for chronic stable angina, 674–675
for hypertension, 651, 653*t*, 654*t*
for mitral stenosis, 632
for pulmonary hypertension, 702
for systemic sclerosis, 848
for vasospastic disorders, 698
calcium docusate, for constipation, 50*t*
calcium gluconate
for GI bleeding, 178
for hypocalcemia, 929
for muscle spasms, 120

calcium oxalate deposition disease, 867
calcium oxalate stones, 780, 781*t*
calcium phosphate stones, 780, 781*t*
calcium polycarbophil, for irritable bowel syndrome, 796*t*
calcium pyrophosphate dihydrate (CPPD) deposition disease, 865–866
calcium therapy
  for colon cancer prevention, 1100
  for hyperkalemia, 16*t*
  for hypermagnesemia, 930
  for hypocalcemia, 929
  for hypoparathyroidism, 929
  for osteoporosis, 934
  for primary biliary cirrhosis, 829
  for primary sclerosing cholangitis, 803
calicivirus infections, 389–390
Calvert formula, 339
campylobacteriosis, 394–395, 403
canagliflozin, for diabetes mellitus, 909*t*
cancer. *See also specific types and sites*
  depression in, 1064
  fatigue in, 133*t*
  hemoptysis in, 148
  infections in patients with, 362–366, 363*t*, 365*f*
  leukocytosis in, 275
  meningitis in, 1038*t*
  neck pain in, 212
  nervous system metastases in, 1011*t*, 1012
  oncologic emergencies, 109–113
  paraneoplastic syndromes
    endocrine, 348–351
    neurologic, 352–355, 352*t*
  prevention of, 1095*t*
  screening for, 1088–1090*t*, 1095–1096
  spinal cord compression in, 98–99
  vaccination of patients with, 369–370*t*, 369–371
  warning signs of, 1101
  weight loss with, 135
cancer chemotherapy
  leukopenia and, 276
  nausea and vomiting in, 160
cancer of unknown primary site (CUPS), 345–348
  biopsy in, 346–347*t*
  clinical manifestations of, 345
  cytogenetics in, 346–347*t*
  cytokeratin markers in, 347*f*
  histology of, 346*t*, 347
  prognosis for, 347
cancrum oris, 475
candesartan
  for heart failure, 690*t*
  for hypertension, 653*t*
  for migraine prophylaxis, 220*t*
  for STEMI, 662
candidiasis, 570–571
  in cancer patients, 364
  in catheter-associated urinary tract infections, 778
  cutaneous, 258, 262
  deeply invasive, 570–571
  esophageal, 166
  meningitis in, 1035*t*
  microbiology and epidemiology of, 570
  mucocutaneous, 570
  prevention of, 571
  treatment of, 262
  vulvovaginal, 262, 400–401, 570
CAP. *See* community-acquired pneumonia
CAPD-associated peritonitis, 383–384
capecitabine
  for breast cancer, 321
  for gastric carcinoma, 323
  for pancreatic cancer, 331
capillary telangiectasia, 84*t*
Capnocytophaga canimorsus infections, 115, 116*t*
capsaicin cream
  for osteoarthritis, 862
  for polyneuropathy, 1044, 1045*t*
capsulitis, adhesive, 870
captopril
  for heart failure, 688, 690*t*
  for hypertension, 653*t*
  for STEMI, 662, 667
carbamazepine
  for bipolar disorder, 1066
  dosage and side effects of, 1078*t*
  for glossopharyngeal neuralgia, 1000
  for multiple sclerosis, 1019
  for pain, 37, 39*t*
  for polyneuropathy, 1045*t*
  for seizures, 967*t*
  for trigeminal neuralgia, 995
carbapenems
  for *Aeromonas* infections, 458
  for enteric GNB infections, 458
  for extraintestinal *E. coli* infections, 454

for *Klebsiella* infections, 456
for nontuberculous mycobacterial infections, 494
for *P. aeruginosa* infections, 460*t*
carbidopa/levodopa, for Parkinson's disease, 978, 980*t*
carbidopa/levodopa/entacapone, for Parkinson's disease, 980*t*
carbimazole, for thyrotoxicosis, 890
carbohydrate requirements, 41
carbon monoxide poisoning, 100, 717
carbon tetrachloride poisoning, 815
carboplatin
for bladder cancer, 334
for head and neck cancer, 309
for ovarian cancer, 339
carbuncle, 427
carcinoid syndrome, 331, 332*t*
carcinoid tumor, 331–332, 349*t*
carcinomatosis, peritoneal, in women, 348
cardiac arrest, 57–60
follow-up of, 60
management of, 57–60, 58*f*, 59*f*, 60*f*
cardiac biomarkers
in STEMI, 658
in UA/NSTEMI, 688
cardiac catheterization
in cardiac tamponade, 647
in cardiomyopathy, 641*t*, 642
in constrictive pericarditis, 648
in pulmonary hypertension, 700
cardiac tamponade, 645, 647
Cardiobacterium hominis infections, 452, 453*t*
cardiogenic shock
approach to, 32, 33*f*
characteristics of, 62*t*
etiology of, 61*t*
treatment of, 64, 664, 665*t*, 666*f*
cardiomyopathy, 639–643
clinical and laboratory features of, 640*t*
dilated, 639–642
hypertrophic. *See* hypertrophic cardiomyopathy
restrictive, 640*t*, 642, 648*t*
cardiopulmonary resuscitation, 57–60, 58*f*
cardiorenal syndrome, 749
cardiovascular disease. *See* heart disease
carnitine palmitoyltransferase deficiency, 1059
carotene, serum, 178
carotid artery pulse, 613, 614*f*
carotid endarterectomy, 90–91
carotid stenosis, 90–91
carpal tunnel syndrome, 1046, 1047*t*
Carrión's disease, 468–469
carvedilol
for heart failure, 688, 690*t*
for hypertension, 652*t*
CASPAR criteria, for psoriatic arthritis, 858*t*
caspofungin
for aspergillosis, 574*t*
for *Candida* esophagitis, 166
pharmacology of, 569
for sepsis/septic shock, 68*t*
cast nephropathy, 772–773, 773*t*
Castleman's disease, 525
cat bite, 115, 116*t*, 417
cataplexy, 225, 243, 244*t*
catfish envenomation, 120–121
catheter-related infections
in cancer patients, 362, 364
urinary tract, 778
cat-scratch disease, 115, 467–468, 467*t*
cauda equina syndrome, 209, 1004
causalgia, 36, 994
cavernous angioma, 84*t*
cavernous sinus, 1001*f*
cavernous sinus syndrome, 1001–1002
CBT. *See* cognitive behavioral therapy
CD (Crohn's disease), 791. *See also* inflammatory bowel disease
CD40 ligand deficiency, 843
cefazolin
for cellulitis, 415*t*
for infective endocarditis, 377*t*
for infective endocarditis prophylaxis, 381*t*
for peritonitis, 383
for staphylococcal infections, 431*t*
for streptococcal infections, 431*t*, 439
cefdinir, for otitis media, 252*t*
cefepime
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 727*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for sepsis/septic shock, 68*t*

cefixime, for gonococcal infections, 406*t*, 407*t*
cefotaxime
for bacterial meningitis, 1024*t*, 1025*t*
for bacterial peritonitis, 188
for brain abscess, 1030
for community-acquired pneumonia, 725*t*
for gonococcal infections, 406*t*, 407*t*
for *H. influenzae* infections, 449
for infectious arthritis, 420
for leptospirosis, 498
for Lyme borreliosis, 496
for meningococcal infections, 445
for nocardiosis, 479
for peritonitis, 382
for pneumococcal infections, 424
for sepsis/septic shock, 68*t*
cefotetan
for gonococcal infections, 406*t*
for pelvic inflammatory disease, 403, 407*t*
cefoxitin
for animal bite infections, 415*t*
for clostridial infections, 474*t*
for gas gangrene, 416*t*
for gonococcal infections, 406*t*
for human bite infections, 116*t*
for nontuberculous mycobacterial infections, 494
for pelvic inflammatory disease, 403
cefpodoxime, for community-acquired pneumonia, 725*t*
ceftaroline, for staphylococcal infections, 431*t*, 432*t*
ceftazidime
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for febrile neutropenia in cancer patient, 113
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for melioidosis, 461*t*
for neutropenia, 287
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for peritonitis, 383
ceftizoxime, for gonococcal infections, 406*t*
ceftriaxone
for bacterial meningitis, 1024*t*, 1025*t*
for *Bartonella* infections, 467*t*
for brain abscess, 1030
for brucellosis, 464
for chancroid, 413
for community-acquired pneumonia, 725*t*
for epididymitis, 400
for gonococcal infections, 406*t*, 407*t*
for *H. influenzae* infections, 449
for HACEK group infections, 453*t*
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for infective endocarditis, 376–378*t*, 379
for infective endocarditis prophylaxis, 381*t*
for leptospirosis, 498
for Lyme borreliosis, 496
for meningococcal infections, 445
for meningococcal prophylaxis, 1025
for nocardiosis, 479
for osteomyelitis, 421*t*
for otitis media, 252*t*
for pelvic inflammatory disease, 403, 406t
for peritonitis, 382
for pneumococcal infections, 424
for proctitis, proctocolitis, enterocolitis, and enteritis, 405
for sepsis/septic shock, 68*t*
for shigellosis, 396
for typhoid fever, 393
for urethritis in men, 399
for Whipple's disease, 482
cefuroxime
for community-acquired pneumonia, 725*t*
for Lyme borreliosis, 496
for otitis media, 252*t*
celecoxib
for colon cancer prevention, 1100
for pain, 38*t*
celiac arteriography, 832
cellulitis
auricular, 249
in cancer patients, 362, 363*t*
clinical manifestations of, 417
clostridial, 473
diagnosis of, 436
E. coli, 454
Klebsiella, 456
microbiology of, 417
Nocardia, 478, 480*t*
pathogenesis of, 417
streptococcal, 436, 436*t*
treatment of, 415*t*

central catheter, clotted, 110
central nervous system (CNS) infections
after HSCT, 367*t*
approach to, 1020, 1021–1022*f*
brain abscess, 478, 1020, 1029–1030
in cancer patients, 364
cryptococcal, 572
encephalitis. *See* encephalitis
listerial, 446
meningitis. *See* meningitis
P. aeruginosa, 459, 460*t*
progressive multifocal leukoencephalopathy, 1030–1031
toxoplasmosis, 597
central pontine myelinolysis, 4
central sleep apnea (CSA), 243, 746
central venous catheter infections, 359*t*, 360
cepacia syndrome, 462
cephalexin
for infective endocarditis prophylaxis, 381*t*
for staphylococcal infections, 433*t*
for streptococcal infections, 436
cephalosporins
for *Aeromonas* infections, 458
for cholecystitis, 801
for epiglottitis, 254
for extraintestinal *E. coli* infections, 454
for *H. influenzae* infections, 449
for infectious arthritis, 420
for *M. catarrhalis*, 452
for meningococcal infections, 445
for necrotizing fasciitis, 416*t*
for peritonitis, 382–383
for pneumococcal infections, 424
for *Proteus* infections, 457
for salmonellosis, 394
for staphylococcal infections, 430
for urinary tract infections, 778
cerebellar degeneration, paraneoplastic, 352*t*, 353*t*, 354
cerebral angiography, 91
cerebral aspergillosis, 572
cerebral herniation, 94, 94*f*
cerebral palsy, 237
cerebral perfusion pressure (CPP), 93
cerebral salt wasting, 92
cerebritis, 1020, 1029
cerebrospinal fluid analysis
in bacterial meningitis, 1023, 1023*t*
in chronic meningitis, 1032
lumbar puncture, 28–30
lumbar puncture for, 29*f*
in viral meningitis, 1026–1027
Cernunnos deficiency, 840
certolizumab
for psoriatic arthritis, 858
for rheumatoid arthritis, 46
ceruloplasmin, serum, 946
Cervarix, 414
cervical angina syndrome, 212
cervical cancer, 340–341
clinical manifestations of, 414
incidence and epidemiology of, 340–341
paraneoplastic syndromes in, 349*t*
prevention of, 341, 414, 1101
risk factors for, 1101
screening for, 341, 1091*t*, 1096–1097*t*
staging and prognosis in, 339*t*, 340
cervical intraepithelial neoplasia, 1101
cervical lymph node metastasis, 348
cervical spine disease, pain in, 139*f*, 141, 212
cervicitis, mucopurulent, 401–402
cestode infections, 606–610
cetirizine
for allergic rhinitis, 838
for urticaria/angioedema, 837
cetuximab
for colorectal cancer, 328
for head and neck cancer, 309
cevimeline, for Sjögren's syndrome, 849
CFS (chronic fatigue syndrome), 134–135, 134*t*, 1064
Chagas' disease, 594–595
chagoma, 594
chancre, syphilitic, 409
chancroid, 404*t*, 413
channelopathy, 1059–1060
Charcot's joint, 867
Charcot's triad, 802
chelation therapy
for hemochromatosis, 944
for Wilson's disease, 946
chest pain, 137–141
in ankylosing spondylitis, 856
approach to, 141
causes of, 137–141, 138*t*
differential diagnosis of, 139*f*, 140*f*
noncardiac, 164
in STEMI, 658
chest wall disease, 138*t*, 143
chest wall pain, 139*f*, 141

chest x-ray (CXR)
in aortic disease, 694
in cardiac tamponade, 647
in cardiomyopathy, 641*t*
in congenital heart disease, 628–630
in cor pulmonale, 692
in heart failure, 687
in hemoptysis, 149, 149*f*
indications for, 23
in interstitial lung disease, 736
in mitral stenosis, 632
normal, 24*f*
in pericarditis, 645
in pneumonia, 724
in pulmonary edema, 144
in pulmonary embolism, 731
in pulmonary hypertension, 700
in respiratory disease, 709
in superior vena cava syndrome, 110
utility of, 23
Cheyne-Stokes respiration, 55*t*, 81
chickenpox, 361, 523
Chikungunya virus infections, 550
Child-Pugh classification, of cirrhosis, 827*t*
Chinese herbal nephropathy, 772
chlamydial infections
adult inclusion conjunctivitis, 514–515
C. pneumoniae, 513
cervicitis, 401–402
clinical manifestations of, 408
diagnosis of, 408
epidemiology of, 408
epididymitis, 400
microbiology of, 408
pelvic inflammatory disease, 402–403
proctitis, proctocolitis, enterocolitis, and enteritis, 403, 405
psittacosis, 515–516
trachoma, 514–515
treatment of, 408
urethritis, 400
vulvovaginal infections, 400–401
chloramphenicol
for anaerobic infections, 476*t*
for *Bartonella* infections, 467*t*
for plague, 466
for Rocky Mountain spotted fever, 504
for scrub typhus, 507
for tick-borne spotted fevers, 505
chlordiazepoxide
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
chloroquine
for inflammatory bowel disease, 794
for malaria, 588*t*
for malaria prophylaxis, 590*t*
for porphyria cutanea tarda, 945
for Whipple's disease, 482
chlorpheniramine
for allergic rhinitis, 838
for urticaria/angioedema, 837
chlorpromazine
for delirium, 52*t*
dosage and side effects of, 1076*t*
for migraine, 218*t*
for tetanus, 470
chlorthalidone, for hypertension, 652*t*
cholangiography, 186, 800*t*
cholangiopancreatography, 800*t*, 802
cholangitis, 802–803
cholecystectomy, 800, 801, 803
cholecystitis, 801–802
choledocholithiasis, 802–803
cholelithiasis, 799–800, 800*t*
cholera, 387, 389
cholestasis, liver function tests in, 184*t*
cholesterol, 936. *See also* hypercholesterolemia
cholesterol gallstones, 799
cholestyramine
for acute viral hepatitis, 814
for dyslipidemia, 938*t*
for erythropoietic protoporphyria, 945
for irritable bowel syndrome, 795, 796*t*
for nephrolithiasis, 781*t*
for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for toxic and drug-induced hepatitis, 815
cholinesterase inhibitors, for Alzheimer's disease, 973
chondrocalcinosis, 865
CHOP regimen
for aggressive lymphoma, 299
for follicular lymphoma, 298
for gastric carcinoma, 324
choreoathetosis, 237
choriocarcinoma, 336, 349*t*
chorioretinitis, in toxoplasmosis, 597
chronic, 802
chronic fatigue syndrome (CFS), 134–135, 134*t*, 1064
chronic interstitial nephritis, 772
chronic kidney disease (CKD)
classification of, 198*t*

differential diagnosis of, 752–753
epidemiology of, 752
etiology of, 752*t*
laboratory testing in, 753
renal transplantation for. *See* renal transplantation
slowing progression of, 754
treatment of, 753–754
uremic syndrome in, 753
chronic low back pain (CLBP), 211. *See also* low back pain
chronic lymphocytic leukemia (CLL)
clinical manifestations of, 296–297
staging of, 296–297, 297*t*
treatment of, 297
chronic lymphoid leukemia/lymphoma, 295*t*, 296*f*
chronic myeloid leukemia (CML), 287–289
clinical manifestations of, 287–288
incidence of, 287
natural history of, 288
response criteria for, 288*t*
treatment of, 288–289
chronic obstructive pulmonary disease (COPD), 718–722
clinical manifestations of, 719
dyspnea in, 142
H. influenzae infection in, 448–449
M. catarrhalis infections in, 451–452
pulmonary function tests in, 718*t*, 719–720
sleep disorders in, 242
treatment of, 720–721
chronic progressive external ophthalmoplegia (CPEO), 1057, 1059
chronic pulmonary aspergillosis, 572
chronic stable angina
clinical manifestations of, 672
imaging in, 673
laboratory testing in, 672
physical examination in, 672
stress testing in, 672, 673*f*, 674*t*
treatment of, 674–676, 675*t*, 676*t*
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis), 851
Chvostek's sign, 928
ciclopirox olamine, for dermatophyte infections, 262
cidofovir
for adenovirus infections, 537
for cytomegalovirus infections, 527
for HSV infections, 522*t*
for viral encephalitis, 1029
ciguatera poisoning, 121
cilostazol, for peripheral arteriosclerosis, 697
cimetidine
for antivenom reaction, 119
for erosive gastropathies, 788
ciprofloxacin
for *Aeromonas* infections, 458
for animal bite infections, 116*t*, 415*t*
for *Bartonella* infections, 467*t*
for chancroid, 413
for cholecystitis, 801
for cholera, 389
for clostridial infections, 474*t*
for community-acquired pneumonia, 725*t*
for diverticulitis, 796
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for inflammatory bowel disease, 794
for intestinal pseudoobstruction, 797
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 446
for murine typhus, 506
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460–461*t*
for perichondritis, 250
for peritonitis prevention, 382
for plague, 466
for Q fever, 510
for sepsis/septic shock, 68*t*
for shigellosis, 396
for staphylococcal infections, 430
for tick-borne spotted fevers, 505
for tuberculosis, 486
for typhoid fever, 393
for urinary tract infections, 778
circadian rhythm disorder, 241
circadian rhythm sleep disorders, 245
circulatory overload, 46
cirrhosis
ascites in, 187, 188*f*
Child-Pugh classification of, 827*t*
clinical manifestations of, 826
complications of, 827, 827*t*
definition of, 826
edema in, 151, 152
etiology of, 826*t*
liver function tests in, 184*t*
primary bacterial peritonitis in, 382
primary biliary, 828–829

cisplatin
for bladder cancer, 334
for cervical cancer, 341
for endometrial cancer, 340
for esophageal carcinoma, 322
for gastric cancer, 323
for head and neck cancer, 309
for lung cancer, 313, 315
for ovarian cancer, 339
for testicular cancer, 336
citalopram, 1072*t*
citrate therapy
for nephrolithiasis, 782*t*
for renal tubular acidosis, 775
Citrobacter infections, 457
CJD (Creutzfeldt-Jakob disease), 970*t*, 971, 975
CKD. *See* chronic kidney disease
cladribine, for follicular lymphoma, 298
clarithromycin
for community-acquired pneumonia, 725*t*
for *H. influenzae* infections, 449
for *H. pylori* eradication, 787*t*
for infective endocarditis prophylaxis, 381*t*
for *Legionella* infections, 512–513
for *M. catarrhalis*, 452
for nontuberculous mycobacterial infections, 494
for pertussis, 451
claudication, intermittent, 696
claustrophobia, 1069
clenched-fist injury, 116*t*, 118
clindamycin
for actinomycosis, 481
for animal bite infections, 116*t*, 415*t*
for asymptomatic GAS carriage, 435
for babesiosis, 592
for bacterial vaginosis, 401
for cellulitis, 415*t*
for clostridial infections, 474*t*
for *Corynebacterium* infections, 443
for diphtheria, 442
for gas gangrene, 416*t*
for infective endocarditis prophylaxis, 381*t*
for lung abscess, 730
for malaria, 588*t*
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for otitis media, 252*t*
for pelvic inflammatory disease, 403, 407*t*
for pneumococcal infections, 424
for *Pneumocystis* infections, 584*t*
for sepsis/septic shock, 68*t*
for sinusitis, 249*t*
for snakebite, 117*t*
for staphylococcal infections, 433*t*, 434
for streptococcal infections, 436*t*, 439
for toxoplasmosis, 598
CLL. *See* chronic lymphocytic leukemia
clobazam, for seizures, 961*t*
clofazimine, for leprosy, 492
clomiphene citrate, for female infertility, 924
clomipramine
dosage and side effects of, 1072*t*
for narcolepsy, 244
for obsessive-compulsive disorder, 1068
pharmacology of, 1071
clonazepam
dosage and action of, 1075*t*
for dyspnea, 51*t*
for myoclonus, 238
for pain, 39*t*
for posthypoxic myoclonus, 101
for seizures, 961*t*, 967*t*
for vertigo, 228*t*
clonidine
for ascites, 188
for menopausal symptoms, 922
for narcotic withdrawal, 1085
for smoking cessation, 1103
for tics, 238
clonorchiasis, 606
clopidogrel
for STEMI, 662, 667
for stroke prevention, 89
for thrombotic disorders, 283
for UA/NSTEMI, 670, 671
clorazepate, 1075*t*
clostridial infections
C. botulinum, 471–472
C. perfringens, 416*t*, 418, 473, 474*t*
C. tetani, 469–471
enteric, 387, 473
skin and soft tissue, 473
treatment of, 474*t*
wound contamination, 473
Clostridium difficile infections
diarrhea, 397–398
nosocomial, 360–361
clotrimazole, for candidiasis, 401

cloxacillin, for infective endocarditis, 377*t*
clozapine
  dosage and side effects of, 1077*t*
  for schizophrenia, 1067
clubbing, 146, 149
cluster headache, 215, 215*t*, 219–220
CML. *See* chronic myeloid leukemia
CMV infections. *See* cytomegalovirus infections
CMV regimen, for bladder cancer, 334
CNS disease. *See* central nervous system disease
coagulase-negative staphylococci (CoNS), 428–429, 430, 431–433*t*
coagulation disorders, 279–280
  intracranial hemorrhage in, 84*t*
  in liver disease, 185
coal tar shampoo, 260
coal worker's pneumoconiosis, 717
coarctation of aorta, 630–631, 649
coccidioidomycosis, 578–579, 1034*t*
Cockcroft-Gault formula, 197
codeine
  abuse, 1084
  for cough, 148
  for dyspnea, 51*t*
  for pain, 38*t*
CODOX-M regimen, for Burkitt's lymphoma, 301
cognitive behavioral therapy (CBT)
  for chronic back pain, 211
  for chronic fatigue syndrome, 135
  for insomnia, 242
  for obsessive-compulsive disorder, 1068
cogwheeling, 976
colchicine
  for amyloidosis, 875
  for gout, 864, 865
  for pericarditis, 645
  for pseudogout, 866
colectomy, 327, 794
colesevelam, for dyslipidemia, 939*t*
colestipol, for dyslipidemia, 939*t*
colistin
  for enteric GNB infections, 458
  for *Klebsiella* infections, 456
  for *P. aeruginosa* infections, 461*t*
colitis
  amebic, 396–397
  ischemic, 798
  ulcerative, 791. *See also* inflammatory bowel disease
collagen vascular disease, 275
colon cut-off sign, 804
colonic angiodysplasia, 798
colonic polyps, 326–327, 326*t*
colonoscopy
  for colonic angiodysplasia, 798
  for colonic polyps, 326
  for colorectal cancer diagnosis, 328
  for colorectal cancer screening, 330, 1095, 1097*t*
  in diarrhea, 170
  for GI bleeding, 175
colorectal cancer, 327–330
  clinical manifestations of, 328
  diagnosis of, 328
  etiology of, 327
  pathology of, 328, 329*f*
  prevention of, 330, 1100
  risk factors for, 327–328, 1100
  screening for, 330, 1089–1090*t*, 1091*t*, 1095, 1097*t*, 1100
  staging and prognosis for, 329*f*
  treatment of, 328
colostomy, for anal cancer, 330
coma, 76, 79–81
  approach to, 79
  differential diagnosis of, 80*t*
  eye movements in, 81
  in head trauma, 97–98
  pupillary signs in, 81
  respiratory patterns in, 81
  responsiveness in, 79
common cold, 247, 533, 534*t*, 535
common variable immunodeficiency (CVID), 843
community-acquired pneumonia (CAP)
  clinical manifestations of, 723
  complications of, 725
  diagnosis of, 724
  epidemiology of, 723
  hospitalization for, 724
  microbiology of, 723
  treatment of, 724–726, 725*t*
complete transposition of great arteries, 631
complex regional pain syndrome, 994
compression stockings, 92
  for orthostatic hypotension, 994
  for peripheral vascular disease, 699
compulsive personality disorder, 1070
computed tomography (CT)
  in acute, catastrophic abdominal pain, 157
  in coma, 81

computed tomography (CT) (*Cont.*):
in heart disease, 625–626, 626*t*
hepatobiliary, 800*t*
in hepatobiliary disease, 185
in increased intracranial pressure, 95
indications for, 25
for lung cancer screening, 1098*t*
in pancreatitis, 805
in respiratory disease, 709
in stroke, 85, 87
in subarachnoid hemorrhage, 91
utility of, 25
COMT inhibitors, for Parkinson's disease, 978
concussion, 96–97
conduction aphasia, 239*t*, 240
condylomata acuminata, 256*f*, 413
condylomata lata, 409
confusion, 76
congenital heart disease, 627–631
acyanotic lesions with left-to-right shunt, 627–629
acyanotic lesions without shunt, 629–631
complex heart lesions, 631
echocardiography in, 625
endocarditis prophylaxis in, 631
pulmonary hypertension in, 629
congenital rubella syndrome, 539–540
conivaptan, for SIADH, 112, 351, 886
conjunctivitis
acute hemorrhagic, 545
adult inclusion, 514–515
trachoma, 514–515
connective tissue disease, 844–845
antiphospholipid syndrome, 849–850
interstitial lung disease in, 738
mixed, 848
rheumatoid arthritis. *See* rheumatoid arthritis
Sjögren's syndrome, 848–849
systemic lupus erythematosus. *See* systemic lupus erythematosus
systemic sclerosis, 847–848
CoNS (coagulase-negative staphylococci), 428–429, 430, 431–433*t*
consciousness, disorders of, 76–82, 96
constipation, 170–174
drug-induced, 171
etiology of, 171
in irritable bowel syndrome, 795, 796*t*
in terminally ill patient, 50, 50*t*
treatment of, 172–173, 173*f*
contact precautions, 357
continuous positive airway pressure (CPAP), 746
continuous renal replacement therapy (CRRT), 751
contraception, 922–923
conversion disorder, 1069
coordination, testing of, 951
COP (cryptogenic organizing pneumonia), 736, 738
COPD. *See* chronic obstructive pulmonary disease
copper metabolism disorders, 945–946
coprolalia, 238
cor pulmonale, 692–693
coronary arteriography, 671, 673
coronary artery bypass grafting (CABG), 664, 671, 676, 676*t*
coronary artery disease (CAD), 627*f*. *See also* chronic stable angina
coronary artery spasm, 672
coronary vasospasm, 676
coronavirus infections, 533, 534*t*, 535
cortical encephalitis, 353
corticosteroid therapy. *See* glucocorticoid therapy
cortisol, excess of, 896
cortisone, for hypopituitarism, 883*t*
Corynebacterium diphtheriae infections, 441–442
Corynebacterium ulcerans infections, 443
Corynebacterium urealyticum infections, 443
costochondral pain, 139
cotton dust, 717
cough, 147–148
cover test, 231
COX-2 inhibitors, for osteoarthritis, 862
Coxiella burnetii endocarditis, 378*t*. *See also* Q fever
coxsackievirus infections, 253, 543, 544. *See also* enteroviral infections
CPAP (continuous positive airway pressure), 746
CPEO (chronic progressive external ophthalmoplegia), 1057, 1059
CPP (cerebral perfusion pressure), 93
CPPD (calcium pyrophosphate dihydrate) deposition disease, 865–866

cranial nerves
CN I. *See* olfactory nerve
CN V. *See* trigeminal nerve
CN VII. *See* facial nerve
CN X. *See* vagus nerve
CN XI. *See* accessory nerve
CN XII. *See* hypoglossal nerve
disorders of, 995–1002
examination of, 947–948
multiple cranial nerve palsies, 1001–1002
C-reactive protein (CRP), 1094
creatinine, serum, 753
creatinine clearance, 197
crescent sign, 869
CREST syndrome, 847
Creutzfeldt-Jakob disease (CJD), 970*t*, 971, 975
critical care medicine, 31–35
critically ill patient, 31–35
initial evaluation of, 31–32
limitation or withdrawal of care for, 35
mechanical ventilation, 32–34
monitoring in ICU, 34
multiorgan system failure, 34
neurologic dysfunction in, 35
prevention of complications in, 34–35
shock, 32, 33*f*
crizotinib, for lung cancer, 315
crocodile tears, 996
Crohn's disease (CD), 791. *See also* inflammatory bowel disease
cromolyn sodium
for allergic rhinitis, 838
for asthma, 714
for systemic mastocytosis, 839
Cronkhite-Canada syndrome, 325
crossed SLR sign, 207
croup, 536–537
CRP (C-reactive protein), 1094
CRRT (continuous renal replacement therapy), 751
crust (skin lesion), 257*t*, 417
cryoglobulinemia, 768*t*
cryoglobulinemic vasculitis, 851
cryoprecipitate, 47, 280
cryotherapy
for HPV infections, 414
for warts, 262
cryptococcosis
clinical manifestations of, 573
diagnosis of, 573, 576
epidemiology of, 573
meningitis, 364, 1034*t*
treatment of, 576
cryptogenic organizing pneumonia (COP), 736, 738
cryptosporidiosis, 391–392
CSA (central sleep apnea), 243, 746
CT. *See* computed tomography
Cullen's sign, 804
CUPS. *See* cancer of unknown primary site
CURB-65, 724
Cushing's syndrome
clinical manifestations of, 896
diagnosis of, 896
etiology of, 895
paraneoplastic, 348–349, 349*t*, 351
treatment of, 896
cutaneous larva migrans, 600
cutaneous leishmaniasis, 593–594
CVID (common variable immunodeficiency), 843
CXR. *See* chest x-ray
cyanide poisoning, 100
cyanosis, 145–146
approach to, 146
causes of, 146*t*
central, 145, 146*t*
peripheral, 145–146, 146*t*
cyclic adenosine monophosphate eyedrops, 849
cyclobenzaprine
for back pain, 211
for multiple sclerosis, 1019
cyclophosphamide
for acute renal failure, 751
for ANCA-associated glomerulonephritis, 762
for breast cancer, 320, 321
for Burkitt's lymphoma/leukemia, 301
for CLL, 297
for gastric carcinoma, 324
for idiopathic thrombocytopenic purpura, 280
for inflammatory myopathy, 1059
for lymphoma, 299
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for polyneuropathy, 1046
for SLE, 762, 845
for systemic sclerosis, 848
for vasculitis, 854
cyclosporiasis, 392

cyclosporine
for aplastic anemia, 274
for focal glomerulosclerosis, 765
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for membranous glomerulonephritis, 764
for myasthenia gravis, 1053
for polyneuropathy, 1046
for primary sclerosing cholangitis, 803
for psoriasis, 259
cyclosporine eyedrops, 849
cyproheptadine, for urticaria/angioedema, 837
cystectomy, 334
cystic fibrosis, 242
cysticercosis, 607–608, 608*t*, 1036*t*
cystine stones, 778, 782*t*
cystitis
definition of, 775
diagnosis of, 246
interstitial, 778–779
cystoisosporiasis, 392
cytarabine
for ALL, 300
for AML, 286*f*, 287
cytoadherence, 586
cytokeratin, in cancer of unknown primary site, 347, 347*f*
cytokine signaling deficiency, 840
cytokines, 275
cytomegalovirus (CMV) infections, 525–527
congenital, 526
diagnosis of, 527
epidemiology of, 525–526
in immunocompromised host, 758–759
microbiology of, 525
mononucleosis, 526
pathogenesis of, 526
perinatal, 526
pharyngitis, 253
in transplant recipients, 368–369, 526–527
treatment of, 527
cytomegalovirus immune globulin, 527
cytopenia, refractory, 290–291*t*

D

dabigatran
for atrial fibrillation, 686
for thrombotic disorders, 282
dacarbazine, for melanoma, 307
DAH (diffuse alveolar hemorrhage), 148, 149
dalbavancin, for staphylococcal infections, 432*t*
dalteparin
for thrombotic disorders, 281
for venous thromboembolism, 733
danazol
for autoimmune hemolysis, 274
for idiopathic thrombocytopenic purpura, 280
dantrolene, for multiple sclerosis, 1019
dapagliflozin, for diabetes mellitus, 909*t*
dapsone
for ANCA-associated glomerulonephritis, 762
for leprosy, 492
for *Pneumocystis* infections, 584*t*
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
daptomycin
for enterococcal infections, 440
for infective endocarditis, 379
for osteomyelitis, 421*t*
for staphylococcal infections, 430, 431*t*, 432*t*
darunavir, for HIV infection, 563*t*
dasatinib, for CML, 288
daunorubicin
for ALL, 300
for AML, 286*f*, 287
daytime sleepiness, excessive, 241, 243–245, 244*t*
DDAVP. *See* desmopressin
death. *See also* terminally ill patient
brain death, 81–82
leading causes by age group, 1088–1090*t*
rates of, 54
death rattle, 55*t*
debranching enzyme deficiency, 1059
decerebrate posturing, 81
decitabine, for myelodysplastic syndromes, 289
decorticate posturing, 79
deep-brain stimulation (DBS), 237, 981
deep-vein thrombosis (DVT)
in critically ill patient, 35
diagnosis of, 731, 732*f*
etiology of, 730

in thrombotic disorders, 281
treatment of, 281–283, 732–733
defecation, 167
deferasirox
for mucormycosis, 577
for thalassemia, 273
deferoxamine
for hemochromatosis, 944
for thalassemia, 273
dehydration, in terminally ill patient, 54*t*
delavirdine, for HIV infection, 559
delayed sleep-wake phase syndrome, 241, 245
delirium
etiologies of, 77*t*
step-wise evaluation of, 78, 78*t*
in terminally ill patient, 52, 56*t*
treatment of, 52, 52*t*, 79
delirium tremens (DTs), 1082
demeclocycline
for hyponatremia, 351
for inappropriate vasopressin secretion, 351
for SIADH, 112, 351, 886
dementia, 968–975. *See also* Alzheimer's disease
approach to, 968, 971, 972*t*
causes of, 969*t*, 974–975
clinical manifestations of, 968
definition of, 968
differential diagnosis of, 968, 969*t*, 970*t*
sleep disorders in, 242
dementia with Lewy bodies (DLB), 970*t*, 971, 974, 991
dengue fever, 550, 552
denosumab, for osteoporosis, 934
dental caries, 475
dental procedures, endocarditis prophylaxis before, 380, 381*t*
dependent personality disorder, 1070
depression
clinical manifestations of, 1064
drug-induced, 1064
with medical illness, 1064
suicide in, 1065
in terminally ill patient, 52
treatment of, 52, 1064–1065, 1065*f*, 1071
weight loss in, 135
in women, 1106
dermatitis, 259–260
allergic contact, 260
atopic, 256*f*, 259–260
contact, 256*f*
irritant contact, 260
seborrheic, 256*f*, 260
stasis, 256*f*
dermatofibroma, 256*f*
dermatomes, 954*f*
dermatomyositis (DM), 1057–1059, 1058*t*
dermatophyte infections, 258, 261–262
desipramine
dosage and side effects of, 39*t*, 1072*t*
for pain, 39*t*
desloratadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
desmopressin (DDAVP)
for diabetes insipidus, 6, 884
for hypernatremia, 6
for hyponatremia, 2, 5
for hypopituitarism, 883*t*
for von Willebrand disease, 281
desquamative interstitial pneumonia (DIP), 738
desvenlafaxine, 1071, 1072*t*
device-related infections, 358–360, 359*t*
DEXA (dual-energy x-ray absorptiometry), 933
dexamethasone
for bacterial meningitis, 1024–1025
for brain tumor, 1008
for *H. influenzae* infections, 449
for hirsutism, 920, 921
for increased intracranial pressure, 95*t*
for multiple myeloma, 302
for pneumococcal infections, 425
for spinal cord compression, 99, 111
for thyroid storm, 891
for typhoid fever, 393
dexamethasone suppression test, 896
dextroamphetamine
for depression, 52
for fatigue, 52
for narcolepsy, 244
dextromethorphan, for cough, 148
DGI (disseminated gonococcal infections), 419
diabetes insipidus
central, 5, 199, 199*t*, 884
drug-induced, 5
gestational, 884
nephrogenic, 5, 199, 199*t*, 884
treatment of, 6, 884

diabetes mellitus (DM), 904–912
cardiovascular disease and, 1093, 1093*t*
clinical manifestations of, 905–906
complications of, 905–906, 907
depression in, 1064
diagnosis of, 904–905
etiology of, 904
in hospitalized patient, 911–912
hypertension in, 655
neuropathy in, 991, 1046
pancreatic cancer and, 331
prevalence of, 904
risk factors for, 905*t*
treatment of, 906–907, 907*t*, 908–910*t*, 911*f*, 1093
type 1, 904
type 2, 905
in women, 1105
diabetic ketoacidosis (DKA), 911
clinical manifestations of, 18*t*, 104
etiology of, 22, 104
laboratory values in, 104, 105*t*
pathogenesis of, 22
treatment of, 19–20, 106*t*
diabetic nephropathy, 765–766
diacetylmorphine, 1084
diagnostic imaging, 23–26
dialysis
hemodialysis. *See* hemodialysis
for hypercalcemia, 927*t*
peritoneal, 751, 755–756, 756*t*
slow low-efficiency, 751
diarrhea, 167–170
from altered intestinal motility, 168
chronic, physical examination in, 169*t*
from decreased absorptive state, 168, 173*t*
exudative, 168
infectious, 168, 386–398
approach to, 388*f*
inflammatory, 386*t*, 392–398
noninflammatory, 386–392, 386*t*
pathogens causing, 386*t*
penetrating, 386*t*
in irritable bowel syndrome, 795, 796*t*
metabolic acidosis in, 18*t*, 19
nosocomial, 360–361
osmotic, 167–168, 170
paraneoplastic, 349*t*
in patients with AIDS, 169*t*
secretory, 168
stool examination, 170
treatment of, 170, 171*f*, 172*f*
diascopy, 258
diastolic failure, 687
diazepam
for alcohol withdrawal, 1083
dosage and action of, 1075*t*
for multiple sclerosis, 1019
for muscle spasms, 120
for STEMI, 661
for vertigo, 228*t*
diazoxide therapy, for hypoglycemia, 109
DIC (disseminated intravascular coagulation), 278
dichloralphenazone, for migraine, 218*t*
diclofenac, for pain, 40
diclofenac K, for migraine, 217*t*
dicloxacillin
for staphylococcal infections, 433*t*
for streptococcal infections, 436
dicyclomine
for diverticular disease, 796
for irritable bowel syndrome, 795
dietary reference intake (DRI), 41
diethylcarbamazine, for filariasis, 603
diffuse alveolar hemorrhage (DAH), 148, 149
diffuse large B cell lymphoma, 299, 323
diffuse white matter disease, 974, 975*f*
digital rectal exam (DRE), 330, 342, 344*f*, 1099*t*
digitalis
for heart failure, 689*t*
for mitral stenosis, 632
toxicity of, 680*t*, 689–690
digoxin
for arrhythmias, 684*t*
for atrial fibrillation, 686
for cor pulmonale, 693
for heart failure, 688–689
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
dihydroartemisinin-piperaquine, for malaria, 588*t*
dihydroergotamine, for migraine, 217*t*, 219*t*
dihydropyridine, for vasospastic disorders, 698
dilated cardiomyopathy, 639–642, 640*t*
diltiazem
for aortic dissection, 695
for arrhythmias, 684*t*

for atrial fibrillation, 686
for hypertension, 653*t*
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for UA/NSTEMI, 670
for Wolff-Parkinson-White syndrome, 686
dimenhydrinate
for nausea and vomiting, 160
for vertigo, 228*t*
dimethyl fumarate, for multiple sclerosis, 1018
dioctyl sodium sulfosuccinate, for hemorrhoids, 798
DIP (desquamative interstitial pneumonia), 738
diphenhydramine
for allergic rhinitis, 838
for anaphylaxis, 114
for antivenom reaction, 119
for urticaria/angioedema, 837
diphenoxylate
abuse, 1084
for diarrhea, 170
for inflammatory bowel disease, 792
for irritable bowel syndrome, 795
diphtheria, 441–442
diphtheria antitoxin, 442
diphtheria toxin, 441
diphtheria vaccine, 442
diphtheria-tetanus vaccine, 369*t*
diphyllobothriasis, 609–610
diplopia, 232, 232*t*
dipyridamole
for stroke prevention, 89
for thrombotic disorders, 283
disease prevention, 1087, 1090–1091*t*
disease-modifying antirheumatic drugs (DMARDs), for rheumatoid arthritis, 846
disequilibrium syndrome, dialysis, 755
disopyramide
for arrhythmias, 683*t*
for hypertrophic cardiomyopathy, 643
disseminated gonococcal infections (DGI), 419
disseminated intravascular coagulation (DIC), 278
distributive shock, 61*t*, 62
disulfiram, for alcoholic rehabilitation, 1084
diuresis, osmotic, 199*t*
diuretics
for ascites, 188
complications of, 8–9, 152, 154*t*, 239*t*
for cor pulmonale, 693
for diabetic nephropathy, 766
for dilated cardiomyopathy, 640
for edema, 151–152
for heart failure, 663–664, 688, 689*t*, 690*t*
for hypernatremia, 6
for hypertension, 651, 652*t*, 654*t*, 655*f*
for mitral stenosis, 632
for nephrolithiasis, 781*t*
for pulmonary hypertension, 702
for restrictive cardiomyopathy, 642
for slowing renal disease progression, 754
for STEMI, 665*t*
for tricuspid regurgitation, 639
divalproex, for generalized anxiety disorder, 1068
diverticular disease, 796
diverticulitis, 796
diverticulosis, 175, 178
Dix-Hallpike maneuver, 226
dizziness, 226
DKA. *See* diabetic ketoacidosis
DLB (dementia with Lewy bodies), 970*t*, 971, 974, 991
DLCO (diffusing capacity of lung), 707
DM (dermatomyositis), 1057–1059, 1058*t*
DM (diabetes mellitus). *See* diabetes mellitus
DMARDs (disease-modifying antirheumatic drugs), for rheumatoid arthritis, 846
DNA-dependent protein kinase gene deficiency, 840
Dobrava-Belgrade virus, 552
dobutamine
for heart failure, 91, 664, 664*t*, 691*t*
for pulmonary edema, 70
for shock, 64, 64*t*
for STEMI, 665*t*
docetaxel, for head and neck cancer, 309
docusate salts
for constipation, 50*t*, 174
in STEMI, 661
dofetilide
for arrhythmias, 684*t*
for dilated cardiomyopathy, 641

dog bite, 115, 116*t*, 417
Döhle bodies, 266
doll's head maneuver, 81
dolutegravir, for HIV infection, 559, 565*t*
domestic violence (intimate partner violence), 1091*t*, 1106
donepezil, for Alzheimer's disease, 973
donovanosis, 404*t*, 413
dopamine
  for anaphylaxis, 114
  for heart failure, 664*t*, 689*t*, 691, 691*t*
  for increased intracranial pressure, 95*t*
  for pulmonary edema, 70
  for shock, 64, 64*t*, 664
  for STEMI, 665*t*
dopamine agonists
  for acromegaly, 881
  for hyperprolactinemia, 880
  for Parkinson's disease, 978, 980*t*
doripenem, for *P. aeruginosa* infections, 460*t*
dorsal root ganglionopathy, paraneoplastic, 352*t*, 353*t*, 354*t*, 355
dosulepin, for migraine prevention, 220*t*
double vision, 232, 232*t*
doxepin
  dosage and side effects of, 39*t*, 1072*t*
  for pain, 39*t*
doxorubicin
  for bladder cancer, 334
  for breast cancer, 320, 321
  for Burkitt's lymphoma/leukemia, 301
  for carcinoid tumor, 332
  for endometrial cancer, 340
  for islet-cell tumors, 333
  for lymphoma, 299
  for multiple myeloma, 302
  for Zollinger-Ellison syndrome, 790
doxycycline
  for actinomycosis, 481
  for adult inclusion conjunctivitis, 515
  for animal bite infections, 415*t*
  for bacillary angiomatosis, 415*t*
  for *Bartonella* infections, 467*t*
  for brucellosis, 464
  for community-acquired pneumonia, 725*t*
  for COPD exacerbations, 721
  for *Corynebacterium* infections, 443
  for donovanosis, 413
  for endemic treponematosis, 497
  for enterococcal infections, 440
  for epidemic typhus, 507
  for epididymitis, 400
  for gonococcal infections, 406*t*
  for human granulocytotropic anaplasmosis, 508
  for human monocytotropic ehrlichiosis, 508
  for infective endocarditis, 378*t*
  for *Legionella* infections, 513
  for leptospirosis, 498
  for Lyme borreliosis, 496
  for Lyme disease prophylaxis, 123
  for lymphatic filariasis, 604
  for lymphogranuloma venereum, 408
  for *M. pneumoniae* infections, 511
  for malaria, 588*t*
  for malaria prophylaxis, 590*t*
  for murine typhus, 506
  for onchocerciasis, 604
  for pelvic inflammatory disease, 403, 406–407t
  for plague, 466
  for proctitis, proctocolitis, enterocolitis, and enteritis, 405
  for Q fever, 509–510
  for relapsing fever, 499
  for rickettsialpox, 505
  for Rocky Mountain spotted fever, 504
  for rodent bite infections, 117*t*
  for scrub typhus, 507
  for sinusitis, 249*t*
  for staphylococcal infections, 433*t*
  for syphilis, 411*t*
  for tick-borne spotted fevers, 505
  for tularemia, 465
  for urethritis in men, 399
  for Whipple's disease, 482
DRE (digital rectal exam), 330, 342, 344*f*, 1099*t*
DRI (dietary reference intake), 41
dronabinol, for weight loss, 137
dronedarone, for arrhythmias, 684*t*
droplet precautions, 357
drug-induced illness
  anemia, 269, 272*t*
  autonomic nervous system disease, 988
  AV block, 678*t*
  constipation/ileus, 171
  delirium, 77*t*

depression, 1064
diabetes insipidus, 5
edema, 151*t*
eosinophilia, 275
fatigue, 132, 133*t*
hepatitis, 815
hirsutism, 920
hyperkalemia, 6–7, 14*f*
hyperprolactinemia, 79
hypoglycemia, 107
hypokalemia, 7–8
insomnia, 242
intracranial hemorrhage, 84*t*
jaundice, 182*t*
leukopenia, 276
lupus, 844
metabolic acidosis, 18*t*
myopathy, 1060*t*, 1061
nausea and vomiting, 159*t*
nephritis, 771–772, 771*t*
neutropenia, 275–276
obesity, 901
pill-related esophagitis, 166
seizure, 59*t*
skin disorders, 263–264
thrombocytopenia, 278, 280
weight loss, 136*t*
DTaP vaccine, 442
DTs (delirium tremens), 1082
dual-energy x-ray absorptiometry (DEXA), 933
Duchenne's muscular dystrophy, 1054
ductal carcinoma in situ, 320
Duke criteria, for infective endocarditis, 374, 375*t*
dulaglutide, for diabetes mellitus, 909*t*
duloxetine
dosage and side effects of, 39*t*, 1072*t*
for fibromyalgia, 868
for pain, 39*t*
pharmacology of, 1071
for polyneuropathy, 1044, 1045*t*
duodenal ulcer, 785–786, 788*t*, 789*t*
durable attorney for health care, 49
Durie-Salmon staging, for multiple myeloma, 303*t*
dutasteride
for prostate cancer prevention, 345, 1100
for prostate hyperplasia, 342
DVT. *See* deep-vein thrombosis
dynamic visual acuity, for vertigo, 226
dysarthria, 83
dysbetalipoproteinemia, 937*t*, 941
dysentery, 386*t*, 389, 396–397
dysesthesia, 36
dysfunctional uterine bleeding, 917
dyskinesia, 978
dyslipidemia. *See also* hypercholesterolemia
in diabetes mellitus, 907
in metabolic syndrome, 656–657, 657*t*
treatment of, 938–939*t*
dysmenorrhea, 919, 920
dyspepsia, 160–161
dysphagia, 162–164, 1000
approach to, 162, 163*f*
esophageal, 164
oropharyngeal, 162–164
in terminally ill patient, 54*t*
dysphonia, 1000
dyspnea, 142–144
approach to, 143, 144*f*
in ARDS, 71
cardiac vs. pulmonary, 144*f*
in pulmonary edema, 144–145
in terminally ill patient, 51, 51*t*
treatment of, 51, 51*t*
dystonia, 237
dysuria, 245–246

E

EAEC (enteroaggregative and diffusely adherent *E. coli*) infections, 455
ear infections
anaerobic, 475
external, 249–250
middle. *See* otitis media
P. aeruginosa, 459, 460*t*
eastern equine encephalitis (EEE), 550
eating disorders
clinical manifestations of, 1079–1080
epidemiology of, 1079
treatment of, 1080
in women, 1106
Ebola virus infection, 552–553
Ebstein anomaly, 631
EBV infections. *See* Epstein-Barr virus infections
ECG. *See* electrocardiography
echinocandins
for candidiasis, 571
for mucormycosis, 577
pharmacology of, 569–570
for scedosporiosis, 582
echinococcosis, 608–609
echinocytes, 265

echocardiography, 622–625
in aortic disease, 624, 626*t*, 694
in aortic regurgitation, 638
in aortic stenosis, 636
in cardiac tamponade, 647
in cardiomyopathy, 641*t*
clinical uses of, 622–623, 622*t*, 624*f*
in congenital heart disease, 625, 628–630
in cor pulmonale, 692
in coronary artery disease, 672, 674*t*
Doppler, 622*t*
in endocarditis, 374
in heart failure, 688
in intracardiac mass, 624, 626*t*
in mitral regurgitation, 634
in mitral valve prolapse, 636
in myocarditis, 644
in palpitations, 142
in pericardial disease, 623–624, 626*t*
in pericarditis, 645, 648
in pulmonary embolism, 731
in pulmonary hypertension, 700
in STEMI, 659
stress, 622*t*, 625
in stroke, 87
transesophageal, 622*t*
2-D, 622*t*, 623*f*
in valvular heart disease, 623, 624*f*, 626*t*
echolalia, 238
echovirus infections, 543, 544, 1037*t*
ecstasy (MDMA), 4
ecthyma gangrenosum, 459
ectoparasites, 610–611
eczema, 256*f*, 259
eczema herpeticum, 517
edema, 150–154
approach to, 152*f*
drug-induced, 151*t*
generalized, 150–151
in heart failure, 688
idiopathic, 151
localized, 150
lymphedema, 699
treatment of, 151–152, 153*t*
EEE (eastern equine encephalitis), 550
EEG. *See* electroencephalography
efavirenz, for HIV infection, 559, 561*t*
effective circulating volume, 1*t*, 3
eflornithine, for sleeping sickness, 596
E:G (erythroid:granulocytic) ratio, bone marrow, 267
ehrlichiosis, 122
human monocytotropic, 502*t*, 507–508
EIEC (enteroinvasive *E. coli*) infections, 455
Eikenella corrodens infections, 452, 453*t*
Eisenmenger syndrome, 629
ejection click (heart sound), 615
elderly, joint pain in, 205–207
electrical nerve stimulation, for chronic back pain, 211
electrocardiography (ECG), 618–622
in cardiac hypertrophy, 619–620, 621*t*
in cardiac tamponade, 647
in cardiomyopathy, 641*t*, 642–643
in congenital heart disease, 628–630
in cor pulmonale, 692
in coronary artery disease, 672
heart rate, 618
in hyperkalemia, 9, 13, 14*f*, 15*f*
lead system, 618*f*
mean axis in, 618
in mitral stenosis, 632
in myocarditis, 643
in palpitations, 142
in pericarditis, 644, 645*t*, 646*f*, 647
PR interval, 618
in pulmonary hypertension, 700
QRS interval, 619
QT interval, 619
in recurrent angina, 667
rhythm, 618
in sinoatrial node dysfunction, 677
in STEMI, 141, 620, 621*f*, 621*t*, 645*t*, 658, 659
ST-T waves, 620, 622
in subarachnoid hemorrhage, 91
in tachyarrhythmias, 679, 680–682*t*
in variant angina, 676
electroconvulsive therapy, 1065
electrodiagnosis
in mononeuropathy, 1047–1049*t*
in muscle disease, 1054
in peripheral neuropathy, 1044
electroencephalography (EEG)
in brain death, 82
in coma, 81
in seizure, 958
in status epilepticus, 103
electrolyte balance, 1, 133*t*
elephantiasis, 603
eletriptan, for migraine, 217*t*, 219*t*
elliptocytes, 265

eltrombopag, for idiopathic thrombocytopenic purpura, 280
elvitegravir, for HIV, 565*t*
embolectomy, 733
embryonal carcinoma, 336
emergencies, medical, 57–60
  anaphylaxis, 114–115
  ARDS, 71–73
  bites, venoms, stings, and marine poisonings, 115–125
  cardiovascular collapse, 57–60
  diabetic ketoacidosis, 104, 106*t*
  head trauma, 96–98
  hyperglycemic hyperosmolar state, 104–105
  hypoglycemia, 107–109
  hypoxic-ischemic encephalopathy, 100–101
  increased intracranial pressure, 93–96
  oncologic, 109–113
  pulmonary edema, acute, 69–70
  respiratory failure, 73–76
  sepsis and septic shock, 65–68
  shock, 61–65
  spinal cord compression, 98–100
  status epilepticus, 101–103
  stroke, 82–91
  stupor and coma, 76–82
  subarachnoid hemorrhage, 91–93
emergency contraceptive pills, 923
emerging disease, 360–361
empagliflozin, for diabetes mellitus, 909*t*
emphysema
  dyspnea in, 143
  mediastinal, chest pain in, 138
empyema
  anaerobic, 475
  streptococcal, 423, 436*t*
emtricitabine, for HIV infection, 561*t*, 566
enalapril/enalaprilat
  for heart failure, 690*t*
  for malignant hypertension, 656*t*
encephalitis
  approach to, 1020, 1021–1022*f*
  in cancer patients, 364
  in measles, 538
  paraneoplastic, 352*t*, 353, 353*t*, 354*t*
  in rabies, 547
  viral
    clinical manifestations of, 1027
    cytomegalovirus, 527
    diagnosis of, 1028, 1028*f*
    differential diagnosis of, 1028–1029
    enteroviral, 544
    etiology of, 1027
    HSV, 521*t*
    prognosis of, 1029
    treatment of, 1029
encephalopathy
  hepatic, 832–833
  hypoxic-ischemic, 100–101
  Wernicke's, 1082–1083
endemic murine typhus, 502*t*, 505–506
endocarditis. *See* infective endocarditis
endocrine disease
  adrenal. *See* adrenal gland disease
  diabetes insipidus. *See* diabetes insipidus
  diabetes mellitus. *See* diabetes mellitus
  female reproductive system disorders, 917–924
  leukocytosis in, 275
  lymphadenopathy and, 190*t*
  male reproductive system disorders, 912–916
  muscle disorders in, 1060–1061
  nausea and vomiting in, 159*t*
  paraneoplastic, 348–351
  pituitary. *See* pituitary disease
  syndrome of inappropriate ADH. *See* syndrome of inappropriate ADH
  thyroid. *See* thyroid disease
  tumors of GI tract and pancreas, 331–333
  weight loss in, 136*t*
endodermal sinus tumor, 336
end-of-life care. *See* terminally ill patient
endometrial cancer, 339*t*, 340
endometritis, 402
endophthalmitis
  Klebsiella, 456
  P. aeruginosa, 461*t*
endoscopic retrograde cholangiopancreatography (ERCP), 800*t*, 802
endoscopic variceal ligation (EVL), 832
endoscopy
  in gastropathies, 788
  in GI bleeding, 175
  in peptic ulcer disease, 786
end-stage renal disease (ESRD), 752. *See also* chronic kidney disease

enfuvirtide, for HIV infection, 559, 564*t*
enoxaparin
  for STEMI, 659, 662
  for thrombotic disorders, 281
  for UA/NSTEMI, 670
  for venous thromboembolism, 733
entacapone, for Parkinson's disease, 980*t*
entecavir, for chronic hepatitis B, 817, 818–819*t*
enteral nutrition, 43–44, 44*f*
enteric bacilli, gram-negative, 453–458
  Aeromonas, 458
  extraintestinal *E. coli*, 454
  intestinal pathogenic *E. coli*, 455
  Klebsiella, 455–456
  Proteus, 456–457
enteric fever, 386*t*, 392–394
enteritis, 403, 405
enteroaggregative and diffusely adherent *E. coli* (EAEC) infections, 455
Enterobacter infections, 421*t*, 457
enterobiasis (pinworm infection), 602–603
enteroclysis, 325
enterococcal infections, 434, 440–441
  endocarditis, 372, 377*t*, 378–379
  microbiology of, 434
  osteomyelitis, 421*t*
enterocolitis, 403, 405, 792
enteroinvasive *E. coli* (EIEC) infections, 455
enteropathic arthritis, 867
enteropathogenic *E. coli* (EPEC) infections, 455
enterotoxigenic *E. coli* (ETEC) infections, 455
enteroviral infections, 534*t*, 544–546
entry inhibitors, for HIV infection, 559, 564*t*
envenomations
  marine, 120–121
  snakebites, 118–120
enzalutamide, for prostate cancer, 343
eosinopenia, 277
eosinophilia, 275, 738–739
eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), 851
eosinophilic pneumonia, 738
EPEC (enteropathogenic *E. coli*) infections, 455
ependymoma, 1010
epidemic disease, 360–361
epidemic (louse-borne) typhus, 502*t*, 506–507
epidermal inclusion cyst, 256*f*
epididymitis, 400
epididymo-orchitis, in mumps, 541
epidural abscess
  neck pain in, 212
  S. aureus, 427
  spinal, 99, 1005
epidural hematoma, 98, 100, 1005
epiglottitis, 254, 448–449
epilepsy. *See also* seizures
  sleep disorders in, 242
  status epilepticus, 101–103
  treatment of, 961–966*t*, 967–968, 967*t*
epinephrine
  for anaphylaxis, 114, 125
  for antivenom reaction, 119
  for croup, 537
  for ventricular fibrillation, 59*f*
epirubicin, for gastric cancer, 323
eplerenone
  for edema, 153*t*
  for heart failure, 664, 688, 689*t*, 690*t*
  for hyperaldosteronism, 21, 898
  for hypertension, 652*t*
  for STEMI, 662
Epley procedure, 229
epoprostenol
  for pulmonary hypertension, 702
  for systemic sclerosis, 848
eprodisate, for amyloidosis, 875
EPSEs (extrapyramidal side effects), 1074
Epstein-Barr virus (EBV) infections
  cancer associated with, 294, 528–529
  clinical manifestations of, 253, 528–529
  diagnosis of, 529
  epidemiology of, 528
  in transplant recipients, 58
  treatment of, 529
eptifibatide
  for thrombotic disorders, 283
  for UA/NSTEMI, 670
ERCP (endoscopic retrograde cholangiopancreatography), 800*t*, 802
erectile dysfunction, 915–916
ergotamine, for migraine, 217*t*, 219*t*

erlotinib
for lung cancer, 315
for pancreatic cancer, 331
erosion (skin lesion), 257*t*
ertapenem
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 725*t*
for sepsis/septic shock, 68*t*
eruptive xanthoma, 940
erysipelas, 261, 417, 436, 436*t*
erythema infectiosum (fifth disease), 542
erythema migrans, 495
erythema multiforme, 263
in cancer patients, 362
in HSV, 522*t*
HSV infection and, 517
erythema nodosum, 263
erythema nodosum leprosum, 491, 492
erythrocytosis. *See* polycythemia
erythroid:granulocytic (E:G) ratio, bone marrow, 267
erythroleukemia, 284*t*
erythromycin
for acne, 262
for bacillary angiomatosis, 415*t*
for *Bartonella* infections, 467*t*
for *C. pneumoniae* infections, 513
for *C. psittaci* infections, 516
for campylobacteriosis, 395
for cellulitis, 415*t*
for chancroid, 413
for diphtheria, 442
for donovanosis, 413
for gastroparesis, 160
for *H. pylori* eradication, 161
for human bite infections, 116*t*
for Lyme borreliosis, 496
for lymphogranuloma venereum, 408
for pertussis, 451
for relapsing fever, 499
for streptococcal infections, 439
erythroplakia, 309
erythropoiesis, 194
erythropoietin, decreased level of, 268–269
erythropoietin therapy
for anemia, 273
for chronic kidney disease, 754
eschar, 417
Escherichia coli infections
enteroaggregative and diffusely adherent, 455
enteroinvasive, 455
enteropathogenic, 455
enterotoxigenic, 455
extraintestinal, 454
intestinal pathogenic, 455
Shiga toxin-producing/enterohemorrhagic, 395–396, 455
escitalopram, 1072*t*
esmolol
for aortic dissection, 695, 696*t*
for arrhythmias, 683*t*
for malignant hypertension, 656*t*
for tetanus, 470
esophageal cancer, 321–322, 349*t*
esophageal inflammation, 165–166
esophageal manometry, 264
esophageal motility disorders, 164–165
esophageal pain, 139*f*, 141
esophageal rupture, 140*f*
esophageal spasm, 165
esophageal ulcer, 161, 166
esophageal varices, 831–832
esophagitis, 165–166
Candida, 166
eosinophilic, 166
in HIV infection, 166
HSV, 518
HSV infections, 522*t*
pill-related, 166
viral, 165
esophagogastroscopy, 162, 322, 832
ESRD (end-stage renal disease), 752. *See also* chronic kidney disease
essential hypertension, 649
essential thrombocytosis, 293
essential tremor (ET), 236, 237*t*
estramustine, for prostate cancer, 343
estrogen therapy
for amenorrhea, 918
cardiovascular risk reduction and, 1093
for hypopituitarism, 883*t*
for menopausal symptoms, 922
oral contraceptives, 922
for osteoporosis, 934
eszopiclone, for insomnia, 242
etanercept
for ankylosing spondylitis, 857
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846

ETEC (enterotoxigenic *E. coli*) infections, 455
ethambutol
  for nontuberculous mycobacterial infections, 494
  for tuberculosis, 486, 487–488*t*
ethanol, for hypertrophic cardiomyopathy, 643
ethinylestradiol/norethisterone, for GI telangiectasis, 178
ethosuximide, for seizures, 962*t*, 967*t*
ethylene glycol poisoning, 17, 18*t*, 19
etoposide
  for AML, 286*f*, 287
  for lung cancer, 313
  for testicular cancer, 336
etravirine, for HIV infection, 559, 561*t*
everolimus
  for islet-cell tumors, 333
  for renal cancer, 335
EVL (endoscopic variceal ligation), 832
Ewingii ehrlichiosis, 502*t*
exanthem subitum, 525
exanthems, enteroviral, 545
exchange transfusion, 46
excoriation, 257*t*
exemestane, for breast cancer, 321
exenatide, for diabetes mellitus, 906, 909*t*
exercise habits, 1094
exercise testing
  in coronary artery disease, 672, 673*f*, 674*t*
  for palpitations, 142
exertional headache, 215*t*, 221
extensively drug-resistant (XDR) tuberculosis, 482
extraarticular tophi, 863
extraintestinal *E. coli* (ExPEC) infections, 454
extrapyramidal side effects (EPSEs), 1074
eye disease
  chlamydial infections, 514–515
  HSV infections, 518, 521*t*
  larva migrans, 600
  in leprosy, 491
  in malnutrition, 42
  Nocardia infections, 478
  P. aeruginosa infections, 459, 460–461*t*
  paraneoplastic, 352*t*, 353*t*
  toxoplasmosis, 598
eye movements, in coma, 81
ezetimibe, for dyslipidemia, 938*t*
ezogabine, for seizures, 962*t*

F
FAB classification
  of AML, 284*t*
  of lymphoid malignancy, 293
facial diplegia, 1001
facial masking, 976
facial myokymia, 996
facial nerve (CN VII)
  anatomy of, 998*f*
  disorders of, 996–998
  examination of, 948
facial numbness, 995–996
facial pain, 221, 995–996
facial weakness, 996–998
facioscapulohumeral dystrophy, 1057
factitious illness, 1069
facultative bacteria, 469
faintness, 222, 226–227
famciclovir
  for genital HSV infections, 412, 415*t*
  for herpes zoster infections, 415*t*
  for HSV infections, 519, 520–522*t*
  for viral meningitis, 1027
  for VZV infections, 524
familial amyotrophic lateral sclerosis (FALS), 984
familial combined hyperlipidemia (FCHL), 941
familial dysbetalipoproteinemia, 937*t*
familial hepatic lipase deficiency, 937*t*
familial hypercholesterolemia (FH), 936, 937*t*
familial hypocalciuric hypercalcemia (FHH), 925
familial polyposis coli (FPC), 326*t*, 327
familial spastic paraplegia, 1007
famotidine, for erosive gastropathies, 788
Fanconi syndrome, 773, 773*t*
Fanconi's anemia, 268
farmer's lung, 717
fasciculations, 233*t*, 235*t*, 951
fascioliasis, 606
fat requirements, 41
fatigability, 233
fatigue
  causes of, 133*t*
  chronic fatigue syndrome, 134–135, 134*t*
  clinical manifestations of, 132
  daytime, 241

differential diagnosis of, 132
drug-induced, 132, 133*t*
generalized, 131–134, 133*t*
laboratory testing in, 132–133
in muscle disease, 1053
in terminally ill patient, 51–52, 54*t*
treatment of, 52, 133–134
fatty liver, 827
FCHL (familial combined hyperlipidemia), 941
febrile neutrophilic dermatosis, in cancer patients, 362
febuxostat, for gout, 865
fecal antigen test, *H. pylori*, 786, 786*t*
fecal DNA testing, 1097*t*
fecal immunochemical testing, 1097*t*
fecal incontinence, 55*t*, 168
fecal occult blood test, 174, 328, 330, 1095, 1097*t*
felbamate, for seizures, 962*t*, 967*t*
female reproductive system disorders, 917–924
femoral neuropathy, 1048*t*
fenofibrate, for dyslipidemia, 939*t*
fenoprofen, for pain, 38*t*
fentanyl
abuse, 1084
for pain, 39*t*
fetal alcohol syndrome, 1106
fever, 127
approach to, 127–128, 365–366, 365*f*
in cancer patient, 113
causes of, 127
with rash, 128
treatment of, 128
fever of unknown origin (FUO), 129, 130*f*
fexofenadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
FFP. *See* fresh-frozen plasma
FGS (focal glomerulosclerosis), 764–765
FH (familial hypercholesterolemia), 936, 937*t*
FHH (familial hypocalciuric hypercalcemia), 925
fiber, dietary, 172, 795
fibrinogen deficiency, 280
fibrinolytic therapy
for STEMI, 659, 661*f*
for thrombotic disorders, 282–283
for venous thromboembolism, 733
fibromyalgia, 868, 1064
fibrosing mediastinitis, 578
fifth disease (erythema infectiosum), 542
filariasis, lymphatic, 603–604
filovirus infections, 552–553
finasteride
for prostate cancer prevention, 345, 1100
for prostate hyperplasia, 342
fingolimod, for multiple sclerosis, 1018
fire coral, 120
fish oil supplementation
for IgA nephropathy, 767
for inflammatory bowel disease, 794
Fisher syndrome, 1046
Fitz-Hugh-Curtis syndrome, 402
flatworm infections, 604–606
flea-borne (murine) typhus, 502*t*, 505–506
flea-borne spotted fever, 501*t*
flecainide, for arrhythmias, 683*t*
floxuridine (FUDR), for colorectal cancer, 328
flucloxacillin, for infective endocarditis, 377–378*t*
fluconazole, 569
for blastomycosis, 581
for candidiasis, 166, 262, 401, 571
for coccidioidomycosis, 580
for cryptococcosis, 576
for *Malassezia* infections, 581
for urinary tract infections, 778
flucytosine, 570
for candidiasis, 571
for cryptococcosis, 576
fludarabine
for CLL, 297
for follicular lymphoma, 298
for idiopathic thrombocytopenic purpura, 280
fludrocortisone
for Addison's disease, 899
for adrenal insufficiency, 112
for hypoaldosteronism, 899
for orthostatic hypotension, 995
for SIADH, 886
for syncope, 225
fluid absorption, in GI tract, 167
fluid replacement, for cholera, 387
fluid restriction
for heart failure, 688
for hyponatremia, 351
for SIADH, 112, 886
fluke infections
liver (biliary) flukes, 606
lung flukes, 606

flunarizine, for migraine prevention, 220*t*
fluoroquinolones
  for *Aeromonas* infections, 458
  for brucellosis, 464
  for *C. pneumoniae* infections, 513
  for campylobacteriosis, 395
  for community-acquired pneumonia, 725*t*
  for *Corynebacterium* infections, 443
  for enterococcal infections, 440
  for extraintestinal *E. coli* infections, 454
  for *H. influenzae* infections, 449
  for HACEK group infections, 453*t*
  for infectious arthritis, 420
  for *Klebsiella* infections, 456
  for *Legionella* infections, 512–513
  for *M. catarrhalis* infections, 452
  for *M. pneumoniae* infections, 511
  for nocardiosis, 479
  for peritonitis, 382–384
  for pneumococcal infections, 424
  for Q fever, 509–510
  for shigellosis, 396
  for sinusitis, 249*t*
  for staphylococcal infections, 430
  for tuberculosis, 486, 487–488*t*
  for typhoid fever, 393
  for urinary tract infections, 777*t*, 778
5-fluorouracil (5-FU)
  for anal cancer, 330
  for breast cancer, 321
  for carcinoid tumor, 332
  for cervical cancer, 341
  for colorectal cancer, 328
  for esophageal carcinoma, 322
  for gastric cancer, 323
  for head and neck cancer, 309
  for pancreatic cancer, 331
  for Zollinger-Ellison syndrome, 790
fluoxetine
  for depression, 52
  dosage and side effects of, 1072*t*
  for menopausal symptoms, 922
  for narcolepsy, 245
  for obsessive-compulsive disorder, 1068
  for systemic sclerosis, 848
fluphenazine
  dosage and side effects of, 1076*t*
  for postherpetic neuralgia, 524
flurazepam, 1075*t*
flutamide
  for hirsutism, 920–921
  for prostate cancer, 343
fluticasone
  for allergic rhinitis, 838
  for eosinophilic esophagitis, 166
fluvastatin, for dyslipidemia, 938*t*
fluvoxamine
  dosage and side effects of, 1072*t*
  for obsessive-compulsive disorder, 1068
focal glomerulosclerosis (FGS), 764–765
focal seizures, 956, 956*t*. *See also* seizures
folate, for alcoholic liver disease, 828
folate deficiency
  anemia in, 269, 273
  leukopenia in, 276
  treatment of, 45*t*
FOLFIRI regimen, for colorectal cancer, 328
FOLFOX regimen, for colorectal cancer, 328
follicle-stimulating hormone (FSH)
  deficiency of, 882, 883*t*
  production of, 877, 878*f*
follicular lymphoma, 294, 296*f*, 298
folliculitis, 256*f*, 417
fondaparinux
  for thrombotic disorders, 282
  for UA/NSTEMI, 670
  for venous thromboembolism, 733
food metabolism, 40
food poisoning
  bacterial, 386–389, 388*f*
  botulism, 471
  S. aureus, 428
foot, muscles and innervation of, 950*t*
foramen magnum, lesions near, 1003
forced vital capacity, 705, 705*f*
forearm, muscles and innervation of, 949*t*
formoterol, for asthma, 713
foscarnet
  for cytomegalovirus infections, 527
  for HSV infections, 522*t*
  for viral encephalitis, 1029
  for viral esophagitis, 165
fosfomycin, for urinary tract infections, 777*t*
fosphenytoin, for status epilepticus, 102*f*
FPC (familial polyposis coli), 326*t*, 327
fracture, osteoporotic, 931, 931*t*
Francisella tularensis. *See* tularemia

fresh-frozen plasma (FFP), 47
for bleeding disorders, 280
for warfarin reversal, 282
Friedreich's ataxia, 983
frontotemporal dementia (FTD), 970*t*, 971, 974
frovatriptan, for migraine, 217*t*, 219*t*
frozen shoulder, 870
FSH. *See* follicle-stimulating hormone
5-FU. *See* 5-fluorouracil
FUDR (floxuridine), for colorectal cancer, 328
fungal infections, 568–582
antifungal agents, 569–570
aspergillosis. *See* aspergillosis
blastomycosis, 580–581, 1035*t*
candidiasis. *See* candidiasis
chronic meningitis in, 1034–1035*t*
coccidioidomycosis, 578–579
cryptococcosis, 573, 576, 1034*t*
fusariosis, 582
histoplasmosis, 577–578, 579*t*, 1035*t*
in HSCT patients, 366–367
lymphadenopathy and, 190*t*
Malassezia infections, 581
mucormycosis, 576–577
nosocomial, 361
paracoccidioidomycosis, 581–582
penicilliosis, 582
scedosporiosis, 582
sporotrichosis, 581
fungus ball, 249
FUO (fever of unknown origin), 129, 130*f*
furosemide
for ascites, 188
for edema, 153*t*
for heart failure, 663, 688, 690*t*
for hypercalcemia, 351, 927*t*
for hyperkalemia, 16*t*
for hypertension, 652*t*
for hyponatremia, 351
for pulmonary edema, 70
for SIADH, 112
for STEMI, 665*t*
furuncle, 427
furunculosis, 260
fusariosis, 582
fusidic acid, for osteomyelitis, 421*t*
Fusobacterium infections, 475

G

G6PD (glucose-6-phosphate dehydrogenase) deficiency, 269, 272*t*, 274
gabapentin
for generalized anxiety disorder, 1068
for menopausal symptoms, 922
for multiple sclerosis, 1019
for pain, 37, 39*t*
for polyneuropathy, 1044, 1045*t*
for postherpetic neuralgia, 524
for seizures, 962*t*, 967*t*
GAD (generalized anxiety disorder), 1067–1068, 1071
gait analysis, 953
galantamine, for Alzheimer's disease, 973
gallstones, 138*t*
gametocyte, 586
gamma knife radiosurgery, 996
gamma-glutamyltranspeptidase (GGT), 185
ganciclovir
for cytomegalovirus infections, 527
for viral encephalitis, 1029
for viral esophagitis, 165
Gardasil, 341, 414
Gardnerella vaginalis infections, 401
Gardner's syndrome, 325, 326*t*, 327
gas exchange, disturbances of, 707–708
gas gangrene (myonecrosis), 416*t*, 418, 473, 474*t*
GAS infections. *See* group A *Streptococcus* infections
gastrectomy, 323
gastric atrophy, 788
gastric carcinoma, 322–324
gastric lavage, 815
gastric tumor, benign, 325
gastric ulcer. *See* peptic ulcer disease
gastrinoma, 332, 332*t*, 789–790
gastritis, 178, 788
gastroesophageal reflux disease (GERD), 160–161
cough in, 147
evaluation of, 161
natural history of, 161
pathophysiology of, 160
sleep disorders in, 242
treatment of, 161
gastroesophageal varices, 174, 178
gastrointestinal bleeding, 174–178
anemia in, 269
in critically ill patient, 35
esophageal varices and, 832
lower, 175–178, 177*f*
upper, 175, 176*f*

gastrointestinal disease
chest pain in, 138*t*, 139*f*
cholecystitis, 801–802
choledocholithiasis/cholangitis, 802–803
cholelithiasis, 799–800
cirrhosis. *See* cirrhosis
colonic angiodysplasia, 798
colonic polyps, 326–327
diverticular disease, 796
endocrine tumors, 331–333
esophageal varices, 831–832
gastric carcinoma, 322–324, 349*t*
gastric tumors, 325
gastropathies, 788–789
hepatitis. *See* hepatitis
infections after HSCT, 367*t*
infections in cancer patients, 364
infectious diarrhea
inflammatory, 386–398, 386*t*, 388*f*
noninflammatory, 386–392
inflammatory bowel disease. *See* inflammatory bowel disease
intestinal pseudoobstruction, 797
irritable bowel syndrome, 794–795, 795*t*, 796*t*
listerial, 446
liver tumors, 330
nausea and vomiting in, 159*t*
pain in, 155*t*
pancreatitis. *See* pancreatitis
peptic ulcer disease. *See* peptic ulcer disease
portal hypertension, 831, 831*t*
primary sclerosing cholangitis, 803
small-bowel tumors, 325
in tuberculosis, 484
vascular, 797–798
weight loss in, 135, 136*t*
Zollinger-Ellison syndrome, 789–790
gastrointestinal function, normal, 167
gastrointestinal stromal cell tumor (GIST), 323, 324
gastrointestinal telangiectasis, 178
gastropathies, 788–789
gastroscopy, 323
gatifloxacin, for tuberculosis, 486
GBS (group B *Streptococcus*), 438–439
GBS (Guillain-Barré syndrome), 991, 1046
gefitinib, for lung cancer, 315
gemcitabine
for bladder cancer, 334
for breast cancer, 321
for pancreatic cancer, 331
gemfibrozil, for dyslipidemia, 939*t*
gemifloxacin, for community-acquired pneumonia, 725*t*
gemigliptin, for diabetes mellitus, 908*t*
generalized anxiety disorder (GAD), 1067–1068, 1071
generalized convulsive status epilepticus (GCSE), 101–103
generalized seizures, 956, 956*t*. *See also* seizures
genital herpes
clinical manifestations of, 404*t*, 412, 517–518
diagnosis of, 412
microbiology and epidemiology of, 412
proctitis, proctocolitis, enterocolitis, and enteritis, 403
treatment of, 412, 520–522*t*
in women, 400–401
genital lesions, ulcerative, 403, 404*t*
genital warts, 413–414, 798
genitourinary tract cancer, 333–337, 349*t*
gentamicin
for bacterial meningitis, 1024*t*, 1025*t*
for *Bartonella* infections, 467*t*
for brucellosis, 464
for enterococcal infections, 440
for health care–associated pneumonia, 727*t*
for infective endocarditis, 376–378*t*, 378
for listerial infections, 447
for pelvic inflammatory disease, 403, 407*t*
for plague, 466
for staphylococcal infections, 430, 433*t*
for streptococcal infections, 438, 440
for tularemia, 465
geographic tongue, 256*f*
GERD. *See* gastroesophageal reflux disease
germ cell tumor
extragonadal, unrecognized, 348–349
ovarian, 338
paraneoplastic syndromes in, 353*t*
German measles. *See* rubella
GFR (glomerular filtration rate), 197, 198*t*, 752, 753

GGT (gamma-glutamyltranspeptidase), 185
GH. *See* growth hormone
giant cell (temporal) arteritis, 231, 851
giant platelets, 266
giardiasis, 390–391, 403
Gilbert's syndrome, 181, 184*t*
gingivitis, 475
gingivostomatitis, HSV, 517
GIST (gastrointestinal stromal cell tumor), 323, 324
glanders, 461*t*, 462
Glasgow Coma Scale, 97*t*
glatiramer acetate, for multiple sclerosis, 1018
glaucoma, 230*f*
glibornuride, for diabetes mellitus, 908*t*
gliclazide, for diabetes mellitus, 908*t*
glimepiride, for diabetes mellitus, 908*t*
glioblastoma, 1009, 1009*f*
glioma, 1008
glipizide, for diabetes mellitus, 908*t*
gliquidone, for diabetes mellitus, 908*t*
global aphasia, 239*t*, 240
globulin, in liver disease, 185
globus pharyngeus, 162
glomerular disease, 759–766, 768*t*
glomerular filtration rate (GFR), 197, 198*t*, 752, 753
glomerulonephritis (GN)
  acute, 759–760, 760*t*
  ANCA-associated, 762
  membranoproliferative, 765
  membranous, 764
  postinfectious, 760
  poststreptococcal, 760
  rapidly progressive, 760–763, 761*t*
  in SLE, 762
glomerulosclerosis, focal, 764–765
glossopharyngeal neuralgia, 1000
glucagon, for hypoglycemia, 109
glucagonoma, 332*t*, 333
glucocorticoid therapy
  for acne, 262–263
  for acute disseminated encephalomyelitis, 1020
  for acute renal failure, 751
  for Addison's disease, 899
  for adhesive capsulitis, 869
  for adult T cell leukemia/lymphoma, 301
  for alcoholic liver disease, 828
  for amiodarone-induced thyrotoxicosis, 892
  for amyloidosis, 875
  for anaphylaxis, 114
  for ANCA-associated glomerulonephritis, 762
  for ankylosing spondylitis, 857
  for asthma, 713–715
  for ataxia, 984
  for autoimmune hemolysis, 274
  for autoimmune hepatitis, 825
  for back pain, 211
  for brain tumor, 1008
  for bursitis, 869
  for CLL, 297
  for COPD, 720–721
  for cough, 148
  for croup, 537
  for dermatitis, 259–260
  for eczema, 259–260
  for enteroviral infections, 545
  for Epstein-Barr virus infections, 529
  for erythema nodosum, 263
  for fatigue, 52
  for fever, 128
  for focal glomerulosclerosis, 765
  for glomerulonephritis, 765
  for gout, 864
  for hirsutism, 921
  for histoplasmosis, 579*t*
  for hymenoptera sting, 125
  for hypercalcemia, 112, 351, 927*t*
  for increased intracranial pressure, 95*t*
  for inflammatory bowel disease, 792
  for inflammatory myopathy, 1059
  for interstitial lung disease, 737
  for larva migrans, 600
  for leprosy, 492
  for lichen planus, 259
  lymphopenia with, 276
  for minimal change disease, 764
  monocytopenia with, 277
  for multiple myeloma, 302
  for muscular dystrophy, 1054
  for myasthenia gravis, 1053
  nasal, for allergic rhinitis, 838
  for nausea and vomiting, 160
  for optic neuritis, 231
  for osteoarthritis, 862
  for pityriasis rosea, 259
  for *Pneumocystis* infections, 584, 584*t*
  for polyneuropathy, 1046

glucocorticoid therapy (*Cont.*):
for primary sclerosing cholangitis, 803
for pseudogout, 866
for psoriasis, 259
for psoriatic arthritis, 859
for reactive arthritis, 860
for rheumatoid arthritis, 846
for sarcoidosis, 872
for schistosomiasis, 605
for Sjögren's syndrome, 849
for SLE, 762, 845
for spinal cord compression, 99
for Stevens-Johnson syndrome, 263
for systemic mastocytosis, 839
for systemic sclerosis, 848
for taeniasis solium and cysticercosis, 607
for tendinitis, 870
for trichinellosis, 600
for tuberculosis, 484
for vasculitis, 854
for vertigo, 229
gluconate, for hyperkalemia, 16*t*
glucosamine and chondroitin, for osteoarthritis, 862
glucose therapy, for hypoglycemia, 109
glucose-6-phosphate dehydrogenase (G6PD) deficiency, 269, 272*t*, 274
glucose-lowering agents, oral, 906, 908–909*t*
glulisine, for diabetes mellitus, 906
gluten-free diet, 984
glyburide, for diabetes mellitus, 908*t*
glyclopyramide, for diabetes mellitus, 908*t*
glycocholic breath test, 170
glycolytic defects, 1059
GN. *See* glomerulonephritis
GNB. *See* gram-negative bacilli
goiter, 887, 892–893
gold salts, for psoriatic arthritis, 859
golimumab
for ankylosing spondylitis, 857
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
gonadotropins
deficiency of, 882, 883*t*
hypersecretion of, 881
gonorrhea
arthritis, 405–406, 419
cervicitis, 401–402, 405
clinical manifestations of, 405–406
epidemiology of, 405
epididymitis, 400
pelvic inflammatory disease, 402–403
proctitis, proctocolitis, enterocolitis, and enteritis, 403, 405
treatment of, 406–407*t*
urethritis, 400, 405
vulvovaginal infections, 400
Goodpasture's syndrome, 763, 768*t*
goserelin
for breast cancer, 320
for prostate cancer, 343
Gottron's sign, 1058
gout, 863–865
gouty arthritis, 865
GPIHBP1 deficiency, 937*t*
graded exercise therapy, for chronic fatigue syndrome, 135
graft-versus-host disease, 46, 47*t*
grain dust, 717
gram-negative bacilli (GNB)
Bartonella, 466–469
Brucella, 462–463
enteric, 453–458
Aeromonas, 458
extraintestinal *E. coli*, 454
intestinal pathogenic *E. coli*, 455
Klebsiella, 455–456
Proteus, 456–457
Francisella tularensis, 464
Yersinia pestis, 465
grand mal (tonic-clonic) seizures, 956. *See also* seizures
granisetron, for nausea and vomiting, 160
Granulicatella infections, 439–440
granuloma inguinale, 404*t*, 413
granulomatosis infantiseptica, 447
granulomatosis with polyangiitis (Wegener's granulomatosis), 851, 1039*t*
granulomatous angiitis, isolated, 1038*t*
granulomatous disease, leukocytosis in, 275
Graves' disease, 889. *See also* thyrotoxicosis
Graves' ophthalmopathy, 1061
gray hepatization, 723
griseofulvin
for dermatophyte infections, 262
for ringworm, 570
group A *Streptococcus* (GAS) infections, 434–437
bacteremia, 437

clinical manifestations of, 435–437
epidemiology of, 434–435
nosocomial, 361
pharyngitis, 253, 435
pneumonia and empyema, 437
prevention of, 437
scarlet fever, 435
skin and soft tissue infections, 435–436, 435–437, 436*t*
toxic shock syndrome, 437, 437*t*
treatment of, 436*t*
group B *Streptococcus* (GBS), 438–439
group C *Streptococcus*, 438
group D *Streptococcus*, 439
group G *Streptococcus*, 438
growth hormone (GH)
deficiency of, 882, 883*t*
hypersecretion of, 880–881
production of, 877, 878*f*
for weight loss, 137
guanfacine, for tics, 238
Guillain-Barré syndrome (GBS), 991, 1046
gumma, 410
gynecologic cancer, 339–341
gynecomastia
evaluation of, 913, 914*f*
paraneoplastic, 349*t*

H

H_2 receptor antagonists
for erosive gastropathies, 788
for peptic ulcer disease, 787
for systemic sclerosis, 848
HACEK group infections
clinical manifestations of, 452
endocarditis, 372, 378*t*, 452
microbiology of, 452
treatment of, 453*t*
Haemophilus ducreyi infections, 404*t*, 413
Haemophilus influenzae infections, 369*t*, 448–449
hallucinations, hypnagogic, 244*t*
halo sign, 573
haloperidol
for delirium, 52*t*
dosage and side effects of, 1076*t*
for nausea and vomiting, 51, 160
haloprogin, for dermatophyte infections, 262
hamartoma, gastric, 325
hand
hygiene, 357
muscles and innervation of, 949*t*
hand-foot-and-mouth disease, 545
Hantaan virus infections, 552
hantavirus pulmonary syndrome, 551
Harris and Benedict formula, 40, 41*f*
Haverhill fever, 118
HCAP. *See* health care-associated pneumonia
HD. *See* Hodgkin's disease
HDL cholesterol, 936. *See also* hypercholesterolemia
head and neck cancer, 308–309
clinical manifestations of, 309
incidence and epidemiology of, 309
infections in, 363*t*
oncologic emergencies, 110–111
paraneoplastic syndromes in, 349*t*
prevention of, 310, 1101
treatment of, 309
head and neck infections
actinomycosis, 480
anaerobic, 475
head impulse test, for vertigo, 226
head louse, 610–611
head trauma
approach to, 96–98
concussion management in sports, 97
increased intracranial pressure in, 93
intracranial hemorrhage and, 84*t*
long-term complications of, 971
post-concussion headache, 215*t*, 221
severity grading, 97*t*
subarachnoid hemorrhage in, 91
headache. *See also specific types*
approach to, 215
causes of, 215*t*
symptoms suggesting serious underlying disorder, 216*t*
health care worker, HIV infection in, 567–568
health care-associated infections, 357–361
endocarditis, 373–374. *See also* infective endocarditis
epidemic and emerging problems, 360–361
hospital-acquired, 357
nosocomial and device-related, 358–360, 359*t*, 427
prevention of, 357, 359*t*
health care-associated pneumonia (HCAP), 722
hospital-acquired pneumonia, 727
ventilator-associated pneumonia. *See* ventilator-associated pneumonia

heart
chamber size and ventricular performance, 622–623
noninvasive examination of, 622–627, 627*f*
physical examination of, 613–617
heart disease
chest pain in, 138*t*
congenital. *See* congenital heart disease
CT in, 625–626, 626*t*
cyanosis in, 145–146, 146*t*
depression in, 1064
dyspnea in, 143, 144*f*
echocardiography in, 622–623
edema in, 150–151, 152
endocarditis prophylaxis, 380, 381*t*
fatigue in, 133*t*
intracardiac mass, 624, 626*t*
in Lyme disease, 495, 496
in men, 1104
MRI in, 625, 626*t*
nausea and vomiting in, 159*t*
prevention of, 1089–1090*t*, 1092–1094, 1093*t*
risk factors for, 667, 1092–1093, 1092*t*
screening for, 1088–1090*t*
syncope in, 24*t*, 222
in syphilis, 410, 411*t*
valvular. *See* valvular heart disease
weight loss in, 136*t*
in women, 1104–1105
heart failure, 687–692
ascites in, 187, 188*f*
conditions that mimic, 688
definition of, 687
diagnosis of, 688
edema in, 150–151, 152, 688
hemodynamic profiles in, 691–692, 691*f*
lymphadenopathy and, 190*t*
precipitating factors, 687
treatment of
after STEMI, 663–664, 664*t*, 665*t*
in chronic disease, 688–692, 689*t*, 690*t*, 691*t*
heart murmurs, 615–617, 616*t*, 617*t*
heart rate, 618
heart sounds, 614–615, 615*f*, 617*t*
heart transplantation
for dilated cardiomyopathy, 642
infections after, 368–369
heartburn, 160–161
heat stroke, 129
heavy chain deposition disease, 773*t*
height, ideal weight for, 42*t*
Heinz bodies, 265
Helicobacter pylori infections
detection of, 786, 786*t*
eradication of, 161, 787, 787*t*
lymphoid malignancies and, 294
peptic ulcer disease and, 161, 785–787
helminth infections, 599–611
cestodes, 606–610
chronic meningitis in, 1036*t*
ectoparasites, 610–611
filarial worms, 603–604
intestinal nematodes, 600–603
tissue nematodes, 599–600
trematodes, 604–606
hemapheresis, 47–48
hematemesis, 174
hematin, for porphyria, 944
hematochezia, 174
hematocrit, 194
hematologic disease
bleeding disorders, 277–281
blood smear, 265–266
bone marrow examination, 266–267
fatigue in, 133*t*
leukocytosis, 274–276
leukopenia, 276–277
monocytosis in, 275
red cell disorders, 268–274
thrombotic disorders, 281–283
hematopoietic stem cell transplant (HSCT)
for ALL, 300
for amyloidosis, 875
for CLL, 297
for CML, 289
for follicular lymphoma, 298
infections after, 367*t*
infections in recipients, 366–368
for myelodysplastic syndromes, 289
for severe combined immunodeficiency, 842
vaccination of recipients, 369–370*t*
hematuria, 201–202
approach to, 202*f*
causes of, 201, 201*t*
of glomerular origin, 766
gross, 201
microscopic, 201
in renal cancer, 335
heme preparations
for acute intermittent porphyria, 944
for erythropoietic protoporphyria, 945

hemianopia, bitemporal, 229, 230*f*
hemiballismus, 237
hemiblock, 619*f*
hemicrania, paroxysmal, 221
hemicrania continua, 221
hemifacial spasm, 997–998
hemiparesis, 83, 97, 234*t*, 235*f*
hemochromatosis, 942–944
  clinical manifestations of, 942
  diagnosis of, 943, 943*f*
  genetic factors in, 942, 943*f*
  transfusion-associated, 46
  treatment of, 944
hemodialysis
  for acute renal failure, 751
  for chronic kidney disease, 754–755
  complications of, 755, 755*t*
  for hyperkalemia, 16*t*
  intermittent, 751
  for tumor lysis syndrome, 113
hemoglobin
  abnormal, 145, 269, 271*t*
  blood concentration, 194
  unstable variants, 269
hemolysis, 194, 275
hemolytic anemia, 269–273
  classification of, 271*t*
  etiology of, 269, 271, 273
  in G6PD deficiency, 272*t*
  laboratory testing in, 273
  pathophysiology of, 194
  treatment of, 274
hemolytic patterns, 434
hemolytic reactions, 46, 47*t*
hemolytic uremic syndrome (HUS), 271*t*
hemophilia A, 279, 280–281
hemophilia B, 279, 281
hemoptysis, 148–150, 149*f*
hemorrhage. *See also specific types and sites*
  in diverticular disease, 796
  leukoerythroblastic reaction in, 275
hemorrhagic fever with renal syndrome (HFRS), 552
hemorrhoidectomy, 798
hemorrhoids, 256*f*, 798
hemostatic disorders, 280
Henderson-Hasselbalch equation, 13–14
Henoch-Schönlein purpura (IgA vasculitis), 763, 768*t*, 851
heparin
  for antiphospholipid antibody syndrome, 850
  for arterial embolism, 697
  for DIC, 280
  for STEMI, 659, 662
  for thrombotic disorders, 281–282
  for venous thromboembolism, 733
heparin-induced thrombocytopenia, 278, 732–733
hepatic artery embolization, 332
hepatic disease. *See* liver disease
hepatic encephalopathy, 832–833
hepatic lipase deficiency, familial, 937*t*
hepatitis
  acute viral, 809, 814–815
  alcoholic, 184*t*, 828
  autoimmune, 185, 825
  chronic, 816–825, 1064
  fulminant, 815–816
  marrow damage in, 268
  toxic/drug-induced, 815
hepatitis A
  acute, 809, 810*t*, 812*f*
  chronic, 817
  prevention of, 812
hepatitis A immune globulin, 812
hepatitis A vaccine, 370*t*, 812, 817
hepatitis B
  acute, 810–811*t*, 812, 813*f*, 814
  chronic, 816–817, 818–821*t*
  hepatocellular carcinoma and, 330–331
  prevention of, 812–813
hepatitis B immune globulin, 812–813
hepatitis B vaccine, 370*t*, 813
hepatitis C
  acute, 810–811*t*, 813, 814–815, 814*f*
  chronic, 817, 822–824*t*
  hepatocellular carcinoma and, 330–331
  prevention of, 813
hepatitis D, 810–811*t*, 814
hepatitis E, 810–811*t*, 814
hepatobiliary disorders
  imaging in, 185–186, 800*t*
  liver function tests in, 184*t*
hepatocellular adenoma, 330
hepatocellular carcinoma, 330–331
hepatocellular disorders, liver function tests in, 184*t*
hepatorenal syndrome (HS), 189
hepatotoxins, 815
hereditary elliptocytosis, 271
hereditary spherocytosis, 271, 273

heroin abuse, 1084
herpangina, 545
herpes gladiatorum, 518
herpes simplex virus (HSV) infections, 516–519
  acyclovir-resistant, 522*t*
  Bell's palsy, 996
  cutaneous, 256*f*, 258, 261
  diagnosis of, 258
  eye, 518, 521*t*
  genital. *See* genital herpes
  meningitis in, 1037*t*
  neonatal, 519, 522*t*
  neurologic disease in, 518, 521*t*
  oral-facial, 517, 520–522*t*
  reactivation of, 517, 520–522*t*
  respiratory, 253, 534*t*
  treatment of, 261, 519, 520–522*t*
  visceral, 518, 522*t*
  whitlow, 518, 522*t*
herpes zoster, 523–524
herpes zoster infections
  clinical manifestations of, 256*f*, 261
  diagnosis of, 258
  neck pain in, 212
  treatment of, 261, 415*t*
herpetiform lesion, 255
heterophile test, 529, 529*f*
HFRS (hemorrhagic fever with renal syndrome), 552
HGA (human granulocytotropic anaplasmosis), 502*t*, 508
HHS (hyperglycemic hyperosmolar state), 104–105, 105*t*
5-HIAA (5-hydroxyindoleacetic acid), urinary, 332
high cardiac output/low systemic vascular resistance shock, 32, 33*f*
hirsutism, 920–921, 921*f*
histoplasmosis, 577–578, 579*t*, 1035*t*
histotoxic hypoxia, 100
histrionic personality disorder, 1070
HIV infection, 554–568
  clinical manifestations of, 557–558, 558*t*
  cytomegalovirus infections in, 526–527
  depression in, 1064
  diagnosis of, 556–557, 556*f*
  diarrhea in, 169*t*
  epidemiology of, 554
  esophagitis in, 166
  etiology and transmission of, 554
  health care workers and, 567–568
  immune abnormalities in, 555
  immune response to HIV, 555–556
  laboratory monitoring in, 557
  meningitis in, 1037*t*
  P. aeruginosa infections in, 459
  pathophysiology and immunopathogenesis of, 554–555
  pharyngitis in, 253
  Pneumocystis infections in, 583–585
  postexposure prophylaxis, 567
  prevention of, 568, 1089*t*
  secondary infections in, 567
  sepsis in, 68*t*
  treatment of, 559–567
    antiretroviral therapy, 559, 560–565*t*, 566–567, 566*t*, 567*t*
    prevention of secondary infections, 567
    principles of, 566–567, 566*t*
  tuberculosis and, 485
  vacuolar myelopathy in, 1006
  in women, 1105
HIV vaccine, 568
HIV-associated nephropathy (HIVAN), 764
HME (human monocytotropic ehrlichiosis), 502*t*, 507–508
Hodgkin's disease (HD), 302, 304
  classification of, 293, 295*t*
  Epstein-Barr virus in, 529
  infections in, 363*t*
  paraneoplastic syndromes in, 353*t*
  staging of, 304, 305*t*
  vaccination in, 369–370*t*
homocysteine, 1094
homonymous, 230*f*
hookworm infections, 601
hormone therapy, for prostate cancer, 343
hormones, ectopic production of, 348–350
hornet sting, 124–125
hospital-acquired pneumonia, 727
hospitalized patient
  care of
    acid-base balance, 13–22
    critical care medicine, 31–35
    electrolyte balance, 1–13
    end-of-life care. *See* terminally ill patient
    enteral nutrition, 43–44
    imaging, 23–26

nutritional status, 40–43
pain and its management, 35–40
parenteral nutrition, 44–45
procedures performed by internists, 26–31
transfusion and pheresis therapy, 46–48
infections in. *See* health care-associated infections
hot-tub folliculitis, 417
Howell-Jolly bodies, 265
HPV. *See* human papillomavirus
HRSV (human respiratory syncytial virus) infections, 534*t*, 535–536
HS (hepatorenal syndrome), 189
HSCT. *See* hematopoietic stem cell transplant
HSV infections. *See* herpes simplex virus infections
human bite, 116*t*, 118, 417
human granulocytotropic anaplasmosis (HGA), 502*t*, 508
human herpesvirus 6 infections, 525
human herpesvirus 7 infections, 525
human herpesvirus 8 infections, 294, 525
human metapneumovirus infections, 534*t*, 536
human monocytotropic ehrlichiosis (HME), 502*t*, 507–508
human papillomavirus (HPV) infections
cervical cancer and, 340, 1097*t*
clinical manifestations of, 414
microbiology of, 413
treatment of, 414
warts, 262, 414
human papillomavirus (HPV) vaccine, 341, 369*t*, 414, 1090*t*, 1101
human respiratory syncytial virus (HRSV) infections, 534*t*, 535–536
human T-lymphotropic virus infections, 294
Hunt-Hess Scale, for subarachnoid hemorrhage, 92*t*
Huntington's disease, 237–238, 974–975
HUS (hemolytic uremic syndrome), 271*t*
hyaluronan, for osteoarthritis, 862
hydralazine
for heart failure, 688, 690, 690*t*
for hypertension, 651
for malignant hypertension, 656*t*
hydralazine-nitrate, for dilated cardiomyopathy, 640
hydrocephalus
normal-pressure, 971, 974
in subarachnoid hemorrhage, 92
hydrochlorothiazide
for diabetes insipidus, 6
for edema, 153*t*
for heart failure, 690*t*
for hypertension, 651, 652*t*
hydrocodone, for dyspnea, 51*t*
hydrocortisone
for Addison's disease, 899
for adrenal insufficiency, 112
for hypopituitarism, 883*t*
for inflammatory bowel disease, 792
for myxedema coma, 889
for sepsis/septic shock, 67
hydroids, 120
hydromorphone
abuse, 1084
for dyspnea, 51*t*
for pain, 38*t*
hydrops fetalis, 542
hydrothorax, 150
hydroxychloroquine
for infective endocarditis, 378*t*
for malaria prophylaxis, 590*t*
for porphyria cutanea tarda, 945
for Q fever, 510
for rheumatoid arthritis, 846
for Sjögren's syndrome, 849
for SLE, 845
for Whipple's disease, 482
5-hydroxyindoleacetic acid (5-HIAA), urinary, 332
hydroxyprogesterone, for endometrial cancer, 340
hydroxyurea
for cervical cancer, 341
for essential thrombocytosis, 293
for sickle cell anemia, 273
for systemic mastocytosis, 839
hydroxyzine
for ciguatera poisoning, 121
for urticaria/angioedema, 837
hymenoptera sting, 124–125
hyoscyamine, for irritable bowel syndrome, 795
hypalgesia, 36
hyperaldosteronism
clinical manifestations of, 898
diagnosis of, 898
etiology of, 897
hypertension in, 650

hyperaldosteronism (*Cont.*):
primary, 897
secondary, 897
treatment of, 21, 898
hyperalgesia, 36
hyperalimentation, 18*t*
hyperbilirubinemia
conjugated (direct), 179
direct, 179*t*
indirect, 179*t*
unconjugated (indirect), 179
hypercalcemia, 924–928
clinical manifestations of, 924, 926
diagnosis of, 926–927, 927*t*
etiology of, 773*t*, 924–925, 925*f*, 926*t*
familial hypocalciuric, 925, 928
paraneoplastic, 111–112, 349*t*, 351, 924, 928
treatment of, 112, 927–928, 927*t*
hypercalciuria, 780, 926
hypercapnia, 21, 708–709, 744
hypercarbia, 73
hypercholesterolemia
approach to, 936
cardiovascular disease and, 1092, 1092*t*
definition of, 936
genetic causes of, 936, 937*t*
with hypertriglyceridemia, 937*t*, 940–941
isolated, 936
treatment of, 938–939*t*, 941–942, 1092, 1093*t*
hypereosinophilic syndromes, 276
hyperesthesia, 36
hyperglobulinemia, 185
hyperglycemia
in critically ill patient, 35
in metabolic syndrome, 657*t*
hyperglycemic hyperosmolar state (HHS), 104–105, 105*t*
hyperhidrosis, 988, 991
hyperkalemia, 6–7, 9–13
approach to, 14*f*
in chronic kidney disease, 754
drug-induced, 14*f*
ECG in, 9, 13, 14*f*, 15*f*
treatment of, 13, 16*t*
hyperkinetic (bounding) pulse, 613, 614*f*
hyperlipoproteinemia, 936, 937*t*. *See also* hypercholesterolemia; hypertriglyceridemia
hypermagnesemia, 930
hypernatremia, 6–7, 6*t*
hyperoxaluria, 780
hyperparathyroidism
primary, 924, 928
secondary, 925, 928
hyperpathia, 994
hyperphosphatemia, 754, 929
hyperprolactinemia, 79, 879–880
hyperpyrexia, 127
hypersegmentation, 266
hypersensitivity disorder, immediate type, 835–839
allergic rhinitis, 837–838
definition of, 835
pathophysiology of, 835, 835*f*
systemic mastocytosis, 838–839
urticaria and angioedema, 835–837, 836*t*
hypersensitivity pneumonitis, 736, 739
hypersomnia, 244*t*, 245
hypersplenism, 192, 273, 276
hypertension, 649–656
approach to, 650
cardiovascular disease and, 1092–1093
in chronic kidney disease, 754
definition of, 649
in diabetes, 655
essential, 649
in hyperaldosteronism, 898
malignant, 86, 655, 656*t*
in metabolic syndrome, 656–657, 657*t*
paraneoplastic, 349*t*
portal, 192, 831, 831*t*
in pregnancy, 651
pulmonary. *See* pulmonary hypertension
secondary, 649–650
supine, 994
treatment of, 1093
approach to, 654*t*, 655*f*
blood pressure goals for, 651
drug therapy for, 651, 652–653*t*, 654*t*
in special circumstances, 651, 655
in women, 1105
hyperthermia, 127, 129, 131
hyperthyroidism. *See also* thyrotoxicosis
depression in, 1064
muscle disorders in, 1061
paraneoplastic, 349*t*
primary, 889

secondary, 889
sleep disorders in, 242
subclinical, 893
hypertonic saline, for hyponatremia, 5
hypertransfusion therapy, 46
hypertriglyceridemia
familial combined, 941
genetic causes of, 937*t*, 940
isolated, 940
treatment of, 939*t*, 940
hypertrophic cardiomyopathy
ECG in, 619–620, 621*t*, 643
echocardiography in, 643
heart sounds in, 616*t*, 640*t*
initial evaluation of, 641*t*
presentation of, 642–643
treatment of, 643
hypertrophic osteoarthropathy, 868
hyperuricemia, 863, 864
hyperventilation
clinical manifestations of, 745
etiology of, 745
faintness with, 226–227
for increased intracranial pressure, 95, 95*t*
treatment of, 745
hyperviscosity syndrome, 48, 196, 773*t*
hypervolemia, 1
hypnozoite, 586
hypoalbuminemia, 151, 185, 187, 928
hypoaldosteronism, 899–900
hypocalcemia, 928–929
hypocupric myelopathy, 1007–1008
hypoglossal nerve (CN XII)
disorders of, 1001
examination of, 948
hypoglycemia, 107–109
clinical manifestations of, 107
diagnosis of, 107–108, 108*f*, 109*t*
etiology of, 107
faintness with, 227
paraneoplastic, 349, 349*t*
vs. syncope, 225
treatment of, 108–109
hypoglycemic unawareness, 107, 108
hypogonadism, 913. *See also* androgen deficiency
hypogonadotropic hypogonadism, 913
hypohidrosis, 988
hypokalemia, 7–9
approach to, 10–11*f*
causes of, 7–8, 7–8*t*
drug-induced, 7–8
treatment of, 8–9
hypokalemic alkalosis, 351
hypomagnesemia, 928, 930
hypomania, 1065–1066
hyponatremia, 1–5
acute symptomatic, 4
approach to, 3*f*
chronic, 4–5
euvolemic, 3*f*, 4
hypervolemic, 2–4, 3*f*, 5
hypovolemic, 2, 3*f*
paraneoplastic, 351
in subarachnoid hemorrhage, 92
treatment of, 4–5
hypoparathyroidism, 928–929
hypophysectomy, for prostate cancer, 343
hypopituitarism, 881–882, 883*t*
hypopnea, 745
hyposegmentation, 266
hyposensitization therapy, for allergic rhinitis, 838
hypotension
orthostatic. *See* orthostatic hypotension
in STEMI, 664, 667
hypothalamic hormones, 878*f*
hypothermia, therapeutic
for cardiac arrest, 60
for hypoxic-ischemic encephalopathy, 101
for increased intracranial pressure, 95*t*
for stroke, 87
hypothyroidism, 886–889
clinical manifestations of, 887–888
clinical (overt), 887
depression in, 1064
diagnosis of, 888, 888*f*
edema in, 151
etiology of, 886–887, 887*t*
muscle disorders in, 1060
subclinical (mild), 887
treatment of, 888–889
hypoventilation, 744–745
hypovolemia, 2, 665*t*
hypovolemic shock, 32, 33*f*
hypoxemia, 73
approach to, 708*f*
in ARDS, 71
mechanisms of, 708–709. *See also* respiratory disease
in pulmonary edema, 144
hypoxia, 100
histotoxic, 100

hypoxia (*Cont.*):
hypoxic-ischemic encephalopathy, 100–101
hysterectomy, 340

I
ibandronate, for osteoporosis, 934
IBD. *See* inflammatory bowel disease
IBM (inclusion body myositis), 1057–1058, 1058*t*
ibritumomab, for follicular lymphoma, 298
ibrutinib, for CLL, 297
IBS (irritable bowel syndrome), 794–795, 795*t*, 796*t*
ibuprofen
for migraine, 217*t*
for pain, 38*t*
for pericarditis, 645
for SLE, 845
ibutilide
for arrhythmias, 684*t*
for Wolff-Parkinson-White syndrome, 686
ICD. *See* implantable cardioverter defibrillator
ICP. *See* intracranial pressure
ICSI (intracytoplasmic sperm injection), 915, 925
icterus. *See* jaundice
ICU (intensive care unit), monitoring in, 34
ICU patient. *See* critically ill patient
idarubicin, for AML, 287
idebenone, for ataxia, 984
idiopathic myelofibrosis, 292–293
idiopathic pulmonary fibrosis (IPF), 737–738
idiopathic thrombocytopenic purpura (ITP), 278
idoxuridine, for HSV infections, 521*t*
ifosfamide, for cervical cancer, 341
IgA deficiency, isolated, 843
IgA nephropathy, 766–767
IgA vasculitis (Henoch-Schönlein purpura), 763, 768*t*, 851
IHD (intermittent hemodialysis), 751
ILD. *See* interstitial lung disease
ileal pouch-anal anastomosis, 794
ileoproctostomy, 327
iloperidone, 1077*t*
iloprost, for pulmonary hypertension, 702
imaging, diagnostic, 23–26
imatinib, for CML, 288
imidazoles, for dermatophyte infections, 262
imipenem
for cholecystitis, 801
for community-acquired pneumonia, 725*t*
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for human bite infections, 116*t*
for melioidosis, 461*t*
for mixed anaerobic infections, 476*t*
for nocardiosis, 479
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460*t*
for peritonitis, 383
for *Proteus* infections, 457
imipenem-cilastatin, for sepsis/septic shock, 68*t*
imipramine
dosage and side effects of, 39*t*, 1072*t*
for noncardiac chest pain, 164
for pain, 39*t*
imiquimod
for HPV infections, 414
for warts, 262
immune reconstitution inflammatory syndrome (IRIS), 1031
immune-complex disorders, 48
immune-mediated myelopathy, 1006
immunization
DTaP, 442
H. influenzae, 449
Hib, 369*t*
HIV, 568
HPV, 369*t*, 414
of immunosuppressed patients, 369–370*t*
influenza, 370*t*, 533
measles, 370*t*, 539
meningococcal, 370*t*, 445–446
mumps, 370*t*, 539, 541
pertussis, 451
pneumococcal, 370*t*, 422, 425
poliovirus, 545–546
rabies, 548, 549*f*
recommendations for, 1088–1090*t*
rotavirus, 390
rubella, 370*t*, 539, 540
Td, 442
tetanus, 442, 471
tuberculosis, 490
VZV, 371*t*, 524

immunocompromised host
cytomegalovirus infections in, 526–527
HSV infections in, 517–519, 520–522*t*
immunization of, 369–370*t*
infections in, 362–371
cancer patients, 362–366, 363*t*, 365*f*
transplant recipients, 366–369, 367*t*
Pneumocystis infections in, 583–585
VZV infections in, 523
immunodeficiency disease
of adaptive immune system, 840–843, 841*t*
classification of, 841*t*
definition of, 840
diagnosis of, 842*t*
immunoglobulin deficiency syndromes, 843
of innate immune system, 840, 841*t*
leukopenia in, 276
regulatory defects, 841*t*
T cell immunodeficiency, 840, 842
immunoglobulin deficiency syndromes, 843
immunohemolytic anemia, 271
immunoproliferative small-intestinal disease (IPSID), 325
immunosuppressive agents
after renal transplantation, 758
for dilated cardiomyopathy, 42
for inflammatory bowel disease, 794
for liver transplantation, 830
for SLE, 845
for vasculitis, 854
impetigo
clinical manifestations of, 260, 417
diagnosis of, 417
microbiology of, 260, 417
pathogenesis of, 417
streptococcal, 436, 436*t*
treatment of, 261
implantable cardioverter defibrillator (ICD)
for dilated cardiomyopathy, 641
for heart failure, 692
for hypertrophic cardiomyopathy, 643
in vitro fertilization (IVF), 924
inactivated poliovirus vaccine (IPV), 546
incidentaloma, 900, 900*f*
inclusion body myositis (IBM), 1057–1058, 1058*t*
indigestion, 160–161
indolent lymphoma, 295*t*, 298
indomethacin
for pain, 38*t*
for pericarditis, 645
for reactive arthritis, 860
indomethacin-responsive headache, 221
infant botulism, 471–472
infections. *See also* antibacterial therapy; *specific diseases and pathogens*
diarrhea with, 168
fatigue in, 133*t*
headache in, 215*t*
health care-associated infections. *See* health care-associated infections
in immunocompromised host, 362–371
cancer patients, 362–366, 363*t*, 365*f*
immunization and, 369–370*t*
transplant recipients, 366–369, 367*t*, 758–759, 759*t*
leukemoid reaction in, 275
leukopenia in, 276
lymphadenopathy and, 190*t*
lymphocytosis in, 275
monocytosis in, 275
neck pain in, 212
nephritis with, 771–772, 771*t*
neutrophilia in, 274–275
sepsis and. *See* sepsis
skin, 260–262
with transfusion, 46, 47*t*
upper respiratory. *See* upper respiratory infections (URIs)
weight loss in, 136*t*
infectious mononucleosis
cytomegalovirus, 526
Epstein-Barr virus, 528–529, 529*f*
infectious myelopathy, 1006
infective endocarditis, 372–381
acute, 372
Bartonella, 467*t*, 468
clinical manifestations of, 373–374
diagnosis of, 374, 375*t*
epidemiology of, 372
etiology of, 72
HACEK group, 372, 378*t*, 452, 453*t*
outcome of, 380
pathogenesis of, 372–373

infective endocarditis (*Cont.*):
prevention of, 380, 381*t*, 631
S. aureus, 372, 427–428
streptococcal, 439
subacute, 372
treatment of, 374, 376, 378*t*, 378–380, 379–381, 379*t*
inferior vena cava filter, 733
infertility
female, 923–924, 923*f*
male, 915
inflammation
basophilia in, 276
neutropenia in, 274–275
inflammatory bowel disease (IBD), 790–794
Crohn's disease, 791
differential diagnosis of, 792
in enteropathic arthritis, 867
epidemiology of, 790–791, 790*t*
extraintestinal manifestations of, 792
treatment of, 792, 793*f*, 794
ulcerative colitis, 791
infliximab
for ankylosing spondylitis, 857
for inflammatory bowel disease, 794
for psoriasis, 259
for psoriatic arthritis, 858
for rheumatoid arthritis, 846
influenza
clinical manifestations of, 531, 534*t*
complications of, 531
epidemiology of, 530–531
laboratory testing in, 531
microbiology of, 530
nosocomial, 360
pathogenesis of, 530
prevention of, 533
treatment of, 531–532, 532*t*
influenza vaccine, 370*t*, 533, 1090*t*
innate immune system, deficiencies of, 841*t*
insomnia, 241–243
drug-induced, 242
long-term (chronic), 241
psychophysiologic, 241
rebound, 242
short-term, 241
treatment of, 242, 243*t*
insulin resistance syndrome. *See* metabolic syndrome
insulin therapy
combinations, 907*t*
for diabetes mellitus, 906–907, 907*t*, 910*t*
for diabetic ketoacidosis, 106*t*
for hyperglycemic hyperosmolar state, 105
for hyperkalemia, 16*t*
long-acting preparations, 907*t*
short-acting preparations, 907*t*
insulinoma, 107, 109*t*, 332–333, 332*t*
integrase inhibitors, for HIV infection, 559, 564–565*t*
intensive care unit (ICU), monitoring in, 34
intercostal neuritis, 141
interferon therapy
for adult T cell leukemia/lymphoma, 301
for HSV infections, 521*t*
for squamous cell carcinoma, 308
interferon-alpha therapy
for carcinoid tumor, 332
for chronic hepatitis B, 817
for essential thrombocytosis, 293
for follicular lymphoma, 298
for hepatocellular carcinoma prevention, 331
for islet-cell tumors, 333
for melanoma, 307
for renal cancer, 335
for Zollinger-Ellison syndrome, 790
interferon-beta therapy, for multiple sclerosis, 1016, 1018
interleukin-2 therapy
for melanoma, 307
for renal cancer, 335
intermittent hemodialysis (IHD), 751
internist, procedures commonly performed by, 26–31
lumbar puncture, 28–30, 29*f*
paracentesis, 30–31
thoracentesis, 27–28, 28*f*
interstitial cystitis, 778–779
interstitial lung disease (ILD), 734–739
alveolar hemorrhage syndromes, 739
approach to, 734, 736–737
classification of, 735–736*t*
in connective tissue disorders, 738
cryptogenic organizing peripheral neuropathy, 738
desquamative interstitial pneumonia, 738
hypersensitivity pneumonitis, 739

idiopathic pulmonary fibrosis, 737–738
management of, 737
nonspecific interstitial pneumonia, 738
pulmonary alveolar proteinosis, 738
pulmonary infiltrates with eosinophilia, 738–739
pulmonary Langerhans cell histiocytosis, 739
interstitial nephritis
acute, 771–772, 771*t*
chronic, 772
intestinal decompression, 797
intestinal hypermotility, paraneoplastic, 349*t*
intestinal infections
botulism, 472
pathogenic *E. coli*, 455
intestinal motility, 167, 168
intestinal pseudoobstruction, 797
intimate partner violence (domestic violence), 1091*t*, 1106
intraabdominal infections, 382–385
abscess, 384–385
clostridial, 473
peritonitis, 382–384
intra-arterial pressure monitoring, 34
intracerebral/intracranial hemorrhage. *See also* subarachnoid hemorrhage
causes of, 84*t*
clinical manifestations of, 83–85
in head trauma, 98
intracranial pressure in, 93
treatment of, 87
intracranial aneurysm, 84*t*
intracranial pressure (ICP)
increased, 93–96
clinical manifestations of, 93–94
impaired consciousness and, 81
treatment of, 94–95, 95*t*
monitoring of, 95, 95*t*, 96*f*
intracranial (saccular) aneurysm, 91
intracranial tumor, 1009–1010
intracytoplasmic sperm injection (ICSI), 915, 924
intraperitoneal abscess, 384
intrauterine contraceptive device, 479, 922
intrauterine insemination (IUI), 924
intravascular device infections, 359*t*, 360
intravenous immunoglobulin
for antiphospholipid antibody syndrome, 850
for *C. difficile* infections, 398
for CLL, 297
for enterovirus, 545
for idiopathic thrombocytopenic purpura, 280
for immunoglobulin deficiency syndromes, 843
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for myasthenia gravis, 1053
for parvovirus infection, 542
for polyneuropathy, 1044, 1046
for staphylococcal infections, 434
for streptococcal infections, 436*t*
invasive pulmonary aspergillosis, 572
iodine deficiency, 892
iodine excess, 889
iodoquinol, for amebiasis, 397
IPF (idiopathic pulmonary fibrosis), 737–738
ipilimumab, for melanoma, 307
ipratropium, for COPD, 720, 721
IPSID (immunoproliferative small-intestinal disease), 325
IPV (inactivated poliovirus vaccine), 546
irbesartan, for heart failure, 690*t*
irinotecan
for breast cancer, 321
for cervical cancer, 341
for colorectal cancer, 328
IRIS (immune reconstitution inflammatory syndrome), 1031
iris lesion, 255
iron
overload, 46
storage disorder. *See* hemochromatosis
supplementation, in chronic kidney disease, 754
iron-deficiency anemia, 268–269, 268*f*, 270*t*, 273
irritable bowel syndrome (IBS), 794–795, 795*t*, 796*t*
ischemic stroke, 82–83
causes of, 87–88, 88*t*
treatment of, 84–87, 86*t*
islet-cell tumor
pancreatic, 332–333, 332*t*
paraneoplastic syndromes in, 349*t*
isocarboxazid, 1073*t*
isolation techniques, 357
isometheptene, for migraine, 218*t*

isoniazid
for latent tuberculosis, 490*t*
for nontuberculous mycobacterial infections, 494
for tuberculosis, 485–486, 487–488*t*, 490
isoproterenol, for tachyarrhythmias, 682*t*
isosorbide dinitrate (ISDN)
for achalasia, 164
for chronic stable angina, 675*t*
for esophageal spasm, 165
for heart failure, 690, 690*t*
isosorbide mononitrate (ISMO), for chronic stable angina, 675*t*
isotretinoin, for acne, 262
itch mite, 610
ITP (idiopathic thrombocytopenic purpura), 278
itraconazole, 569
for aspergillosis, 574*t*
for blastomycosis, 581
for *Candida* esophagitis, 166
for candidiasis, 571
for coccidioidomycosis, 580
for dermatophyte infections, 262
for histoplasmosis, 579*t*
for paracoccidioidomycosis, 582
for penicilliosis, 582
for sporotrichosis, 582
IUI (intrauterine insemination), 924
IV drug use, endocarditis and, 373
ivabradine, for heart failure, 580
ivermectin
for ascariasis, 601
for cutaneous larva migrans, 600
for lymphatic filariasis, 604
for onchocerciasis, 604
for scabies, 610
for strongyloidiasis, 602
IVF (in vitro fertilization), 924
Ixodes ticks, 495

J

Japanese encephalitis, 550
Jarisch-Herxheimer reaction, 410–411, 496, 499
jaundice, 178–181, 331
approach to, 180, 180*f*
causes of, 179, 179*t*
cholestatic conditions producing, 182–183*t*
definition of, 178
drug-induced, 182*t*
hepatocellular conditions producing, 182*t*
JC virus, 1030–1031
jellyfish sting, 120
jet lag, 241, 245
joint disease, neuropathic, 867–868
joint infections
anaerobic, 476
arthritis, 418–420, 427, 430
osteomyelitis. *See* osteomyelitis
P. aeruginosa, 459, 460*t*
in tuberculosis, 484
joint pain, 203–207
assessment of, 203
diagnosis of, 204*f*
in elderly, 205–207
historic features in, 203–204
imaging in, 205, 205*t*
laboratory testing in, 205
physical examination in, 204–205
joint replacement surgery, 862, 869
joints, muscles and innervation of, 949–950*t*
josamycin, for tick-borne spotted fevers, 505
jugular foramen syndrome, 1000
jugular venous pulsation (JVP), 613
Junin/Argentinian hemorrhagic fever, 551
juvenile polyposis, 326*t*, 327

K

kala-azar (visceral leishmaniasis), 593–594
kaolin-pectin, for diarrhea, 170
Kaposi's sarcoma, 525, 558
Katayama fever, 605
kayexalate, for hyperkalemia, 16*t*
Kenya tick typhus, 504
keratinolytic agents, for warts, 262
keratoconjunctivitis sicca (KCS), 849
keratosis pilaris, 256*f*
ketoconazole
for adrenal carcinoma, 896
for *Candida* esophagitis, 166
for ectopic ACTH syndrome, 351
ketorolac, for pain, 38*t*, 40
kidney cancer. *See* renal cancer
kidney disease. *See* renal disease
kidney stones, 385
Kingella kingae infections, 452, 453*t*
Klebsiella infections
enteric, 455–456
K. granulomatosis, 404*t*, 413
Klinefelter's syndrome, 913

Koplik's spots, 538
Kussmaul sign, 613
kwashiorkor, 41
kyphoscoliosis, 143

L
labetalol
  for aortic dissection, 695, 696*t*
  for hypertension, 651, 652*t*
  for malignant hypertension, 656*t*
labyrinthine dysfunction, 227
labyrinthitis, 227
lacosamide, for seizures, 963*t*, 967*t*
lactic acidosis, 17, 18*t*, 19
lactose hydrogen breath test, 170
lactulose
  for constipation, 50*t*, 174
  for hepatic encephalopathy, 833
  for irritable bowel syndrome, 796*t*
lacunar syndromes, 82, 83
Lambert-Eaton myasthenic syndrome (LEMS), 352*t*, 354*t*, 1050
laminectomy, decompressive, 99
lamivudine
  for chronic hepatitis B, 817, 818–819*t*
  for HIV infection, 560*t*, 566
lamotrigine
  for bipolar disorder, 1066
  dosage and side effects of, 1078*t*
  for seizures, 963*t*, 967*t*
  for trigeminal neuralgia, 995
lanreotide autogel, for acromegaly, 881
lansoprazole
  for *H. pylori* eradication, 787*t*
  for Zollinger-Ellison syndrome, 789–790
larva migrans, 600
laryngeal palsy, 1000
laryngitis, 253–254
laser therapy, for esophageal carcinoma, 322
Lassa fever, 551
Laurence-Moon-Biedl syndrome, 901
laxatives, 50*t*
  for constipation, 174
  for hemorrhoids, 798
LBP. *See* low back pain
LCM (lymphocytic choriomeningitis), 549, 1037*t*
LDL cholesterol, 936. *See also* hypercholesterolemia
lead-time bias, 1095
leech infestation, 611
leflunomide
  for psoriatic arthritis, 859
  for rheumatoid arthritis, 846
left ventricular hypertrophy, 620, 620*f*
Legionella infections, 361, 511–513
Legionnaires' disease, 512
leiomyoma, 325
leiomyosarcoma, 323, 324
leishmaniasis, 593–594
Lemierre's syndrome, 475
LEMS (Lambert-Eaton myasthenic syndrome), 352*t*, 354*t*, 1050
lenalidomide
  for multiple myeloma, 302
  for myelodysplastic syndromes, 289
length bias, 1095
lepirudin
  for heparin-induced thrombocytopenia, 280
  for thrombotic disorders, 282
leprosy, 490–492
  clinical manifestations of, 491
  complications of, 491
  diagnosis of, 491
  epidemiology of, 490
  lepromatous, 491–492
  microbiology of, 490
  treatment of, 492
  tuberculoid, 491
leptomeningeal metastasis, 1001*t*, 1011
leptospirosis, 497–498
Leriche syndrome, 696
letrozole, for breast cancer, 321
leucovorin
  for colorectal cancer, 328
  for gastric cancer, 323
  for *Pneumocystis* prophylaxis, 585*t*
leukapheresis, 48
leukemia, 268. *See also specific types*
  definition of, 293
  infections in, 363*t*
  monocytopenia in, 277
  oligoblastic, 289
leukemoid reaction, 275
leukocytes
  inclusion and nuclear abnormalities, 266
  normal values in blood, 274*t*
leukocytosis, 274–276
leukoerythroblastic reaction, 275
leukopenia, 276–277
leukoplakia, 256*f*, 309, 528, 529, 1101
leuprolide, for prostate cancer, 343
levetiracetam
  for myoclonus, 238
  for seizures, 963*t*, 967*t*

levocetirizine
for allergic rhinitis, 838
for urticaria/angioedema, 837
levodopa, for Parkinson's disease, 978, 980*t*
levofloxacin
for *C. pneumoniae* infections, 513
for community-acquired pneumonia, 725*t*
for epididymitis, 400
for health care–associated pneumonia, 727*t*
for *Legionella* infections, 513
for *M. pneumoniae* infections, 511
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 461*t*
for pneumococcal infections, 424
for *S. maltophilia* infections, 461*t*
for sepsis/septic shock, 68*t*
for tuberculosis, 486
levomilnacipran, 1073*t*
levorphanol, for pain, 38*t*
levosimendan, for heart failure, 691*t*
levothyroxine
for hypothyroidism, 888–889
for myxedema coma, 889
for thyroid neoplasms, 894
for thyroiditis, 891
LH. *See* luteinizing hormone
Lhermitte's symptom, 1013
lice, human, 610–611
lichen planus, 256*f*, 259
lichen simplex chronicus, 256*f*
lichenification, 257*t*
Liddle's syndrome, 20
lidocaine
for arrhythmias, 683*t*
for polyneuropathy, 1044, 1045*t*
for postherpetic neuralgia, 524
for tachyarrhythmias, 681–682*t*
for ventricular fibrillation, 59*f*
Li-Fraumeni syndrome, 317
light chain deposition disease, 772–773, 773*t*
lightheadedness, 226–227
limb dystonia, 237
limb-girdle dystrophy, 1054
limbic encephalitis, paraneoplastic, 352*t*, 353, 353*t*, 354*t*
linagliptin, for diabetes mellitus, 908*t*
linear skin lesion, 255
linezolid
for community-acquired pneumonia, 725*t*
for enterococcal infections, 440
for health care–associated pneumonia, 727*t*
for MRSA infections, 416*t*
for nocardiosis, 479
for staphylococcal infections, 430, 431*t*, 433*t*
linitis plastica, 323
liothyronine, for thyroid neoplasms, 894–895
lipase, serum, 804
lipemia retinalis, 940
lipoma, small-bowel, 325
lipoprotein lipase deficiency, 937*t*, 940
liquid nitrogen, for warts, 262
liraglutide, for diabetes mellitus, 906, 909*t*
lisinopril
for heart failure, 690*t*
for hypertension, 653*t*
listerial infections, 446–447
lithium
for amiodarone-induced thyrotoxicosis, 892
for bipolar disorder, 1066
for cluster headache prevention, 219
dosage and side effects of, 6, 1078*t*
pharmacology of, 1078, 1078*t*
liver abscess, 384–385, 396–397
liver biopsy, percutaneous, 186
liver disease
alcoholic, 827–828
benign tumors, 330
cirrhosis. *See* cirrhosis
coagulation disorders in, 279, 281
encephalopathy in, 832–833
hepatitis. *See* hepatitis
imaging in, 185–186
jaundice in, 178–179
liver flap, 238
liver function tests, 181–185, 181*f*, 184*t*
liver transplantation
for alcoholic liver disease, 828
for amyloidosis, 875
for ascites, 188
for chronic hepatitis B, 820–821*t*
complications of, 830
contraindications to, 830*t*
donor selection for, 830
for fulminant hepatitis, 816
for hepatic encephalopathy, 833
immunosuppressive agents for, 830
indications for, 829*t*
infections after, 369

for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for toxic and drug-induced hepatitis, 815
for Wilson's disease, 946
LMWH. *See* low-molecular-weight heparin
lockjaw, 470
lofexidine, for narcotic withdrawal, 1085
Löffler's syndrome, 601
Löfgren's syndrome, 871
lomitapide, for dyslipidemia, 939*t*
loperamide
for diarrhea, 170
for inflammatory bowel disease, 792
for irritable bowel syndrome, 795, 796*t*
loratadine
for allergic rhinitis, 838
for urticaria/angioedema, 837
lorazepam
for delirium, 52*t*
dosage and action of, 1075*t*
for dyspnea, 51*t*
for nausea, 51
for status epilepticus, 102*f*
for STEMI, 661
losartan
for heart failure, 690*t*
for hypertension, 653*t*
for systemic sclerosis, 848
louse-borne epidemic typhus, 502*t*, 506–507
louse-borne relapsing fever, 498–499
lovastatin, for dyslipidemia, 938*t*
low back pain (LBP), 207–307
etiology of, 209–211
examination in, 207–208, 208*t*
laboratory testing in, 208–209
risk factors for structural cause, 209*t*
treatment of, 211
types of, 207
low back strain/sprain, 210
lower esophageal sphincter, disorders of, 164–165
low-molecular-weight heparin (LMWH)
for STEMI, 662
for thrombotic disorders, 281–282
for UA/NSTEMI, 670
for venous thromboembolism, 733
loxapine, 1076*t*
lubiprostone, for irritable bowel syndrome, 796*t*
Ludwig's angina, 475
lumbar disk disease, back pain in, 209
lumbar puncture
in meningococcal infections, 445
technique for, 28–30, 29*f*
lumbar puncture headache, 221
lumpectomy, 320
lung abscess, 726, 729–730
lung biopsy, 737
lung cancer, 310–316
adenocarcinoma, 314*t*, 315
causes of, 716–718
chest pain in, 138*t*
clinical manifestations of, 311
diagnosis of, 709
etiology of, 310, 311*f*
histologic classification of, 310
incidence of, 310
non-small cell, 314*t*, 315
oncologic emergencies in, 110–111
paraneoplastic syndromes in, 349, 349–350*t*, 353*t*, 354*t*
prevention of, 1100
prognosis of, 315, 316*t*
risk factors for, 1100
screening for, 315, 1095, 1098*t*
small-cell, 314*t*, 315
staging of, 311, 312–313*t*
treatment of, 313, 314–315*t*, 315
lung disease. *See* respiratory disease
lung flukes, 606
lung transplant
for COPD, 721
infections after, 369
for interstitial lung disease, 737
lung volume reduction surgery, 721
lung volumes, 705*f*
lupus, drug-induced, 844
lupus pernio, 871
lurasidone, 1077*t*
luteinizing hormone (LH)
deficiency of, 882, 883*t*
production of, 877, 878*f*
Lyme borreliosis, 494–497
clinical manifestations of, 495
diagnosis of, 496
epidemiology of, 495
meningitis in, 1033*t*
microbiology of, 494
prevention of, 122–123, 496
treatment of, 496

lymphadenitis, in tuberculosis, 483
lymphadenopathy, 189–191
  approach to, 191
  diseases associated with, 190*t*
  etiology of, 189, 190*t*
  in HIV infection, 558
  in nontuberculous mycobacterial infections, 493
  treatment of, 191
lymphangiectasia, intestinal, 276
lymphedema, 699
lymphocutaneous disease, *Nocardia*, 478, 480*t*
lymphocytes, defective egress of, 840
lymphocytic choriomeningitis (LCM), 549, 1037*t*
lymphocytic leukemia, chronic. *See* chronic lymphocytic leukemia
lymphocytosis, 275
lymphoepithelioma, 309
lymphogranuloma venereum, 404*t*, 408
lymphoid malignancies, 293–305. *See also specific types*
  classification of, 293–294, 295*t*
  diagnosis and staging of, 294, 296
  etiology of, 294
  incidence and etiology of, 294, 296*f*
lymphoma, 293, 525. *See also specific types*
  aggressive, 295*t*, 299
  anaplastic large cell, 294, 296*f*
  Burkitt's, 294, 296*f*, 300–301
  definition of, 293
  diffuse large B cell, 299
  Epstein-Barr virus in, 529
  fever of unknown origin in, 129
  follicular, 294, 296*f*, 298
  indolent, 295*t*, 298
  infections in, 363*t*
  lymphopenia with, 276
  MALT, 294, 296*f*
  mantle cell, 294
  non-Hodgkin's, 296*f*, 298–299, 300*t*
  oncologic emergencies, 110–111
  primary CNS, 1010
lymphopenia, 276–277
lymphoproliferative disease, Epstein-Barr virus, 528, 529
Lynch syndrome, 326*t*, 327, 338

M
M component, 301
MAC (*Mycobacterium avium* complex) infections, 492–494
Machupo/Bolivian hemorrhagic fever, 551
macrolides
  for *C. pneumoniae* infections, 513
  for community-acquired pneumonia, 725*t*
  for *Corynebacterium* infections, 443
  for *H. influenzae* infections, 449
  for *Legionella* infections, 513
  for Lyme borreliosis, 496
  for *M. catarrhalis* infections, 452
  for *M. pneumoniae* infections, 511
  for nontuberculous mycobacterial infections, 494
  for pertussis, 451
  for pneumococcal infections, 424
macular degeneration, 230*f*, 231
maculatum disease, 501*t*
macules, 257*t*, 362
magnesium citrate, for constipation, 50*t*
magnesium hydroxide (Milk of Magnesia)
  for constipation, 50*t*
  for irritable bowel syndrome, 796*t*
magnesium sulfate
  for tetanus, 470
  for ventricular fibrillation, 59*f*
magnesium therapy
  for alcoholic liver disease, 828
  for hypomagnesemia, 930
  for torsades de pointes, 682*t*
magnetic resonance angiography (MRA), in stroke, 85, 87
magnetic resonance imaging (MRI)
  for breast cancer screening, 1096*t*
  in coma, 81
  in heart disease, 625, 626*t*
  hepatobiliary, 800*t*
  in hepatobiliary disease, 186
  indications for, 26
  in optic neuritis, 231
  in respiratory disease, 709
  in spinal cord compression, 98
  in spinal epidural abscess, 98
  in STEMI, 659
  in stroke, 87
  utility of, 26
  in vertigo, 227
malabsorption syndromes, 170, 173*t*
malaria, 586–591
  clinical manifestations of, 587
  diagnosis of, 587
  microbiology and epidemiology of, 586

pathogenesis of, 586–587
in pregnancy, 587
prevention of, 589, 590–591*t*
treatment of, 587, 588–589*t*
Malassezia infections, 581
malathion, for pediculiasis, 611
maldigestion, 173*t*
male gender, cardiovascular disease and, 1093
male reproductive system disorders, 912–916
malingering, 1069
malnutrition, 41–43, 187
MALT lymphoma. *See* mucosa-associated lymphoid tissue lymphoma
mammography, 318, 1095, 1096*t*
mandibular positioning device, 746
mania, 1065–1066
mannitol therapy
for increased intracranial pressure, 95, 95*t*
for stroke, 87
mantle cell lymphoma, 294
MAOIs. *See* monoamine oxidase inhibitors
marasmus, 41
maraviroc, for HIV infection, 559, 564*t*
Marburg virus infection, 552–553
march hemoglobinuria, 273
Marfan's syndrome, 694
marine envenomations, 120–121
invertebrate, 120
vertebrate, 120–121
marine poisoning, 121–122
massage, for chronic back pain, 211
mastectomy
bilateral prophylactic, 1100
for breast cancer, 320
mastitis, 427
mastocytosis, systemic, 838–839, 839*t*
mastoiditis, 251
McArdle's disease, 1059
MCTD (mixed connective tissue disease), 848
MDMA (ecstasy), 4
MDR (multidrug-resistant) tuberculosis, 482
MDS. *See* myelodysplastic syndromes
measles, mumps, and rubella (MMR) vaccine, 370*t*, 539, 1090*t*
measles inclusion-body encephalitis (MIBE), 538
measles (rubeola), 538–539
measles vaccine, 370*t*, 539
mebendazole
for ascariasis, 601
for enterobiasis, 603
for hookworm, 601
for trichinellosis, 599
mechanical ventilation. *See* ventilatory support
meclizine
for nausea and vomiting, 51, 160
for vertigo, 228*t*
mediastinal mass, 743
mediastinitis, 743
mediastinitis, fibrosing, 578
mediastinoscopy, 711
medical emergencies. *See* emergencies, medical
medicinal leech, 611
Mediterranean spotted fever, 501*t*, 504
medroxyprogesterone
for amenorrhea, 918
for menopausal symptoms, 922
medulloblastomas, 1010
mefloquine, for malaria, 589, 591*t*
megakaryoblastic leukemia, 284*t*
megestrol
for endometrial cancer, 340
for weight loss, 137
meglumine antimonate, for leishmaniasis, 594
melanoma, 305–307
acral lentiginous, 306
lentigo maligna, 306
nodular, 306
paraneoplastic syndromes in, 353*t*
risk factors for, 306, 306*t*
superficial spreading, 306
melarsoprol, for sleeping sickness, 596
melasma, 256*f*
melena, 174
melioidosis, 461*t*, 462
melphalan
for amyloidosis, 875
for multiple myeloma, 302
memantine, for Alzheimer's disease, 973
membranoproliferative glomerulonephritis (MPGN), 765
MEN 1 (multiple endocrine neoplasia type 1), 332, 789, 924
Ménière's disease, 227, 228*t*, 229
meningeal syphilis, 410
meningioma, 230*f*, 1010, 1011*f*

meningitis
approach to, 1020, 1021–1022*f*
bacterial, 1022–1025
clinical manifestations of, 1022–1023
differential diagnosis of, 1023
E. coli, 454
etiology of, 1022, 1025*t*
H. influenzae, 448–449
laboratory features of, 1023, 1023*t*
listerial, 446–447
meningococcal, 444–445
pneumococcal, 423–425
prognosis of, 1025
streptococcal, 438
treatment of, 1024–1025, 1024*t*, 1025*t*
in cancer patients, 364
chronic
approach to, 1032, 1040
bacterial, 1033–1034*t*
clinical manifestations of, 1031–1032, 1032*t*
etiology of, 1032
fungal, 1034–1035*t*
helminthic, 1036*t*
noninfectious, 1038–1039*t*
protozoal, 1035–1036*t*
viral, 1037*t*
in coccidioidomycosis, 579
in poliovirus infection, 543
in tuberculosis, 484
viral
clinical manifestations of, 1025
diagnosis of, 1026–1027
differential diagnosis of, 1027
enteroviral, 544
etiology of, 1026, 1026*t*
HSV, 518, 521*t*
treatment of, 1027
meningococcal infections, 443–446
clinical manifestations of, 444–445
diagnosis of, 445
epidemiology of, 443–444
etiology of, 443
pathogenesis of, 444
prevention of, 445–446
prognosis of, 445
treatment of, 445
meningococcal vaccine, 370*t*, 445–446
meningococcemia, 444
meningoencephalitis, listerial, 446
meningovascular syphilis, 410
menopause, 242, 921–922
mental status exam, 947
meperidine
abuse, 1084
for cholecystitis, 801
for pain, 39*t*
meralgia paresthetica, 1049*t*
6-mercaptopurine
for Burkitt's lymphoma, 301
for inflammatory bowel disease, 794
meropenem
for *B. cepacia* infections, 461*t*
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for cholecystitis, 801
for community-acquired pneumonia, 725*t*
for glanders, 461*t*
for health care–associated pneumonia, 727*t*
for melioidosis, 461*t*
for mixed anaerobic infections, 476*t*
for *P. aeruginosa* infections, 460*t*
for sepsis/septic shock, 68*t*
for Whipple's disease, 482
merozoite, 586
MERS-CoV (Middle East respiratory syndrome coronavirus), 535
mesalamine enema, for inflammatory bowel disease, 792
mesenchymal tumors, 349*t*
mesenteric arteriography, 175, 832
mesenteric insufficiency, chronic, 797
mesenteric ischemia, 797
mesothelioma, 716
metabolic acidosis, 15–20, 18*t*
anion-gap, 17, 18*t*, 19, 22
causes of, 15, 17, 18*t*, 19
drug-induced, 18*t*
hyperchloremic, 19
nomogram for, 17*f*
non-anion-gap, 18*t*, 19, 22
metabolic alkalosis, 17*f*, 20–21, 21*f*
metabolic disease
abdominal pain in, 155*t*
fatigue with, 133*t*
muscle disorders in, 1061
nausea and vomiting in, 159*t*
neutropenia and, 275
weight loss in, 136*t*
metabolic syndrome, 905
cardiovascular disease risk and, 1093, 1093*t*
clinical manifestations of, 657
definition of, 656, 657*t*

etiology of, 656–657
treatment of, 658
metabolism, of food, 40
metformin
for diabetes mellitus, 906, 908*t*
for polycystic ovarian syndrome, 918
methadone
abuse, 1084
for narcotic withdrawal, 1085
for opioid maintenance, 1086
for pain, 38*t*
methanol poisoning, 17, 18*t*, 19
methemoglobinemia, 145
methenamine, for nephrolithiasis, 782*t*
methicillin-resistant *S. aureus* (MRSA) infections
endocarditis, 377*t*
epidemiology of, 426
osteomyelitis, 421*t*
skin and soft tissue, 416*t*, 428
treatment of, 68*t*, 430, 431–433*t*
methimazole, for thyrotoxicosis, 890
methotrexate
for ANCA-associated glomerulonephritis, 762
for ankylosing spondylitis, 857
for bladder cancer, 334
for head and neck cancer, 309
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for multiple sclerosis, 1019
for polyneuropathy, 1046
for primary sclerosing cholangitis, 803
for psoriasis, 259
for psoriatic arthritis, 859
for reactive arthritis, 860
for rheumatoid arthritis, 846
for vasculitis, 854
methylcellulose, for irritable bowel syndrome, 796*t*
methyldopa, for hypertension, 651
methylphenidate
for depression, 52
for fatigue, 52
for narcolepsy, 244
methylprednisolone
for anaphylaxis, 114
for ANCA-associated glomerulonephritis, 762
for asthma exacerbations, 715
for multiple sclerosis, 1018, 1019
for optic neuritis, 231
for renal transplant rejection, 758
for vertigo, 228*t*
methysergide, for migraine prevention, 220*t*
metoclopramide
for *H. pylori* eradication, 161
for migraine, 218*t*
for nausea and vomiting, 51, 160
for systemic sclerosis, 848
metolazone
for edema, 152, 153*t*
for heart failure, 688, 690*t*
for hypertension, 655
metoprolol
for aortic dissection, 695
for arrhythmias, 683*t*
for heart failure, 690*t*
for hypertension, 651, 652*t*
for migraine prevention, 220*t*
for STEMI, 662, 667
for UA/NSTEMI, 670
metronidazole
for acne, 263
for amebiasis, 397
for bacterial meningitis, 1024*t*, 1025*t*
for bacterial vaginosis, 401
for brain abscess, 1030
for *C. difficile* infections, 398
for clostridial infections, 474*t*
for diverticulitis, 796
for giardiasis, 391
for *H. pylori* eradication, 787*t*
for hepatic encephalopathy, 833
for inflammatory bowel disease, 794
for intestinal pseudoobstruction, 797
for mixed anaerobic infections, 476*t*
for necrotizing fasciitis, 416*t*
for pelvic inflammatory disease, 403, 406*t*
for peritonitis, 383
for tetanus, 470
for trichomoniasis, 401
for urethritis in men, 400
metyrapone
for adrenal carcinoma, 896
for ectopic ACTH syndrome, 351
mexiletine
for arrhythmias, 683*t*
for myotonic dystrophy, 1057
for polyneuropathy, 1045*t*
MG. *See* myasthenia gravis
MGUS (monoclonal gammopathy of uncertain significance), 302

MI (myocardial infarction). *See* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
MIBE (measles inclusion-body encephalitis), 538
micafungin, 569, 574*t*
miconazole, for candidiasis, 401
microaerophilic bacteria, 469
microbial bioterrorism, 361
micrographia, 976
micronutrient deficiency, 45, 45*t*
microscopic polyangiitis, 851
midazolam
  for delirium, 52*t*
  for dyspnea, 51*t*
  for increased intracranial pressure, 95*t*
  for scorpion sting, 124
  for status epilepticus, 102*f*
Middle East respiratory syndrome coronavirus (MERS-CoV), 535
midodrine
  for ascites, 188
  for hepatorenal syndrome, 189
  for orthostatic hypotension, 994
  for syncope, 225
midsystolic click (heart sound), 615
mifepristone, for emergency contraception, 923
miglitol, for diabetes mellitus, 908*t*
migraine, 215–218
  diagnosis of, 216*t*
  epidemiology of, 215*t*
  prevention of, 220–221*t*
  sleep disorders and, 242
  treatment of, 216, 217–218*t*
  vertigo in, 228*t*, 229
  visual loss and, 231
migrating motor complex, 167
miliary disease, 484
milk alkali syndrome, 20
milnacipran, for fibromyalgia, 868
milrinone
  for heart failure, 664*t*, 691, 691*t*
  for pulmonary edema, 70
miltefosine, for leishmaniasis, 594
Milwaukee shoulder, 866
mineral deficiencies, 45*t*
mineral oil, for constipation, 174
minimal change disease, 764
Mini-Mental status examination, 947
minitransplant, 297
Minnesota tube, for esophageal varices, 832
minocycline
  for actinomycosis, 481
  for leprosy, 492
  for nocardiosis, 479
  for staphylococcal infections, 430, 433*t*
  for Whipple's disease, 482
mipomersen, for dyslipidemia, 939*t*
mirtazapine, 1071, 1073*t*
misoprostol, for erosive gastropathies, 788
mite-borne spotted fevers, 505
mitiglinide, for diabetes mellitus, 909*t*
mitochondrial myopathies, 1059
mitomycin, for anal cancer, 330
mitotane
  for adrenal carcinoma, 896
  for ectopic ACTH syndrome, 351
mitoxantrone
  for multiple sclerosis, 1018, 1019
  for prostate cancer, 343
mitral regurgitation (MR)
  clinical manifestations of, 634
  echocardiography in, 624*f*, 634
  etiology of, 634
  heart sounds in, 616*t*
  in STEMI, 667
  treatment of, 634, 635*f*
mitral stenosis (MS)
  diagnosis of, 632
  echocardiography in, 624*f*, 632
  etiology of, 632
  heart sounds in, 616*t*
  treatment of, 632, 633*f*
mitral valve disease, antithrombotic therapy for, 89*t*
mitral valve prolapse (MVP), 616*t*, 634, 636
mittelschmerz, 919
mixed connective tissue disease (MCTD), 848
MM (mononeuropathy multiplex), 1046
MMCB (multifocal motor neuropathy with conduction block), 987
MMR (measles, mumps, and rubella) vaccine, 370*t*, 539
modafinil
  for circadian rhythm sleep disorders, 245
  for depression, 52
  for narcolepsy, 244
Mohs micrographic surgery, 308

molindone, 1076*t*
Mollaret's meningitis, 1039*t*
monkey bite, 117*t*, 118
monoamine oxidase inhibitors (MAOIs)
  dosage and side effects of, 1073*t*
  for Parkinson's disease, 978
  pharmacology of, 1071
monoclonal gammopathy of uncertain significance (MGUS), 302
monoclonal immunoglobulins, renal disease and, 772–773
monocytic leukemia, 284*t*
monocytopenia, 277
monocytosis, 275
mononeuritis multiplex, 1046
mononeuropathy
  approach to, 1040–1042, 1041*f*
  clinical manifestations of, 1046, 1047–1049*t*
  definition of, 1040
  diagnosis of, 1047–1049*t*
mononeuropathy multiplex (MM), 1046
monoparesis, 235*f*
montelukast
  for allergic rhinitis, 838
  for asthma, 714
  for urticaria/angioedema, 837
mood disorders, 1063–1066
mood stabilizers, 1078, 1078*t*
MOPP regimen, for Hodgkin's disease, 304
MOPP-ABV regimen, for Hodgkin's disease, 304
Moraxella catarrhalis infections, 451–452
morbilliform lesion, 255
Morganella infections, 457
morphine
  abuse, 1084
  for dyspnea, 51*t*
  for increased intracranial pressure, 95*t*
  for pain, 38*t*
  for pulmonary edema, 70
  for STEMI, 659
  for tetanus, 470
  for UA/NSTEMI, 671
mortality, age-specific, 1088–1090*t*
motion sickness, 160, 228*t*
motor examination, 948, 949–950*t*, 951
motor fluctuations, 978
motor neuron disease, 985*t*. *See also* amyotrophic lateral sclerosis
  clinical manifestations of, 233, 233*t*, 234*t*, 235*t*
  etiology and investigation of, 986–987*t*
motor unit disorders, 233, 235*t*
movement disorders, 236–238, 242
moxifloxacin
  anaerobic infections, 476*t*
  for community-acquired pneumonia, 725*t*
  for health care–associated pneumonia, 727*t*
  for *Legionella* infections, 513
  for pneumococcal infections, 424
  for sepsis/septic shock, 68*t*
  for sinusitis, 249*t*
  for tuberculosis, 486
MPGN (membranoproliferative glomerulonephritis), 765
MR. *See* mitral regurgitation
MRA (magnetic resonance angiography), in stroke, 85, 87
MRI. *See* magnetic resonance imaging
MRSA infections. *See* methicillin-resistant *S. aureus* infections
MS. *See* mitral stenosis; multiple sclerosis
MSA (multiple system atrophy), 991
MSLT (multiple sleep latency test), 243, 244*t*
mucormycosis, 576–577
mucosa-associated lymphoid tissue (MALT) lymphoma
  epidemiology of, 296*f*
  etiology of, 294
  pathophysiology of, 323
  treatment of, 324
mucosal leishmaniasis, 593–594
mucous membranes
  dry, in terminally ill patient, 56*t*
  in malnutrition, 42
mucous patch, 409
multidrug-resistant (MDR) tuberculosis, 482
multifocal motor neuropathy with conduction block (MMCB), 987
multi-infarct dementia, 974
multiorgan system failure, 34
multiple cranial nerve palsies, 1001–1002
multiple endocrine neoplasia type 1 (MEN 1), 332, 789, 924

multiple myeloma
classification of, 295*t*
clinical manifestations of, 301–302
infections in, 301, 363*t*
oncologic emergencies, 110–111
pathogenesis of, 301–302
renal disease in, 768*t*, 772–773, 773*t*
staging of, 302, 303*t*
treatment of, 302
multiple sclerosis (MS), 1012–1020
acute (Marburg's variant), 1019
clinical manifestations of, 1012–1013
clinical variants of, 1019
diagnostic criteria for, 1013, 1013–1014*t*
disorders that mimic, 1015*t*
facial nerve involvement in, 997
imaging in, 1015, 1016*f*
laboratory features of, 1015
spinal cord involvement in, 1006
subtypes of, 1013, 1015
treatment of
acute relapses, 1018–1019
decision-making algorithm for, 1017*f*
disease-modifying therapies, 1016, 1018
progressive symptoms, 1019
symptomatic therapy, 1019
multiple sleep latency test (MSLT), 243, 244*t*
multiple system atrophy (MSA), 991
mumps, 540–541, 1037*t*
mumps vaccine, 370*t*, 539, 541
Munchausen's syndrome, 1069
mupirocin, for streptococcal infections, 436
murine (flea-borne) typhus, 502*t*, 505–506
murmur. *See* heart murmur
Murphy's sign, 801
muscle contracture, 1054
muscle cramp, 1053
muscle diseases, 1053–1061
approach to, 1053–1054, 1055*f*, 1056*f*
disorders of energy metabolism, 1059
drug-induced, 1060*t*, 1061
endocrine and metabolic myopathies, 1060–1061
inflammatory myopathies, 1057–1059, 1058*t*
mitochondrial myopathies, 1059
muscular dystrophies. *See* muscular dystrophy
paraneoplastic, 352*t*, 354*t*, 355
periodic paralysis, 1059–1060
muscular dystrophy, 1054
Duchenne's, 1054
facioscapulohumeral, 1057
limb-girdle, 1054
myotonic, 1054, 1057
oculopharyngeal, 1057
musculoskeletal complaints. *See* joint pain
musculoskeletal infections
E. coli, 454
S. aureus, 427
mushrooms, poisonous, 815
M-VAC regimen, for bladder cancer, 334
MVP (mitral valve prolapse), 616*t*, 634, 636
myalgia, 1053
myasthenia gravis (MG), 1050–1053
differential diagnosis of, 1050
diplopia in, 232
drug interactions in, 1052*t*
laboratory testing in, 1051–1052
paraneoplastic, 352*t*, 354*t*
treatment of, 1051*f*, 1052–1053
myasthenic crisis, 1053
mycetoma, 249
Mycobacterium avium complex (MAC) infections, 492–494
Mycobacterium infections
M. abscessus, 492–494
M. chelonae, 492
M. fortuitum, 492–494
M. kansasii, 492–494
M. leprae. *See* leprosy
M. marinum, 492–494
M. tuberculosis. *See* tuberculosis (TB)
M. ulcerans, 492–494
mycophenolate mofetil
for ANCA-associated glomerulonephritis, 762
for immunosuppression after renal transplantation, 758
for inflammatory myopathy, 1059
for myasthenia gravis, 1053
for SLE, 762, 845
for vasculitis, 854
Mycoplasma pneumoniae infections, 510–511
mycoplasmal infections, urogenital, 399, 401–402, 408–409

myelitis, paraneoplastic, 352*t*, 353*t*, 354*t*
myeloblastic leukemia, 284*t*
myelodysplastic syndromes (MDS), 284*t*, 289
  classification of, 290–291*t*
  with isolated del(5q), 290*t*
  prognostic scoring system for, 292*t*
  treatment of, 289
  unclassified, 291*t*
myelofibrosis
  blood abnormalities in, 268, 275
  idiopathic, 292–293
myeloid leukemia
  acute. *See* acute myeloid leukemia
  chronic. *See* chronic myeloid leukemia
myelomonocytic leukemia, 284*t*
myelopathy
  hypocupric, 1007–1008
  immune-mediated, 1006
  infectious, 1006
myelophthisis, 268, 275
myeloproliferative syndromes, 275, 276, 292–293
myiasis, 611
myocardial infarction. *See* ST-segment elevation myocardial infarction; unstable angina/non-ST-elevation myocardial infarction
myocardial ischemia, 138, 138*t*, 139*f*
myocarditis, 544, 643–644
myoclonus, 101, 238
myonecrosis (gas gangrene), 416*t*, 418, 473, 474*t*
myopathy, 1053
  drug-induced, 1060*t*, 1061
  inflammatory, 1057–1059, 1058*t*
  weakness in, 233*t*, 234–235*t*
myophosphorylase deficiency, 1059
myositis, 418, 436*t*
myotonia, 1054
myotonic dystrophy, 1054, 1057
myxedema coma, 888, 889

N

nadolol
  for esophageal varices, 832
  for variceal bleeding, 178
nafcillin
  for bacterial meningitis, 1024*t*, 1025*t*
  for cellulitis, 415*t*
  for infective endocarditis, 377*t*, 378*t*
  for osteomyelitis, 421*t*
  for staphylococcal infections, 430, 431*t*
nail lesions, 257
naloxone
  for morphine side effects, 659
  for opiate overdose, 1085
naltrexone
  for alcoholic rehabilitation, 1084
  for narcotic withdrawal, 1085
  for opioid dependence, 1086
  for primary biliary cirrhosis, 829
naproxen
  for migraine, 217*t*
  for pain, 38*t*
naratriptan, for migraine, 217*t*, 219*t*
narcissistic personality disorder, 1070
narcolepsy, 243–244, 244*t*
narcotic abuse, 1084–1086
  clinical manifestations of, 1084–1085
  prevention of, 1086
  treatment of, 1085–1086
narcotics
  for abdominal pain, 158
  for back pain, 211
  for dyspnea, 51, 51*t*
  for migraine, 218*t*
  for pain management, 37, 38–39*t*, 40
nasopharyngeal cancer, Epstein-Barr virus in, 528
natalizumab
  for inflammatory bowel disease, 794
  for multiple sclerosis, 1018
nateglinide, for diabetes mellitus, 909*t*
native valve endocarditis (NVE). *See also* infective endocarditis
  etiology of, 372
  HACEK group, 452, 453*t*
  staphylococcal, 430
  treatment of, 430
nausea and vomiting, 158–160
  causes of, 159, 159*t*
  complications of, 160
  drug-induced, 159*t*
  evaluation of, 160
  in terminally ill patient, 50–51
  treatment of, 50–51, 160
NBTE (nonbacterial thrombotic endocarditis), 372–373
Necator americanus infections, 601
neck cancer. *See* head and neck cancer
neck pain, 212–214
neck weakness, 1000

necrotizing fasciitis, 416*t*, 417–418, 436*t*, 437
necrotizing myelopathy, 352*t*
nedocromil sodium, for asthma, 714
nefazodone, 1071
Negri bodies, 547
Neisseria gonorrhoeae infections. *See* gonorrhea
Neisseria meningitidis infections. *See* meningococcal infections
nematocysts, 120
nematode infections, 599–604
  filarial worms, 603–604
  intestinal, 600–603
  tissue, 599–600
neomycin, for hepatic encephalopathy, 833
neonatal disease
  cytomegalovirus infections, 526
  generalized enteroviral infections, 544
  HSV infections, 519, 522*t*
  listerial infections, 446–447
  streptococcal infections, 438
nephrectomy, 335
nephritic syndrome, 201, 759
nephritis
  acute interstitial, 771–772, 771*t*
  chronic interstitial, 772
  drug-induced, 771, 771*t*
nephrolithiasis, 779–782
  clinical manifestations of, 780
  stone composition, 780
  treatment of, 781, 781–782*t*
  uric acid, 864
  workup for, 780–781, 781*t*
nephropathy. *See also* renal disease
  acute uric acid, 864
  analgesic, 772
  Balkan endemic, 772
  cast, 772–773, 773*t*
  diabetic, 765–766
  HIV-associated, 764
  IgA, 766–767
  thin basement membrane, 766
  urate, 864
nephrostomy tube, 784
nephrotic syndrome (NS), 201, 763–766
  ascites in, 188*f*
  etiology of, 763–764, 763*t*
  evaluation of, 766*t*
nerve abscess, in leprosy, 491
nervous system tumors, 1008–1012
  approach to, 1008
  imaging of, 1009*f*, 1011*f*
  metastatic from other locations, 1010–1012, 1011*t*
  primary intracranial, 1009–1010
  treatment of, 1008*f*, 1012
nesiritide
  for heart failure, 691, 691*t*
  for pulmonary edema, 70
neuralgia, 36
neuraminidase inhibitors, for influenza, 532
neurocysticercosis, 607
neurogenic shock, 61*t*
neuroleptic malignant syndrome (NMS), 1074
neuroleptics, for delirium, 52*t*
neurologic disease
  abdominal pain in, 155*t*
  ataxia. *See* ataxia
  autonomic nervous system disorders. *See* autonomic nervous system (ANS) disorders
  cranial nerve disorders, 995–1002
  in critically ill patient, 35
  dementia. *See* dementia
  depression in, 1064
  epilepsy. *See* epilepsy
  fatigue in, 133*t*
  in HIV infection, 558
  in HSV infection, 518, 521*t*
  infections. *See* central nervous system (CNS) infections
  in leprosy, 491
  in Lyme disease, 495
  in malnutrition, 43
  in measles, 538
  motor neuron disease. *See* amyotrophic lateral sclerosis; motor neuron disease
  multiple sclerosis. *See* multiple sclerosis
  in mumps, 541
  myasthenia gravis. *See* myasthenia gravis
  paraneoplastic, 352–355, 352*t*, 353*t*, 354*t*
  Parkinson's disease. *See* Parkinson's disease
  peripheral neuropathy. *See* peripheral neuropathy
  in rabies, 547
  seizures. *See* seizures
  sleep disorders in, 242

spinal cord disease. *See* spinal cord disease
tumors. *See* nervous system tumors
varicella-zoster virus infections, 523
weakness and paralysis in, 233
weight loss in, 136*t*
neurologic examination, 947–955
anatomic localization of problem, 953, 955*t*
coordination and gait, 951
cranial nerve exam, 947–948
in head trauma, 98
in low back pain, 208, 208*t*
mental status exam, 947
motor examination, 948, 949–950*t*, 951
reflexes, 951
sensory, 951
neuromuscular blockers, 32–33
neuromuscular junction disorders, 234*t*, 235*t*
neuromyelitis optica (NMO), 231, 1019
neuropathic pain, 36, 36*t*
neuropathy. *See specific types*
neuroprotection, for stroke, 87
neurosyphilis, 410, 411*t*, 412
neutropenia, 276
in cancer patient, 113
drug-induced, 275
febrile, 276
approach to, 365–366, 365*f*
P. aeruginosa infections, 460*t*
P. aeruginosa infections in, 459
treatment of, 276
refractory, 290*t*
sepsis and, 68*t*
treatment of, 113, 276
neutrophilia, 274–275
nevirapine, for HIV infection, 559, 561*t*
niacin deficiency, 45*t*
nicardipine, for malignant hypertension, 656*t*
nicotine, for inflammatory bowel disease, 794
nicotine addiction, 1102–1103. *See also* smoking cessation
nicotine replacement therapy, 720, 1103
nicotinic acid, for dyslipidemia, 939*t*
nifedipine
for achalasia, 164
for aortic regurgitation, 638
for esophageal spasm, 165
for hypertension, 651, 653*t*
for pulmonary hypertension, 702
for systemic sclerosis, 848
for vasospastic disorders, 698
nifurtimox, for Chagas' disease, 595
nilotinib, for CML, 288
nimodipine, for subarachnoid hemorrhage with vasospasm, 93
Nissen fundoplication, 161
nitazoxanide
for *C. difficile* infections, 398
for cryptosporidiosis, 392
for giardiasis, 391
nitrates
for chronic stable angina, 674, 675*t*
for heart failure, 688, 690*t*
nitrofurantoin, for urinary tract infections, 777, 777*t*
nitroglycerin
for anal fissures, 798
for chronic stable angina, 674, 675*t*
for heart failure, 663, 664*t*, 690–691, 691*t*
for malignant hypertension, 656*t*
for pulmonary edema, 70
for STEMI, 659, 665*t*
for systemic sclerosis, 848
for UA/NSTEMI, 670
nitroprusside
for aortic dissection, 695, 696*t*
for heart failure, 663, 664*t*, 690–691, 691*t*
for malignant hypertension, 656*t*
for mitral regurgitation, 634
for STEMI, 665*t*
for STEMI complications, 667
nits, 610
NIV (noninvasive ventilation), 74, 75*t*, 722
nivolumab
for melanoma, 307
for renal cancer, 335
NMO (neuromyelitis optica), 231, 1019
NMS (neuroleptic malignant syndrome), 1074
nocardiosis, 477–479, 480*t*, 1034*t*
nodule (skin lesion), 257*t*, 417
noma, 475
nonbacterial thrombotic endocarditis (NBTE), 372–373
non-Hodgkin's lymphoma, 296*f*, 300*t*
noninvasive ventilation (NIV), 74, 75*t*, 722

nonnucleoside reverse transcriptase inhibitors, for HIV infection, 559, 561–563*t*
nonpolyposis syndrome, 326*t*, 327
nonspecific interstitial pneumonia, 738
non-ST-elevation myocardial infarction. *See* unstable angina/non-ST-elevation myocardial infarction
nonsteroidal anti-inflammatory drugs (NSAIDs)
  for adhesive capsulitis, 870
  for ankylosing spondylitis, 857
  for bursitis, 869
  for calcium apatite deposition disease, 866
  for cholecystitis, 801
  for colon cancer prevention, 1100
  for colonic polyps, 327
  for colorectal cancer prevention, 330
  for diabetes insipidus, 6
  for enteropathic arthritis, 867
  for erythema multiforme, 263
  for erythema nodosum, 263
  for fever, 128
  for fibromyalgia, 868
  for gout, 864
  for low back pain, 211
  for migraine, 216, 217*t*, 219*t*
  for neck and back pain, 214
  for osteoarthritis, 862
  for osteonecrosis, 869
  for pain, 37, 38*t*
  for pelvic pain, 920
  for pericarditis, 645
  for pseudogout, 866
  for psoriatic arthritis, 859
  for reactive arthritis, 860
  for rheumatoid arthritis, 846
  for SLE, 845
  for systemic mastocytosis, 839
  for tendinitis, 870
  for tension-type headache, 218
  for thyroiditis, 891
nontuberculous mycobacterial (NTM) infections, 492–494
  clinical manifestations of, 493
  diagnosis of, 493
  epidemiology of, 492
  microbiology of, 492
  treatment of, 494
norepinephrine
  for increased intracranial pressure, 95*t*
  for shock, 64, 64*t*
  for subarachnoid hemorrhage with vasospasm, 93
normal-pressure hydrocephalus (NPH), 971, 974
norovirus infections
  diarrhea, 389–390
  nosocomial, 361
nortriptyline
  dosage and side effects of, 39*t*, 1072*t*
  for migraine prevention, 220*t*
  for pain, 39*t*
  for smoking cessation, 1103
nosocomial infections. *See* health care-associated infections
NS. *See* nephrotic syndrome
NSAIDs. *See* nonsteroidal anti-inflammatory drugs
NSTEMI. *See* unstable angina/non-ST-elevation myocardial infarction
NTM infections. *See* nontuberculous mycobacterial infections
nuclear cardiology, 625, 626*t*
nuclear medicine imaging, in respiratory disease, 709–710
nuclear myocardial perfusion assessment, 625, 659, 674*t*
nucleoside/nucleotide analogues, for HIV infection, 559, 560–561*t*
5'-nucleotidase (5'-NT), 183–184
nummular lesion, 255
nutcracker esophagus, 165
nutrients, absorption of, 167
nutrition
  fatigue and, 133*t*
  leukopenia and, 276
nutritional status, assessment of, 40–43
nutritional support, 43
  in critically ill patient, 35
  decision tree for initiating, 44*f*
  enteral nutrition, 43–44
  parenteral nutrition, 44–45
  in sepsis/septic shock, 67
NVE. *See* native valve endocarditis
nystagmus, 226, 227
nystatin, for candidiasis, 262, 571

O

obesity, 901–903
  central, 901
  classification of, 901*t*
  clinical manifestations of, 902
  drug-induced, 901
  etiology of, 901–902
  in metabolic syndrome, 656–657, 657*t*

sleep disorders in, 244*t*
treatment of, 902–903, 903*f*
in women, 1105
obinutuzumab, for CLL, 297
obsessive-compulsive disorder (OCD), 1068, 1071
obstructive shock, extracardiac, 61*t*
obstructive sleep apnea/hypopnea syndrome (OSAHS), 243, 745–746
obturator neuropathy, 1048*t*
occipital cortex lesions, 230
occipital neuralgia, 221
occlusional injury, 116*t*, 118
ocrelizumab, for multiple sclerosis, 1019
octreotide
for acromegaly, 350, 881
for carcinoid tumor, 332
for esophageal varices, 178, 832
for hepatorenal syndrome, 189
for hypoglycemia, 109
for islet-cell tumors, 333
octreotide scintigraphy, 332, 790
ocular gonorrhea, 405
ocular larva migrans, 600
ocular motor nerve palsy, 232
oculocephalic reflex, 81
oculopharyngeal dystrophy, 1057
odynophagia, 162
ofatumumab, for CLL, 297
ofloxacin
for leprosy, 492
for *M. pneumoniae* infections, 511
for meningococcal prophylaxis, 446
OH. *See* orthostatic hypotension
olanzapine
for delirium, 52*t*
dosage and side effects of, 1077*t*
for schizophrenia, 1067
olfactory nerve (CN I)
disorders of, 998, 999*t*, 1000
examination of, 947
oligemic shock, 61*t*, 62
oligoanuria, 199
oligoblastic leukemia, 289
oligodendroglioma, 1009
oligomenorrhea, 917
oliguria, 199
olopatadine, for allergic rhinitis, 838
omalizumab, for asthma, 714
omega-3 fatty acids, for dyslipidemia, 939*t*
omeprazole
for *H. pylori* eradication, 787, 787*t*
for indigestion, 161
for noncardiac chest pain, 164
for peptic ulcer disease, 787
for systemic sclerosis, 848
for Zollinger-Ellison syndrome, 789–790
onchocerciasis, 604
onchocercomata, 604
oncologic emergencies, 109–113
paraneoplastic syndromes, 111–112
structural/obstructive, 110–111
treatment complications, 112–113
ondansetron, for nausea and vomiting, 160
oophoritis, in mumps, 541
opening snap (heart sound), 614
ophthalmia neonatorum, 405
ophthalmoplegia
chronic progressive external, 1057, 1059
diffuse, 232
etiology of, 1001
ophthalmoscopic examination, 229
opioids/opiates. *See* narcotics
opisthorchiasis, 606
opsoclonus-myoclonus syndrome, 352*t*, 354
optic chiasm compression, 230*f*
optic neuritis, 230*f*, 231
optic neuropathy, 230*f*
oral contraceptives, 920, 921, 922
oral disease
actinomycosis, 480
anaerobic infections, 475
in malnutrition, 42
oral dissolution therapy, for gallstones, 800
oral hairy leukoplakia, 256*f*, 528, 529
oral leukoplakia, 1101
oral poliovirus vaccine (OPV), 546
oral rehydration solution (ORS), for cholera, 387
oral-facial HSV infections, 520–522*t*
orchiectomy, 336
orchitis, in mumps, 541
Orientia tsutsugamushi infections, 503*t*, 507
orlistat, for obesity, 902
Oroya fever, 467*t*, 469
orthostatic hypotension (OH)
approach to, 988, 990
definition of, 990
etiology of, 224, 224*t*
in pheochromocytoma, 649
treatment of, 994–995, 994*t*

OSAHS (obstructive sleep apnea/hypopnea syndrome), 243, 745–746
oseltamivir, for influenza, 532, 532*t*
osmolar gap, 19
osmoregulation, 1*t*
osmotic demyelination syndrome, 5
osteoarthritis, 210, 861–862
osteomalacia, 349*t*, 935
osteomyelitis
  clinical manifestations of, 420
  Klebsiella, 456
  neck pain in, 212
  pathogenesis and epidemiology of, 420
  S. aureus, 427, 430
  treatment of, 420–422, 421*t*
  vertebral, low back pain in, 210
osteonecrosis (avascular necrosis), 869, 934
osteoporosis, 931–934
  clinical manifestations of, 931
  definition of, 931
  diagnosis of, 933, 934*t*
  diseases associated with, 932–933*t*
  epidemiology of, 931
  etiology of, 931
  fracture risk in, 931, 931*t*
  low back pain in, 210
  postmenopausal, 922, 1105
  screening for, 1090*t*, 1091*t*
  treatment of, 933–934
ostium primum, 627
ostium secundum, 627
otitis externa
  acute diffuse, 250
  acute localized, 250
  chronic, 250
  malignant or necrotizing, 250
  P. aeruginosa, 459, 460*t*
otitis media
  acute, 250–251
  chronic, 251
  M. catarrhalis, 451–452
  pneumococcal, 424
  serous, 251
  treatment of, 252*t*
ovarian cancer, 339–340, 339*t*
  infections in, 363*t*
  paraneoplastic, 353*t*
  paraneoplastic syndromes in, 349*t*
  screening for, 1098*t*
  staging and prognosis in, 339*t*
ovarian cyst, 338
ovarian tumor, 338
overdiagnosis, 1095
oxacillin
  for cellulitis, 415*t*
  for infective endocarditis, 377*t*, 378*t*
  for osteomyelitis, 421*t*
  for staphylococcal infections, 430, 431*t*
oxaliplatin, for colorectal cancer, 328
oxazepam
  dosage and action of, 1075*t*
  for STEMI, 661
oxcarbazepine
  dosage and side effects of, 1078*t*
  for generalized anxiety disorder, 1068
  for pain, 39*t*
  for seizures, 964*t*, 967*t*
  for trigeminal neuralgia, 995
5-oxoprolinuria, 17–18, 18*t*, 19
oxybutynin, for bladder hyperreflexia, 1019
oxycodone
  abuse, 1084
  for dyspnea, 51*t*
  for pain, 38*t*
oxygen therapy
  for anaphylaxis, 114
  for asthma exacerbations, 715
  for cluster headache, 219
  for COPD, 721, 722
  for cor pulmonale, 693
  for heart failure, 663
  for interstitial lung disease, 737
  for pulmonary edema, 70
  for pulmonary hypertension, 702
  for shock, 64, 664
  for STEMI, 661
oxytocin, 883

P

packed red blood cell transfusion, 46, 828
paclitaxel
  for bladder cancer, 334
  for breast cancer, 320
  for head and neck cancer, 309
  for ovarian cancer, 339
pain. *See also specific types and sites*
  approach to, 35–36
  chronic, 36, 40
  management of, 35–40, 38–39*t*, 796, 1071
  neuropathic, 36, 36*t*, 40
  pathophysiology of, 37, 37*f*
  somatic, 36, 36*t*, 156

spontaneous, 994
visceral, 36, 36*t*, 156
painful bladder syndrome, 778–779
paliperidone, 1077*t*
palivizumab, 536
palliative care. *See* terminally ill patient
palmar xanthoma, 941
palpation, precordial, 613–614
palpitations, 141–142
pamidronate, for hypercalcemia, 112, 351, 927*t*
pancreatectomy, 808
pancreatic abscess, 807
pancreatic cancer, 331, 349–350*t*
pancreatic endocrine tumors, 331–333
pancreatic enzyme replacement, 808
pancreatic exocrine insufficiency, 808*t*
pancreatic islet-cell tumor, 332–333, 349*t*
pancreatic necrosis, 807
pancreatic pseudocyst, 807
pancreatitis, 804–809
acute, 804–807
clinical manifestations of, 804
complications of, 806–807
differential diagnosis of, 805
etiology of, 805*t*
imaging in, 804–805
laboratory testing in, 804
severe, 806*t*
treatment of, 806
ascites in, 188*f*
chronic, 807–809
classification of, 808*t*
complications of, 809
laboratory testing in, 807
treatment of, 808
interstitial, 804
necrotizing, 804
pancreatic cancer and, 331
panic disorder, 1067, 1071
panitumumab, for colorectal cancer, 328
pantoprazole
for erosive gastropathies, 788
for *H. pylori* eradication, 787*t*
PAP (pulmonary alveolar proteinosis), 738
PAP (pulmonary artery pressure), 707
Pap smear, 341, 1096*t*, 1101
papillary necrosis, 776
papilledema, 230*f*, 231
Pappenheimer bodies, 265
papule (skin lesion), 257*t*, 417
papules, in cancer patients, 362
papulosquamous disorders, 258–259
paracentesis, 30–31, 188
paracoccidioidomycosis, 581–582
paragonimiasis, 148
parainfluenza virus infections, 534*t*, 536–537
paralysis, 233–235
approach to, 233
periodic, 1059–1060
site of responsible lesion, 233, 234*t*
paralytic disease, in poliovirus infections, 543–544
paralytic shellfish poisoning, 122
paraneoplastic syndromes
emergent, 111–112
endocrine, 348–351
in lung cancer, 311
neurologic, 352–355, 352*t*
in renal cancer, 335
paranoid personality disorder, 1070
paraparesis, 235*f*, 234*t*
parasitic infections
blood, 265
eosinophilia in, 275
in HSCT patients, 367
lymphadenopathy and, 190*t*
parasympathetic system, 989*f*, 990*t*
parathyroidectomy, for hyperparathyroidism, 928
parcopa, for Parkinson's disease, 980*t*
parenchymatous syphilis, 410
parenteral nutrition, 44–45, 44*f*
paresis, 233, 410
parkinsonism, 236, 976, 977, 977*t*
Parkinson's disease (PD), 976–981
autonomic dysfunction in, 991
dementia in, 971
differential diagnosis of, 976*t*, 977, 977*t*
sleep disorders in, 242
treatment of, 978–981, 979*f*, 980*t*
tremor in, 236
paromomycin
for amebiasis, 397
for leishmaniasis, 594
parotitis, in mumps, 540–541
paroxetine
for depression, 52
dosage and side effects of, 1072*t*
for irritable bowel syndrome, 795
for menopausal symptoms, 922
paroxysmal nocturnal hemoglobinuria (PNH), 268, 271, 271*t*

parvovirus B19 infections, 541–542
Pastia's lines, 435
patch (skin lesion), 257*t*
patch tests, 258
patent ductus arteriosus, 616*t*, 629
patent foramen ovale, antithrombotic therapy for, 89*t*
patient-controlled analgesia (PCA), 40
PBP (primary bacterial peritonitis), 382–383
PCA (patient-controlled analgesia), 40
PCI. *See* percutaneous coronary intervention
PCOS (polycystic ovarian syndrome), 918, 920
PD. *See* Parkinson's disease
PE. *See* pulmonary embolism
peau d'orange appearance, 261
pediculiasis, 610–611
PEEP (positive end-expiratory pressure), 72, 76
pegloticase, for gout, 865
pegvisomant, for acromegaly, 881
pegylated interferon (PEG IFN)
  for chronic hepatitis B, 817, 818–819*t*
  for chronic hepatitis C, 817, 822–824*t*
Pelger-Hüet anomaly, 266
pelvic infections
  actinomycosis, 481
  anaerobic, 475
pelvic inflammatory disease (PID), 402–403, 406–407*t*, 919
pelvic pain, 919–920, 919*t*
pemetrexed, for lung cancer, 315
pemoline, for depression, 52
penciclovir, for HSV infections, 520–522*t*
penicillamine
  for nephrolithiasis, 782*t*
  for systemic sclerosis, 848
penicillin/penicillin G/penicillin V
  for actinomycosis, 481
  for asymptomatic GAS carriage, 435
  for bacterial meningitis, 1024*t*, 1025*t*
  for clostridial infections, 474*t*
  for diphtheria, 442
  for gas gangrene, 416*t*
  for HACEK group infections, 453*t*
  for infective endocarditis, 376–377*t*
  for leptospirosis, 498
  for listerial infections, 447
  for Lyme borreliosis, 496
  for meningococcal prophylaxis, 446
  for necrotizing fasciitis, 416*t*
  for osteomyelitis, 421*t*
  for peritonitis, 383
  for pneumococcal infections, 424
  for relapsing fever, 499
  for rheumatic fever prophylaxis, 632
  for rodent bite infections, 117*t*
  for staphylococcal infections, 430, 431*t*
  for streptococcal infections, 436*t*, 438–439
  for syphilis, 411*t*
  for tetanus, 470
penicillin VK, for pharyngitis, 253
penicilliosis, 582
pentamidine
  for *Pneumocystis* infections, 584*t*
  for *Pneumocystis* prophylaxis, 585*t*
  for sleeping sickness, 596
pentamidine isethionate, for leishmaniasis, 594
pentazocine abuse, 1084
"pentobarb coma," 95*t*
pentobarbital, for status epilepticus, 102*f*
pentoxifylline
  for alcoholic liver disease, 828
  for peripheral arteriosclerosis, 697
peptic ulcer disease (PUD), 787–788
  approach to, 788
  bleeding in, 175
  causes and risk factors for, 785
  clinical manifestations of, 786
  diagnosis of, 786, 786*t*
  treatment of, 787, 787*t*, 788*t*
Peptostreptococcus infections, 474
peramivir, for influenza, 532
percutaneous coronary intervention (PCI)
  advantages and disadvantages of, 676*t*
  for cardiogenic shock, 665*t*
  for chronic stable angina, 675–676
  for STEMI, 659, 660*f*, 671
percutaneous needle aspiration, of lung, 710
percutaneous transhepatic cholangiogram, 800*t*
periappendicitis, 402
periarticular disorders, 869–870
pericardial disease. *See* pericarditis
pericardial effusion/tamponade, 110, 648–649
pericardial stripping/window, 110

pericardiectomy, for pericarditis, 645
pericardiocentesis, for cardiac tamponade, 647
pericarditis
  acute
    chest pain in, 138, 138*t*, 140*f*
    etiology of, 645*t*
    laboratory features of, 644–645, 645*t*, 646*f*
  constrictive, 110, 647–648, 648*t*
  enteroviral, 544
  in STEMI, 667
  in tuberculosis, 484
perichondritis, 250
perihepatitis, 402
perimenopause, 921
perinephric abscess, 385
periodic leg movements of sleep, 242
periodic limb movements of sleep (PLMS), 242
periodic paralysis, 1059–1060
periodontal disease, 475
periorbital edema, 150
peripheral nerves, cutaneous areas supplied by, 952–953*f*
peripheral neuropathy (PN), 1040–1049
  approach to, 1040–1042, 1041*f*
  autonomic involvement in, 933*t*, 991
  in diabetes mellitus, 991, 1046
  diagnosis of, 1044
  mononeuropathy, 1040, 1046, 1047–1049*t*
  paraneoplastic, 352*t*, 353*t*, 355
  patterns of, 1043–1044*t*
  polyneuropathy. *See* polyneuropathy
  treatment of, 1044, 1045*t*
  weakness in, 234*t*, 235*t*
peripheral vascular disease, 696–699
  arterial embolism, 697
  atheroembolism, 697–698
  atherosclerosis, 696–697
  superficial thrombophlebitis, 698
  vasospastic disorders, 697–698
  venous disease, 698–699
  venous insufficiency, chronic, 699
peristalsis, 167
peritoneal carcinomatosis, 188*f*, 348
peritoneal dialysis, 751, 755–756, 756*t*
peritoneal disease
  ascites in, 187
  pain in, 155*t*
peritoneal fluid, paracentesis, 30–31
peritonitis, 382–384
  bacterial, 188
  CAPD-associated, 383–384
  E. coli, 454
  primary bacterial, 382–383
  secondary, 383
peritonsillar abscess, 475
perleche, 256*f*
permethrin cream
  for pediculiasis, 611
  for scabies, 610
peroneal nerve entrapment, 1046, 1049*t*
perphenazine, 1076*t*
personality disorders, 1070
pertussis
  clinical manifestations of, 450
  diagnosis of, 450
  epidemiology of, 450
  microbiology of, 449–450
  prevention of, 451
  treatment of, 451
  vaccine, 451
PET (positron emission tomography), 26
petit mal (absence) seizures, 956. *See also* seizures
Peutz-Jeghers syndrome, 325, 326*t*, 327
phagocytic cells, deficiencies of, 841*t*
pharmacologic stress testing, 672, 674*t*
pharyngeal gonorrhea, 405
pharyngitis
  clinical manifestations of, 253
  diagnosis of, 253
  etiology of, 251, 253
  HSV, 517
  streptococcal, 253, 435, 436*t*
  treatment of, 253
pharyngoconjunctival fever, 537
phenelzine, 1073*t*
phenobarbital
  for seizures, 964*t*, 967*t*
  for status epilepticus, 102*f*
  for tetanus, 470
phentolamine, for malignant hypertension, 656*t*
phenylephrine
  for increased intracranial pressure, 95*t*
  for shock, 64, 64*t*
  for subarachnoid hemorrhage with vasospasm, 93
phenytoin
  adenopathy with, 191
  for multiple sclerosis, 1019

phenytoin (*Cont.*):
for myotonic dystrophy, 1057
for polyneuropathy, 1045*t*
for seizures, 964*t*, 967*t*
for status epilepticus, 102*f*
for trigeminal neuralgia, 995
pheochromocytoma, 649–650, 895, 900
pheresis therapy, 47–48
phlebotomy
for hemochromatosis, 944
for polycythemia, 196
for polycythemia vera, 292
phobic disorders, 1069
phosphofructokinase deficiency, 1059
phosphorus therapy, for alcoholic liver disease, 828
physical activity, 40
physical therapy
for adhesive capsulitis, 870
for tendinitis, 870
for vertigo, 228*t*
PID (pelvic inflammatory disease), 402–403, 919
pigment gallstones, 799
pill rolling, 976
pilocarpine, for Sjögren's syndrome, 849
pinta, 497
pinworm infection (enterobiasis), 602–603
pioglitazone, for diabetes mellitus, 909*t*
piperacillin-tazobactam
for community-acquired pneumonia, 725*t*
for health care–associated pneumonia, 727*t*
for mixed anaerobic infections, 476*t*
for osteomyelitis, 421*t*
for *P. aeruginosa* infections, 460*t*
for peritonitis, 382
for sepsis/septic shock, 68*t*
piracetam, for myoclonus, 238
pitavastatin, for dyslipidemia, 938*t*
pitting, 191
pituitary adenoma, 877–879
ACTH-secreting, 896
clinical manifestations of, 877
diagnosis of, 879
gonadotropin-secreting, 881
growth hormone-secreting, 880
nonfunctioning, 881
prolactin-secreting, 879
thyroid-stimulating hormone-secreting, 881, 889
treatment of, 879
pituitary apoplexy, 877
pituitary disease
hormone hypersecretion syndromes, 879–881
hypopituitarism, 881–882, 883*t*
tumors. *See* pituitary adenoma
pituitary hormones, 877, 878*f*
pituitary tumor, 230*f*
pityriasis rosea, 256*f*, 259
pivmecillinam
for shigellosis, 396
for urinary tract infections, 777*t*
pizotifen, for migraine prevention, 220*t*
plague, 465–466
plantar reflex, 951
plaque (lesion of MS), 1012
plaque (skin lesion), 257*t*
plasma cell disorders, 295*t*, 296*f*, 301–305
plasma exchange
for acute renal failure, 751
for multiple sclerosis, 1019
plasmacytoma, 302
plasmapheresis, 48
for acute renal failure, 751
for ANCA-associated glomerulonephritis, 762
for autoimmune hemolysis, 274
for erythropoietic protoporphyria, 945
for myasthenia gravis, 1053
for polyneuropathy, 1044
for primary biliary cirrhosis, 829
for thrombotic thrombocytopenic purpura, 280
for vasculitis, 854
Plasmodium, 586. *See also* malaria
platelet clumping, 266
platelet disorders, 277–279
platelet transfusion, 47
plateletpheresis, 48
PLCH (pulmonary Langerhans cell histiocytosis), 736, 739
pleural biopsy, 710
pleural effusion, 726
approach to, 742*f*
differential diagnosis of, 740–741*t*
exudative, 740
thoracentesis for, 27–28, 28*f*
transudative, 740
pleurisy, 138
pleurodynia, enteroviral, 544

pleuropulmonary infections, anaerobic, 475
PLMS (periodic limb movements of sleep), 242
Plummer's nails, 889
PM (polymyositis), 1057–1059, 1058*t*
PML (progressive multifocal leukoencephalopathy), 1030–1031
PMR (polymyalgia rheumatica), 869
PMS (premenstrual syndrome), 919
PN. *See* peripheral neuropathy
pneumococcal infections, 422–425
  epidemiology of, 422
  meningitis, 423–425
  microbiology of, 422
  pathogenesis of, 422–423
  pneumonia, 423–425
  prevention of, 425
pneumococcal vaccine, 370*t*, 422, 425, 1090*t*
Pneumocystis infections, 583–585
  clinical manifestations of, 583
  diagnosis of, 584
  microbiology and epidemiology of, 583
  pathogenesis of, 583
  prevention of, 585, 585*t*
  treatment of, 584–585, 584*t*
pneumonia
  acute interstitial, 736
  aspiration, 475
  C. pneumoniae, 513
  in cancer patients, 364
  classification of, 722
  community-acquired. *See* community-acquired pneumonia
  cryptogenic organizing, 736, 738
  desquamative interstitial, 738
  E. coli, 454
  eosinophilic, 738–739
  H. influenzae, 448
  health care-associated, 722
  hemoptysis in, 148
  hospital-acquired, 727
  human RSV, 535
  in influenza, 531
  Klebsiella, 456
  Legionella, 511–513
  M. catarrhalis, 451
  M. pneumoniae, 510–511
  in measles, 538
  Nocardia, 478
  nosocomial, 358, 359*t*
  P. aeruginosa, 458–459, 460*t*
  pain in, 141
  pathophysiology of, 722–723
  pneumococcal, 423–425
  Pneumocystis, 583–585, 584*t*
  S. aureus, 427
  secondary bacterial, 531
  streptococcal, 436*t*, 437
  toxoplasmosis, 597
  varicella-zoster virus, 523
  ventilator-associated. *See* ventilator-associated pneumonia
Pneumonia Severity Index (PSI), 724
pneumonic plague, 466
pneumonitis
  HSV, 518, 522*t*
  hypersensitivity, 736, 739
  necrotizing, 475
pneumothorax (Ptx), 140*f*, 743
PNH (paroxysmal nocturnal hemoglobinuria), 268, 271, 271*t*
podagra, 863
podophyllin
  for HPV infections, 414
  for warts, 262
poikilocytosis, 265
poison control center, 119
poliovirus infections, 543–544
poliovirus vaccine, 370*t*, 545–546
polyarteritis, glomerular disease in, 768*t*
polyarthropathy, in parvovirus infection, 542
polychondritis, relapsing, 868
polycystic kidney disease, 773–774
polycystic ovarian syndrome (PCOS), 918, 920
polycythemia, 194–196
  causes of, 195
  complications of, 195
  differential diagnosis of, 196*f*
  treatment of, 196
polycythemia vera, 195, 292
polydipsia, 4, 884
polyene, for candidiasis, 571
polyethylene glycol-containing solution
  for constipation, 174
  for irritable bowel syndrome, 796*t*
polymyalgia rheumatica (PMR), 869
polymyositis (PM), 1057–1059, 1058*t*
polymyxin B
  for enteric GNB infections, 458
  for *Klebsiella* infections, 456

polyneuropathy
acute inflammatory demyelinating, 1046
approach to, 1040–1042, 1041*f*
chronic inflammatory demyelinating, 1046
definition of, 1040
diagnosis of, 1042, 1044
patterns of, 1043–1044*t*
treatment of, 1044, 1045*t*
polyposis syndromes, 325, 326–327, 326*t*
polyps
colonic, 326–327, 326*t*
gastric, 325
polysomnography, 244*t*
polyuria, 199, 199*t*, 200*f*, 926
Pompe's disease, 1059
ponatinib, for CML, 289
Pontiac fever, 512
porphyria cutanea tarda, 945
porphyrias, 944–945
acute intermittent, 944, 991
erythropoietic protoporphyria, 945
porphyria cutanea tarda, 945
Porphyromonas infections, 474
portal hypertension, 192, 831, 831*t*
Portuguese man-of-war injury, 120
posaconazole
for aspergillosis, 574*t*
for fusariosis, 582
for mucormycosis, 577
pharmacology of, 569
positive end-expiratory pressure (PEEP), 72, 76
positron emission tomography (PET), 26
post-concussion headache, 215*t*, 221
postherpetic neuralgia, 261, 523
postmeningococcal reactive disease, 444–445
postmenopausal hormone therapy, 922
postpolio syndrome, 544
postradiation fibrosis, 213
posttraumatic stress disorder (PTSD), 1068–1069, 1071
postural hypotension. *See* orthostatic hypotension
postural orthostatic tachycardia syndrome (POTS), 991
potassium, disorders of, 6–13
hyperkalemia, 6–7, 9–13, 14*f*, 15*f*
hypokalemia, 7–8*t*, 7–9, 10–11*f*
potassium chloride
for hypokalemia, 9
for periodic paralysis, 1060
potassium hydroxide preparation, 257–258
potassium iodide, for thyroid storm, 891
potassium perchlorate, for amiodarone-induced thyrotoxicosis, 892
potassium restriction, for hyperkalemia, 754
potassium therapy, for alcoholic liver disease, 828
Pott's disease, 484
Pott's puffy tumor, 248
PPMS (primary progressive multiple sclerosis), 1015
Prader-Willi syndrome, 901
pramipexole
for Parkinson's disease, 980*t*
for restless legs syndrome, 242
pramlintide, for diabetes mellitus, 906, 909*t*
prasugrel, for UA/NSTEMI, 670, 671
pravastatin, for dyslipidemia, 938*t*
praziquantel
for echinococcosis, 609
for lung fluke infections, 606
for schistosomiasis, 606
for taeniasis solium and cysticercosis, 607
for tapeworm infections, 607
prazosin, for vasospastic disorders, 698
precordial palpation, 613–614
prednisolone
for alcoholic liver disease, 828
for autoimmune hepatitis, 825
prednisone
for alcoholic liver disease, 828
for ALL, 300
for autoimmune hepatitis, 825
for Bell's palsy, 997
for Burkitt's lymphoma/leukemia, 301
for cluster headache prevention, 219
for COPD exacerbations, 722
for gastric carcinoma, 324
for hirsutism, 921
for hypercalcemia, 927*t*
for hypopituitarism, 883*t*
for idiopathic thrombocytopenic purpura, 280
for immunosuppression after renal transplantation, 758

for inflammatory bowel disease, 792
for inflammatory myopathy, 1059
for interstitial lung disease, 737
for lymphoma, 299
for multiple myeloma, 302
for multiple sclerosis, 1018
for muscular dystrophy, 1054
for myasthenia gravis, 1053
for optic neuritis, 231
for pericarditis, 645
for *Pneumocystis* infections, 584*t*
for polymyalgia rheumatica, 869
for postherpetic neuralgia, 524
for relapsing polychondritis, 868
for sarcoidosis, 872
for thyrotoxicosis, 891
for vasculitis, 854
preexcitation syndrome. *See* Wolff-Parkinson-White syndrome
pregabalin
dosage and side effects of, 39*t*
for fibromyalgia, 868
for generalized anxiety disorder, 1068
for multiple sclerosis, 1019
for polyneuropathy, 1045*t*
pregnancy
ectopic, 919
gonorrhea in, 405
hypertension in, 651
listerial infections in, 447
malaria in, 587
streptococcal infections in, 438
syphilis in, 411*t*
toxoplasmosis in, 597
urinary tract infections in, 778
prehypertension, 1093
preleukemia, 289
premenstrual syndrome (PMS), 919
pressure-control ventilation, 76
pressure-support ventilation (PSV), 74, 75*t*
preventive medicine, 1087
Preventive Services Task Force, U.S., recommendations of, 1090–1091*t*
Prevotella infections, 474
prilocaine, for polyneuropathy, 1045*t*
primaquine
for malaria, 587, 588*t*
for malaria prophylaxis, 591*t*
for *Pneumocystis* infections, 584*t*
primary biliary cirrhosis, 828–829
primary progressive multiple sclerosis (PPMS), 1015
primary sclerosing cholangitis (PSC), 803
primary (spontaneous) bacterial peritonitis (PBP), 382–383
primidone
for myoclonus, 238
for seizures, 965*t*, 967*t*
for tremor, 236
Prinzmetal's variant angina, 676
PRL. *See* prolactin
probenecid
for gonococcal infections, 406*t*
for gout, 865
for syphilis, 411*t*
procainamide
for arrhythmias, 683*t*
for tachyarrhythmias, 681*t*
for ventricular fibrillation, 59*f*
for Wolff-Parkinson-White syndrome, 686
procaine penicillin
for diphtheria, 442
for streptococcal infections, 436*t*
for syphilis, 411*t*
prochlorperazine
for migraine, 218*t*
for nausea and vomiting, 160
proctitis
clinical manifestations of, 403
etiology of, 403
HSV, 521*t*
treatment of, 405
proctocolitis, 403, 405
progressive multifocal leukoencephalopathy (PML), 1030–1031
prolactin (PRL)
deficiency of, 882
hypersecretion of, 879–880
production of, 877, 878*f*
prolactinoma, 879–880
promethazine, for vertigo, 228*t*
promyelocytic leukemia, acute, 284*t*, 285
propafenone, for arrhythmias, 683*t*
Propionibacterium acnes infections, 474
propofol
for delirium, 52*t*
for increased intracranial pressure, 95*t*
for status epilepticus, 102*f*
propoxyphene abuse, 1084

propranolol
for aortic dissection, 696*t*
for esophageal varices, 832
for hypertension, 652*t*
for hypokalemia, 9
for migraine prevention, 220*t*
for thyroid storm, 891
for thyrotoxicosis, 890
for tremor, 236
for variceal bleeding, 178
propylene glycol poisoning, 17, 18*t*, 19
propylthiouracil (PTU), for thyrotoxicosis, 890–891
Prostascint scanning, 343
prostate biopsy, transrectal ultrasound, 343, 344*f*
prostate cancer, 342–345
oncologic emergencies, 110–111
osteoblastic bone metastasis in, 348
paraneoplastic syndromes in, 349*t*
prevention of, 345, 1100–1101
risk factors for, 1100
screening for, 1090–1091*t*, 1095, 1098–1099*t*
treatment of, 343–345
prostate hyperplasia, 342
prostatectomy, radical retropubic, 343
prostate-specific antigen (PSA), 342, 343, 344*f*, 1095, 1098*t*
prostatitis, 776–777, 778
prosthetic device-related infections
coagulase-negative staphylococci, 429
joint, 420
S. aureus, 428
treatment of, 430
prosthetic valve endocarditis (PVE). *See also* infective endocarditis
clinical manifestations of, 374
etiology of, 372
HACEK group, 452, 453*t*
pathogenesis of, 372–373
staphylococcal, 430
treatment of, 380, 430
protamine, to reverse anticoagulation, 282, 733
protease inhibitors, for HIV infection, 559, 563*t*
protein malnutrition, 41
protein requirements, 41
protein restriction, in chronic kidney disease, 754
proteinuria, 199–201, 766–767
Proteus infections, 456–457
prothrombin time, 184*t*
protozoal infections, 586–598
babesiosis, 592
chronic meningitis in, 1035–1036tt
leishmaniasis, 592–594
malaria. *See* malaria
toxoplasmosis, 596–598
trypanosomiasis, 594–596
protriptyline, for narcolepsy, 244
Providencia infections, 457
prune juice, 50*t*
pruritus ani, 798
PS (pulmonic stenosis), 616*t*, 629–630
PSA. *See* prostate-specific antigen
PSC (primary sclerosing cholangitis), 803
pseudocyst, pancreatic, 807
pseudoephedrine
for allergic rhinitis, 838
for syncope, 225
pseudogout, 865–866
pseudohyponatremia, 2
pseudomelena, 174
Pseudomonas aeruginosa infections
clinical manifestations of, 458–459
epidemiology of, 458
microbiology of, 458
osteomyelitis, 421*t*, 459
treatment of, 459–461, 460–461*t*
pseudoseizures, 957
pseudothrombocytopenia, 279
pseudotumor cerebri, 231
PSI (Pneumonia Severity Index), 724
psittacosis, 515–516
psoralens, for polycythemia vera, 292
psoriasis, 256*f*, 258–259
psoriatic arthritis, 857–859
PSV (pressure-support ventilation), 74, 75*t*
psychiatric disorders, 1063–1070
anxiety disorders, 1067–1070
bipolar disorder, 1065–1066
depression. *See* depression
eating disorders, 1079–1080
fatigue in, 133*t*
nausea and vomiting in, 159*t*
personality disorders, 1070
schizophrenia, 1066–1067
sleep disorders and, 242
vs. syncope, 225
weight loss in, 136*t*
in women, 1106
psychiatric medications, 1071–1078
antidepressants. *See* antidepressants

antipsychotics. *See* antipsychotics
anxiolytics. *See* anxiolytics
mood stabilizers, 1078, 1078*t*
principles of use of, 1071
psychotic disorders, 1066–1067
psyllium
for diverticular disease, 796
for hemorrhoids, 798
for irritable bowel syndrome, 795, 796*t*
PTSD (posttraumatic stress disorder), 1068–1069
PTU (propylthiouracil), for thyrotoxicosis, 890–891
Ptx (pneumothorax), 140*f*, 743
pubic louse, 610–611
PUD. *See* peptic ulcer disease
puddle sign, 187
pulmonary alveolar proteinosis (PAP), 738
pulmonary angiography, 709
pulmonary artery catheters, 34
pulmonary artery pressure (PAP), 707
pulmonary circulation, disturbances of, 707
pulmonary disease. *See* respiratory disease
pulmonary edema, 150
cardiogenic, 69
causes of, 70*t*
cyanosis in, 145–146
dyspnea in, 144–145
noncardiogenic, 70, 70*t*
precipitants of, 69*t*
treatment of, 69–70
pulmonary embolism (PE)
chest pain in, 138, 138*t*, 140*f*
complications of, 730
diagnosis of, 731, 732*f*
dyspnea in, 143
hemoptysis in, 148
massive, 730
in thrombotic disorders, 281
treatment of, 281–283, 732–733, 734*f*
pulmonary fibrosis
idiopathic, 736, 737–738
progressive massive, 717
pulmonary function tests
in asthma, 712
in COPD, 718*t*, 719–720
in pulmonary hypertension, 700
pulmonary hypertension, 699–702
approach to, 701*f*
arterial, 700*t*
classification of, 700*t*
congenital heart disease and, 629
differential diagnosis of, 702
etiology of, 707
heart sounds in, 615*f*
laboratory features of, 702
treatment of, 702
pulmonary infiltrate, with eosinophilia, 738–739
pulmonary Langerhans cell histiocytosis (PLCH), 736, 739
pulmonary nodule, solitary, 315
pulmonary rehabilitation, 737
pulmonary thromboendarterectomy, 733
pulmonary vascular resistance (PVR), 707
pulmonic stenosis (PS), 616*t*, 629–630
pulmonic valve regurgitation, 616*t*
pulse oximetry, 708
pulseless disease, 696
pulseless electrical activity, 60, 60*f*
pulsus alternans, 613, 614*f*
pulsus bisferiens, 613, 614*f*
pulsus paradoxus, 613
pulsus parvus, 613, 614*f*
pulsus tardus, 613, 614*f*
pupillary signs, in coma, 81
pure alexia, 239*t*
pure red cell aplasia, in parvovirus infections, 542
pure word deafness, 239*t*
purging behavior, 1079
purine metabolism deficiency, 840
purpura, 264
pustule, 257*t*
Puumala virus infection, 552
PUVA, for psoriasis, 259
PVE (prosthetic valve endocarditis), 372–374, 380. *See also* infective endocarditis
PVR (pulmonary vascular resistance), 707
pyelonephritis, 385, 776
emphysematous, 776
xanthogranulomatous, 776
pyloroplasty, 788*t*
pyomyositis, 418, 427
pyrazinamide, for tuberculosis, 486, 487–488*t*
pyridostigmine
for myasthenia gravis, 1052
for orthostatic hypotension, 995
pyridoxine deficiency, 45*t*

pyrimethamine
for cystoisosporiasis, 392
for *Pneumocystis* prophylaxis, 585*t*
for toxoplasmosis, 598
pyrogen, 127
pyroglutamic aciduria, 17, 18*t*
pyruvate kinase deficiency, 269
pyuria, 203

Q
Q fever, 503*t*, 509–510
quadrantanopia, 234*t*
quadrantopia, 230*f*
quadriparesis, 234*t*, 235*f*
quantitative sudomotor axon reflex test (QSART), 990–991
quetiapine
dosage and side effects of, 1077*t*
for schizophrenia, 1067
quinidine
for arrhythmias, 683*t*
for malaria, 587, 589*t*
quinine
for babesiosis, 592
for malaria, 588–589*t*
quinolones. *See* fluoroquinolones
quinsy, 475
quinupristin-dalfopristin
for enterococcal infections, 440
for staphylococcal infections, 430, 431*t*

R
RA. *See* rheumatoid arthritis
rabies, 546–548
clinical manifestations of, 547
diagnosis of, 547–548
epidemiology of, 546
microbiology of, 546
pathogenesis of, 546–547
postexposure prophylaxis, 115, 118, 548, 549*f*
preexposure prophylaxis, 548
treatment of, 548
rabies immune globulin, 118, 548, 549*f*
rabies vaccine, 118, 548, 549*f*
radial neuropathy at spiral groove, 1048*t*
radiation therapy
for adrenal carcinoma, 896
for anal cancer, 330
for bladder cancer, 334
for brain tumor, 1008
for breast cancer, 320, 321
for cervical cancer, 341
for colorectal cancer, 328
for endometrial cancer, 340
for esophageal carcinoma, 322
for follicular lymphoma, 298
for head and neck cancer, 309
for Hodgkin's disease, 304
leukopenia in, 276
for lung cancer, 315
for multiple myeloma, 302
for nervous system tumors, complications of, 1012
for prostate cancer, 343
for spinal cord compression, 99, 111
for testicular cancer, 336
radiculopathy
cervical, 212, 213–214, 213*t*
lumbosacral, 208*t*
subacute, 212
radioiodine
for nontoxic goiter, 893
for thyroid neoplasms, 894–895
for thyrotoxicosis, 890–891
for toxic adenoma, 893
for toxic multinodular goiter, 893
radionuclide scan
in hepatobiliary disease, 186
utility of, 26
ragged red fibers, 1059
raloxifene
for breast cancer prevention, 1100
for osteoporosis, 934
raltegravir, for HIV infection, 559, 564*t*
ramipril
for heart failure, 690*t*
for hypertension, 653*t*
Ramsay Hunt syndrome, 523, 997
ramucirumab, for gastric carcinoma, 323
ranitidine
for *H. pylori* eradication, 787*t*
for indigestion, 161
for urticaria/angioedema, 837
ranolazine, for chronic stable angina, 675
rapid shallow breathing index (RSBI), 34
rapid urease test, 786, 786*t*
rasagiline, for Parkinson's disease, 980*t*
rasburicase, for tumor lysis syndrome, 113
rash
in alphavirus infections, 550–551
drug-related, 362

in measles, 538–539
in rubella, 539
rat-bite fever, 118
Raynaud's disease, 698*t*
Raynaud's phenomenon, 698, 698*t*
reactive arthritis, 859–860
C. trachomatis, 408
clinical manifestations of, 419, 859–860
definition of, 859
diagnosis of, 860
etiology of, 419
pathogenesis of, 859
treatment of, 860
recluse spider bite, 123
recombinase activating gene deficiency, 840
recommended dietary allowance (RDA), 41
rectal cancer, 330
red blood cells (RBCs)
disorders of, 267–274
anemia. *See* anemia
intracellular abnormalities, 269
maturation disorders, 269
membrane abnormalities, 271
polycythemia, 194–196
inclusions, 265–266
increased mass, 292
morphology of, 265
RBC indices, 194
transfusion, 46
red hepatization, 723
REE (resting energy expenditure), 40
reentrant AV nodal tachycardia, 680*t*
referred pain
abdominal, 155*t*
low back, 207
neck, 212
pathophysiology of, 36
shoulder, 214
reflex sympathetic dystrophy, 994
reflexes, testing of, 951
refractory anemia, 290*t*
refractory anemia with excess blasts, 290*t*
refractory anemia with ringed sideroblasts, 290*t*
refractory cytopenia with multilineage dysplasia, 290*t*
refractory cytopenia with unilineage dysplasia, 290*t*
refractory neutropenia, 290*t*
refractory thrombocytopenia, 290*t*
regurgitation, 158
rehydration, in diarrhea, 170
relapse prevention, 1084
relapsing fever, 498–499
relapsing polychondritis, 868
relapsing-remitting multiple sclerosis (RRMS), 1013
renal abscess, 385
renal artery stenosis, 649, 650
renal cancer, 334–335
clinical manifestations of, 335
epidemiology of, 334–335
etiology of, 335
infections in, 363*t*
oncologic emergencies, 111–112
paraneoplastic syndromes in, 349*t*
pathology of, 335
treatment of, 335
renal disease. *See also* acute renal failure; chronic kidney disease
azotemia in, 197–198, 198*f*, 198*t*
edema in, 151
fatigue in, 133*t*
glomerular, 759–766
hypertension in, 649, 650, 655
infections after HSCT, 367*t*
infections in cancer patients, 364
metabolic acidosis in, 18*t*, 19
nephrolithiasis. *See* nephrolithiasis
tubular. *See* renal tubular disease
urinary abnormalities in, 199–203
urinary tract obstruction, 782–784, 783*f*
renal transplantation, 756–759
complications of, 758–759
contraindications to, 757*t*
epidemiology of, 756–757
factors influencing graft survival, 757–758, 757*t*
focal glomerulosclerosis following, 765
immunosuppressive therapy after, 758
infections after, 368, 758–759, 759*t*
rejection after, 758
renal tubular disease, 767–775
acute interstitial nephritis, 771–772, 771*t*
chronic interstitial nephritis, 772
etiology of, 767–770*t*
monoclonal immunoglobulins and, 772–773, 773*t*
polycystic kidney disease, 773–774
renal tubular acidosis, 18*t*, 774–775
transport dysfunction in, 770*t*
repaglinide, for diabetes mellitus, 909*t*

repositioning exercises, for vertigo, 228*t*, 229
reproductive tract infections. *See* sexually transmitted infections (STI)
residual volume, 705, 705*f*
resistance, to antibacterial therapy, 361
respiratory acidosis, 17*f*, 21
respiratory alkalosis, 17*f*, 21–22
respiratory bronchiolitis, 738
respiratory disease. *See also* respiratory tract infections
  categories of, 706*t*
  in coma, 81
  cor pulmonale, 692–693
  cyanosis in, 145, 146*t*
  diagnosis of
    invasive procedures for, 710–711
    noninvasive procedures for, 709–710
  diffuse parenchymal, 143
  dyspnea in, 142–144, 144*f*
  environmental, 715–718
    inorganic dusts, 716–717
    organic dusts, 717
    toxic chemicals, 717–718
  fatigue in, 133*t*
  gas exchange disturbances, 707–708
  hypoxemia in, 708–709, 708*f*
  interstitial lung disease. *See* interstitial lung disease
  mechanisms of, 708–709
  obstructive, 706–707, 706*t*
  pulmonary circulation disturbances, 707
  pulmonary hypertension in, 700*t*
  restrictive, 706–707, 706*t*
  ventilatory function disturbances, 705–707
respiratory failure, 73–76, 75*t*
respiratory rate, 708
respiratory syncytial virus, human, 534*t*, 535–536
respiratory tract infections. *See also* pneumonia; upper respiratory infections
  actinomycosis, 480
  after HSCT, 367*t*
  aspergillosis, 572, 574*t*
  bacterial
    anaerobic, 475
    C. pneumoniae, 513
    diphtheria, 441–442
    M. pneumoniae, 510–511
    nontuberculous mycobacterial, 492–494
    S. aureus, 427
    tuberculosis. *See* tuberculosis
  in cancer patients, 364
  coccidioidomycosis, 579
  cryptococcal, 573
  mucormycosis, 577
  nocardiosis, 478, 480*t*
  viral
    adenovirus, 537
    clinical manifestations of, 534*t*
    coronavirus, 533, 535
    human metapneumovirus, 536
    human RSV, 535–536
    influenza. *See* influenza
    parainfluenza virus, 536–537
    rhinovirus, 533
  weight loss in, 136*t*
resting energy expenditure (REE), 40
restless legs syndrome (RLS), 242, 244*t*
restrictive cardiomyopathy, 640*t*, 642, 648*t*
retching, 158
reteplase, for thrombotic disorders, 282
reticular dysgenesis, 840
reticulocyte index (RI), 194
reticulocytes, 265
retinal artery occlusion, 230*f*
retinal detachment, 231
retinal vein occlusion, 230*f*, 231
retinitis, cytomegalovirus, 527
retinitis pigmentosa, 230*f*
retinoic acid
  for acne, 262
  for head and neck cancer, 310
  for head and neck cancer prevention, 1101
  for squamous cell carcinoma, 308
trans-retinoic acid, for AML, 287
retinoid, for psoriasis, 259
retinopathy, paraneoplastic, 352*t*, 353*t*, 355
reverse SLR sign, 208–209
Reye's syndrome, 531
rhabdomyolysis, 202
rheumatic fever, prophylaxis for, 632
rheumatic heart disease, 632
rheumatic mitral valve disease, 89*t*
rheumatic (Sydenham's) chorea, 237
rheumatoid arthritis (RA)
  clinical manifestations of, 845–846
  differential diagnosis of, 846–847
  evaluation of, 846
  neck pain in, 212

pathogenesis of, 845
treatment of, 846–847
rheumatoid factor, 852, 856
rhinitis, allergic, 837–838
rhinocerebral mucormycosis, 576
rhinophyma, 263
rhinosinusitis. *See* sinusitis
rhinovirus infections, 533, 534*t*
Rhizomucor infections. *See* mucormycosis
Rhizopus oryzae. *See* mucormycosis
Rhodococcus infections, 443
RI (reticulocyte index), 194
ribavirin
for adenovirus infections, 537
for chronic hepatitis C, 817, 822–824*t*
for croup, 537
for human RSV infections, 536
for viral encephalitis, 1029
for viral hemorrhagic fever with renal syndrome, 552
for viral hemorrhagic fevers, 552
Richter's syndrome, 296
Rickettsia africae infections, 501*t*, 505
Rickettsia conorii infections, 501*t*, 504–505
rickettsial disease, 500–510, 501–503*t*
ehrlichioses and anaplasmosis, 502*t*, 508–509
endemic murine typhus, 502*t*, 505–506
epidemic typhus, 502*t*, 506–507
lymphadenopathy and, 190*t*
Q fever, 503*t*, 509–510
rickettsialpox, 501*t*, 505
Rocky Mountain spotted fever, 500, 501*t*, 504
scrub typhus, 503*t*, 507
tick-borne spotted fevers, 501*t*, 504–505
rickettsialpox, 501*t*, 505
rifabutin
for nontuberculous mycobacterial infections, 494
for tuberculosis, 486
rifampin
for asymptomatic GAS carriage, 435
for *Bartonella* infections, 467*t*
for brucellosis, 464
for *Corynebacterium* infections, 443
for diphtheria, 442
for enterococcal infections, 440
for human granulocytotropic anaplasmosis, 508
for infectious arthritis, 420
for infective endocarditis, 377*t*, 380
for latent tuberculosis, 490*t*
for *Legionella* infections, 513
for leprosy, 492
for meningococcal prophylaxis, 446, 1025
for nontuberculous mycobacterial infections, 494
for osteomyelitis, 421*t*
for pneumococcal infections, 424
for primary biliary cirrhosis, 829
for Q fever, 510
for staphylococcal infections, 430, 433*t*
for tuberculosis, 486, 487–488*t*
rifapentine, for tuberculosis, 486, 487–488*t*, 490*t*
rifaximin
for *C. difficile* infections, 398
for hepatic encephalopathy, 833
for irritable bowel syndrome, 795
Rift Valley fever, 551
right ventricular hypertrophy, 620, 620*f*
right ventricular systolic pressure (RVSP), 622–623
rilpivirine, for HIV infection, 559, 563*t*
riluzole, for ALS, 987
rimantadine, for influenza, 532, 532*t*
Ringer's lactate, for cholera, 389
ringworm, 261
risedronate, for osteoporosis, 934
risperidone
for delirium, 52*t*
dosage and side effects of, 1077*t*
for schizophrenia, 1067
ritonavir, for HIV infection, 563*t*
rituximab
for ANCA-associated glomerulonephritis, 762
for autoimmune hemolysis, 274
for CLL, 297
for gastric carcinoma, 324
for glomerulonephritis, 765
for idiopathic thrombocytopenic purpura, 280
for inflammatory myopathy, 1059
for lymphoma, 299
for multiple sclerosis, 1019
for posttransplantation lymphoproliferative disease, 529
for rheumatoid arthritis, 847
for vasculitis, 854

rivaroxaban
for atrial fibrillation, 686
for thrombotic disorders, 282
rivastigmine, for Alzheimer's disease, 973
river blindness, 604
rizatriptan, for migraine, 217*t*, 219*t*
RLS (restless legs syndrome), 242, 244*t*
Rocky Mountain spotted fever, 500, 501*t*, 504
rodent bite, 117*t*, 118
roflumilast, for COPD exacerbation prophylaxis, 721
Romaña's sign, 594
Romberg maneuver, 951
ropinirole
for Parkinson's disease, 980*t*
for restless legs syndrome, 242
rosacea. *See* acne rosacea
rose spots, 393
roseola infantum, 525
rosetting, 586
rosiglitazone, for diabetes mellitus, 909*t*
Ross River virus infections, 551
rosuvastatin, for dyslipidemia, 938*t*
rotavirus infections, 390
rotavirus vaccine, 390
rotigotine, for Parkinson's disease, 980*t*
rouleaux formation, 265
RRMS (relapsing-remitting multiple sclerosis), 1013
RSBI (rapid shallow breathing index), 34
rubella, 539–540
rubella vaccine, 370*t*, 539, 540
rubeola (measles), 538–539
rufinamide, for seizures, 965*t*, 967*t*
rumination, 158
RVSP (right ventricular systolic pressure), 622–623

S

SAAG (serum-ascites albumin gradient), 187, 188*f*
Saccharomyces boulardii therapy, for *C. difficile* infections, 398
saccular (intracranial) aneurysm, 91
salicylates
acid-base disorders with, 17, 18*t*, 22
for osteoarthritis, 862
for seborrheic dermatitis, 260
for warts, 262
saline therapy
for diabetic ketoacidosis, 106*t*
for hypercalcemia, 112, 351, 927*t*
for hyperglycemic hyperosmolar state, 105
for hypernatremia, 5–6
for hyponatremia, 5, 351
for increased intracranial pressure, 95*t*
for metabolic alkalosis, 20
for SIADH, 112
for tumor lysis syndrome, 113
salmeterol, for asthma, 713
salmonellosis, 392–394
nontyphoidal, 394–395
typhoid fever, 393–394
salpingitis, 402
salpingo-oophorectomy, 1100
samarium-153 therapy, 345
sarcoidosis, 870–873, 872*f*, 1038*t*
sarcoma, paraneoplastic syndromes in, 349*t*
Sarcoptes scabiei infestation. *See* scabies
SARS (severe acute respiratory syndrome), 535
sausage digits, 857
saxagliptin, for diabetes mellitus, 908*t*
scabies, 610
scale (skin lesion), 257*t*
scar, 257*t*
scar carcinoma, 308
scarlet fever, 435
SCC. *See* squamous cell carcinoma
scedosporiosis, 582
Schilling test, 170
schistocytes, 265
schistosomiasis, 334, 605–606
schizoid personality disorder, 1070
schizophrenia, 1066–1067
schizotypal personality disorder, 1070
schwannoma, 1010
sciatic neuropathy, 1049*t*
SCID (severe combined immunodeficiency), 840
sclerodactyly, 847
scleroderma (systemic sclerosis), 165, 847–848
scombroid poisoning, 122
scopolamine
for nausea and vomiting, 51, 160
for vertigo, 228*t*
scorpion sting, 124
scorpionfish envenomation, 120–121
scotoma, 229, 230*f*
screening recommendations, 1087

scrub typhus, 503*t*, 507
sea anemone injury, 120
seborrheic keratosis, 256*f*
secondary progressive multiple sclerosis (SPMS), 1013
secretin stimulation test, 170, 807
seizures, 956. *See also* epilepsy
  approach to, 956, 960*f*
  classification of, 956, 956*t*
  differential diagnosis of, 957, 958*t*
  drug-induced, 959
  EEG in, 958
  etiology of, 956, 957*t*
  imaging in, 960, 967
  laboratory testing in, 958
  vs. syncope, 225
  treatment of, 961–966*t*, 967–968, 967*t*
selection bias, 1095
selective serotonin reuptake inhibitors (SSRIs), 1071, 1072*t*
selegiline
  dosage and side effects of, 1073*t*
  for Parkinson's disease, 980*t*
selenium sulfide, for seborrheic dermatitis, 260
semen analysis, 915
seminoma, 336, 337*f*
senna, for constipation, 50*t*
sensitization, 36
sensory examination, 951
sensory level, 110
sensory loss, 233, 234*t*
sentinel node biopsy, in breast cancer, 320
sepsis/septic shock, 65–68
  approach to, 32, 33*f*, 62
  clinical manifestations of, 62, 65, 66
  clostridial, 473, 474*t*
  complications of, 66
  in critically ill patient, 35
  definition of, 65
  epidemiology of, 65–66
  etiology of, 65
  laboratory features of, 62, 62*t*, 67
  pathophysiology of, 66
  prevention of, 67
  prognosis of, 67
  S. aureus, 427
  severe, 65
  streptococcal, 438
  treatment of, 67, 68*t*
septal panniculitis, 263
septicemia
  listerial, 446–447
  meningococcal, 444
serous otitis media (SOM), 251
Serratia infections, 457
sertraline
  dosage and side effects of, 1072*t*
  for obsessive-compulsive disorder, 1068
serum-ascites albumin gradient (SAAG), 187, 188*f*
sevelamer, for hyperphosphatemia, 929
severe acute respiratory syndrome (SARS), 535
severe combined immunodeficiency (SCID), 840
sexual assault, 1106
sexually transmitted infections (STI), 399
  chancroid, 404*t*, 413
  chlamydial infections. *See* chlamydial infections
  donovanosis, 404*t*, 413
  epididymitis, 400
  genital herpes. *See* genital herpes
  gonorrhea. *See* gonorrhea
  HPV infections, 413–414
  lymphogranuloma venereum, 404*t*, 408
  mucopurulent cervicitis, 401–402
  mycoplasmal infections, 399–400, 401–402, 408–409
  pelvic inflammatory disease, 402–403
  proctitis, proctocolitis, enterocolitis, and enteritis, 403
  syphilis. *See* syphilis
  urethritis
    in men, 399–400
    in women, 400
shift work, 241, 245
Shiga toxin-producing/enterohemorrhagic *E. coli* (STEC/EHEC), 395–396, 455
shigellosis, 395–396, 403
shingles. *See* herpes zoster
shock, 61–65. *See also specific types*
  approach to, 33*f*, 62
  cardiogenic, 32, 61*t*, 62*t*
  forms of, 61*t*
  in GI bleeding, 175
  hemodynamic profiles in, 63*f*
  high cardiac output/low systemic vascular resistance, 32, 33*f*
  hypovolemic, 32, 33*f*
  physiologic characteristics of, 62*t*
  treatment of, 63–65, 63*f*, 64*t*

shoulder, muscles and innervation of, 949*t*
shoulder pain, 212–214
  in adhesive capsulitis, 870
  etiology of, 212–214
  mechanical, 214
  treatment of, 214
shunting, hypoxemia in, 708
SIADH. *See* syndrome of inappropriate ADH
sick euthyroid syndrome, 892
sick sinus syndrome (SSS), 677
sickle cell anemia, 269, 272*f*, 273
sickled cells, 265
sideroblastic anemia, 269, 271*t*
sigmoidoscopy
  in colonic polyps, 327
  for colorectal cancer screening, 330, 1097*t*
  in diarrhea, 170
  in GI bleeding, 175
"signet-ring sign," 729
sildenafil
  for achalasia, 164
  for erectile dysfunction, 916
  for pulmonary hypertension, 702
  for systemic sclerosis, 848
silent ischemia, 672
silicosis, 716–717
simple phobia, 1069
SIMV (synchronized intermittent mandatory ventilation), 74, 75*t*
simvastatin, for dyslipidemia, 938*t*
Sin Nombre virus, 551
Sindbis virus infections, 550
single photon emission computed tomography (SPECT), 26
sinoatrial node dysfunction, 677
sinus infections, 247–249
  acute, 247–248, 249*t*
  bacterial, 248
  chronic, 248–249
  fungal, 249
  nosocomial, 248
  treatment of, 248
  viral, 248
sinus rhythm, 618
sinus tachycardia, 663, 680*t*
sinus venosus, 627
sinusitis
  anaerobic, 475
  aspergillosis, 572
  Klebsiella, 456
  M. catarrhalis, 451
  pneumococcal, 424
sinusoidal obstruction syndrome, 188*f*
sipuleucel-T, for prostate cancer, 345
sirolimus, for immunosuppression after renal transplantation, 758
Sister Mary Joseph's nodule, 187
sitagliptin, for diabetes mellitus, 908*t*
sitosterolemia, 937*t*
Sjögren's syndrome, 848–849
SK. *See* streptokinase
skin biopsy, 256
skin cancer, 305–310
  basal cell carcinoma, 307
  melanoma. *See* melanoma
  paraneoplastic syndromes in, 349*t*
  prevention of, 308
  screening for, 1099*t*
  squamous cell carcinoma, 308
skin disease
  acne, 262–263
  arrangement and shape of lesions, 255, 256*f*
  in cancer patients, 362
  diagnosis of, 256–258
  distribution of lesions, 255
  drug-induced, 263–264
  eczematous, 259–260
  history in, 256
  infections, 260–262
  lesion characteristics, 255, 256*f*
  in malnutrition, 42
  papulosquamous, 258–259
  physical examination in, 255
  primary lesions, 255, 257*t*
  secondary lesions, 255, 257*t*
  vascular disorders, 263–264
skin infections
  anaerobic, 476
  aspergillosis, 572
  in cancer patients, 362, 363*t*
  cellulitis, 415*t*, 417
  clinical manifestations of, 415–417
  clostridial, 473
  cryptococcal, 573
  diphtheria, 441
  group A *Streptococcus*, 436, 436*t*
  mucormycosis, 577
  necrotizing fasciitis, 416*t*, 417–418
  nontuberculous mycobacterial, 493
  P. aeruginosa, 459
  S. aureus, 427, 430, 433*t*
  in transplant recipients, 367*t*
  treatment of, 415–416*t*
skin tag, 256*f*
skull fracture, 96
SLE. *See* systemic lupus erythematosus

sleep apnea, 243, 745–746
sleep disorders
approach to, 241–242
circadian rhythm, 245
excessive daytime sleepiness, 243–245, 244*t*
fatigue in, 133*t*
insomnia, 241–242, 243*t*
in women, 1106
sleep hygiene, 241, 243*t*
sleep paralysis, 243, 244, 244*t*
sleeping sickness, 595–596
slit-lamp examination, 229
slow low-efficiency dialysis (SLED), 751
SLR (straight leg raising) sign, 207–208
small-bowel tumor, 325
smell, disorders of sense of, 998, 999*t*, 1000
smoke inhalation, 717
smoking
bladder cancer and, 333
COPD and, 719
cough and, 147
lung cancer and, 310
pancreatic cancer and, 331
prevention of, 1103–1104
relative risks for current smokers, 1102*t*
in women, 1106
smoking cessation, 1087, 1102–1103
approach to, 1102
clinical practice guidelines, 1103*t*
for COPD, 720
for disease prevention, 1088–1090*t*
for head and neck cancer prevention, 310
for heart disease prevention, 1092
for interstitial lung disease, 737
for lung cancer prevention, 315
methods of, 1102–1103
for myocardial infarction prevention, 671
for osteoporosis, 934
for peripheral arteriosclerosis, 697
for vasospastic disorders, 698
snakebite
clinical manifestations of, 119
epidemiology of, 118–119
prognosis of, 119
treatment of, 117*t*, 119–120
snoring, 244*t*
SNS (specialized nutrition support), 43, 44*f*
social phobia, 1069
sodium, disorders of, 1–6
hypernatremia, 5–6, 6*t*
hyponatremia, 1–5, 3*f*
sodium bicarbonate, for metabolic acidosis, 20
sodium citrate, for metabolic acidosis, 20
sodium docusate, for constipation, 50*t*
sodium ipodate, for amiodarone-induced thyrotoxicosis, 892
sodium oxybate, for narcolepsy, 245
sodium phosphate enema, for constipation, 50*t*
sodium restriction
for aldosteronism, 898
for ascites, 188
for cor pulmonale, 693
for edema, 151–152
for heart failure, 688, 689*t*
for hypertension, 651
for restrictive cardiomyopathy, 642
for vertigo, 228*t*, 229
sodium stibogluconate, for leishmaniasis, 594
sodium tyropanoate, for amiodarone-induced thyrotoxicosis, 892
soft tissue infections
anaerobic, 476
in cancer patients, 362, 363*t*
cellulitis, 415*t*, 417
clinical manifestations of, 415–417
clostridial, 473
group A *Streptococcus*, 436, 436*t*
Klebsiella, 456
myositis and myonecrosis, 418
necrotizing fasciitis, 416*t*, 417–418
nontuberculous mycobacterial, 493
P. aeruginosa, 459
S. aureus, 426–427, 430, 433*t*
treatment of, 415–416*t*
SOM (serous otitis media), 251
somatic pain, 36, 36*t*
somatic symptom disorder, 1069–1070
somatostatin therapy
for acromegaly, 881
for esophageal varices, 832
somatostatinoma, 332*t*, 333
somatotropin, for hypopituitarism, 883*t*
sorafenib
for hepatocellular carcinoma, 331
for renal cancer, 335
sorbitol
for irritable bowel syndrome, 796*t*
for paralytic shellfish poisoning, 122

sotalol, for arrhythmias, 684*t*
South American blastomycosis, 581–582
soy-based products, 922
spastic colon, 794
specialized nutrition support (SNS), 43, 44*f*
SPECT (single photon emission computed tomography), 26
spectinomycin, for gonococcal infections, 407y
spermatogenesis, 915
spherocytes, 265
spider bite, 123–124
spinal cord, 004*f*
spinal cord compression, 98–100
  approach to, 98
  epidural abscess, 99
  epidural hematoma, 100
  from metastases, 1001*t*, 1012
  neoplastic, 98–99, 1005, 1005*f*
  as oncologic emergency, 110–111
  treatment of, 99, 111, 111*f*
spinal cord disease, 1002–1008
  acute and subacute, 1005–1006
  autonomic dysfunction in, 991, 1002
  cauda equina, 1004
  cervical, 1004
  chronic, 1006–1107
  complications of, 1007–1008
  extramedullary, 1005
  foramen magnum lesions, 1003
  intramedullary, 1005
  lumbar, 1004
  sacral, 1004
  thoracic, 1003
  treatable, 1003*t*
  weakness in, 234*t*
spinal cord infarction, 1005–1006
spinal manipulation, for chronic back pain, 211
spinal stenosis, 210–211
spinocerebellar ataxia, 893*f*, 983
Spirillum minor infections, 118
spirochetal infections
  endemic treponematosis, 497
  leptospirosis, 497–498
  Lyme borreliosis, 494–497
  relapsing fever, 498–499
spirometry, 148, 705–706, 705*f*
spironolactone
  for ascites, 188
  for edema, 152, 153*t*
  for heart failure, 664, 688, 689*t*, 690*t*
  for hirsutism, 920
  for hyperaldosteronism, 20–21, 898
  for hypertension, 652*t*
  for STEMI, 662
splenectomy, 193, 385
  for idiopathic thrombocytopenic purpura, 280
  for polycythemia vera, 292
  sepsis following, 68*t*
  for thalassemia, 273
splenic abscess, 385
splenomegaly, 191–193
  diseases associated with, 192–193*t*
  mechanism of, 192, 192–193*t*
SPMS (secondary progressive multiple sclerosis), 1013
spondylitic myelopathy, 1006
spondylolisthesis, 210
spondylosis
  cervical, 212, 214
  low back pain in, 210
spontaneous breathing trial, 33–34
sporotrichosis, 581, 1035*t*
sporozoite, 586
spotted fevers
  flea-borne, 501*t*
  tick- and mite-borne, 500–505, 501*t*
spur cell anemia, 271
sputum analysis
  in pneumonia, 724
  in respiratory disease, 710
sputum cytology, for cough, 148
squamous cell carcinoma (SCC)
  infections in, 363*t*
  location of, 256*f*
  risk factors for, 308
  treatment of, 308
  types of, 308
SSPE (subacute sclerosing panencephalitis), 538
SSRIs (selective serotonin reuptake inhibitors), 1071, 1072*t*
SSS (sick sinus syndrome), 677
SSSS (staphylococcal scalded-skin syndrome), 428
stabbing headache, primary, 215*t*, 221
standard precautions, 357
staphylococcal infections, 425–434
  arthritis, 418–420
  coagulase-negative, 428–429
  endocarditis, 372–373, 377*t*, 380
  microbiology of, 425
  osteomyelitis, 420, 421*t*. *See also* osteomyelitis

S. aureus. *See Staphylococcus aureus* infections
S. moniliformis, 118
skin, 415*t*, 417
treatment of, 430, 431–433*t*
staphylococcal scalded-skin syndrome (SSSS), 428
Staphylococcus aureus infections, 426–428
bacteremia and sepsis, 427
diagnosis of, 426
endocarditis, 372, 427–428, 430
epidemiology of, 426
food poisoning, 387
impetigo, 261
invasive disease, 426
methicillin-resistant. *See* methicillin-resistant *S. aureus* (MRSA) infections
musculoskeletal, 427
osteomyelitis, 430
pathogenesis of, 426
prevention of, 428
prosthetic device-related, 428
respiratory tract, 427
skin and soft tissue, 426–427, 430, 433*t*
spinal epidural abscess, 99
toxin-mediated disease, 426, 428, 429*t*, 430
treatment of, 430, 431–433*t*
urinary tract, 428
starvation, 41
stasis ulcer, 256*f*
statins
for dyslipidemia, 938*t*, 941
indications for, 1093*t*
for UA/NSTEMI, 670, 671
status epilepticus, 101–103
after hypoxic-ischemic insult, 101
clinical manifestations of, 103
etiology of, 103
nonconvulsive, 103
prognosis of, 103
treatment of, 102*f*, 103
Stauffer's syndrome, 335
steatorrhea, 170
STEC/EHEC (Shiga toxin-producing/enterohemorrhagic *E. coli*), 395–396, 455
stellate ganglion blockade, 994
STEMI. *See* ST-segment elevation myocardial infarction
Stenotrophomonas maltophilia infections, 461–462, 461*t*
stenting, vascular
for angina pectoris, 675–676, 676*t*
for superior vena cava syndrome, 110
stereognosis, 951
sterilization, 922
steroid therapy. *See* glucocorticoid therapy
Stevens-Johnson syndrome, 263
STI. *See* sexually transmitted infections
stiff-person syndrome, 352*t*, 353*t*, 354*t*
stingray envenomation, 120–121
stonefish envenomation, 120–121
stool analysis, 170
stool softeners, 50*t*, 798
straight leg raising (SLR) sign, 207–208
strawberry tongue, 435
Streptobacillus moniliformis infections, 118
streptococcal infections, 434–440
arthritis, 418–420
endocarditis, 372, 376–377*t*, 378–379
erysipelas, 261
glomerulonephritis following, 760
group A. *See* group A *Streptococcus* (GAS) infections
group B, 438
group D, 439
groups C and G, 438
hemolytic patterns, 434
microbiology of, 434
osteomyelitis, 421*t*. *See also* osteomyelitis
pharyngitis, 253
skin, 415–416*t*, 417
viridans streptococci, 439
Streptococcus pneumoniae infections. *See* pneumococcal infections
streptokinase (SK)
for STEMI, 659
for thrombotic disorders, 282
streptomycin
for *Bartonella* infections, 467*t*
for brucellosis, 464
for enterococcal infections, 440
for infective endocarditis, 377*t*, 378
for plague, 466
for tuberculosis, 486, 487–488*t*
for tularemia, 465
streptozotocin
for carcinoid tumor, 332
for islet-cell tumors, 333
for Zollinger-Ellison syndrome, 790

stress testing, in coronary artery disease, 672, 673*f*, 674*t*
stroke, 82–91
  anatomic localization in, 83*t*
  causes of, 87–88, 88*t*
  hemorrhagic, 82, 85
  ischemic, 82–83
    causes of, 87–88, 88*t*
    treatment of, 84–87, 86*t*
  pathophysiology of, 82
  prevention of, 89–91
  risk factors for, 89
  small-vessel, 82, 83
  treatment of, 84–87, 85*f*
stromal tumor, 338
strongyloidiasis, 601–602
strontium-89 therapy, 345
struvite stones, 780, 782*t*
ST-segment elevation myocardial infarction (STEMI)
  chest pain in, 138, 140*f*, 658
  complications of
    acute mechanical, 667
    arrhythmias, 663–664
    cardiogenic shock, 664, 665*t*, 666*f*
    heart failure, 663–664, 664*t*, 665*t*
    hypotension, 664, 667
    hypovolemia, 665*t*
    pericarditis, 667
    ventricular aneurysm, 667
  ECG in, 141, 620, 621*f*, 621*t*, 645*t*, 658
  laboratory features of, 658–659
  pericarditis following, 645*t*
  physical examination in, 658
  prevention of, 283, 667
  risk factors for, 667
  syncope in, 222
  treatment of, 659–662, 660*f*, 661*f*
stupor, 76
subacute sclerosing panencephalitis (SSPE), 538
subarachnoid hemorrhage (SAH), 91–93
  grading scales for, 91, 92*t*
  headache in, 215*t*
  with hydrocephalus, 92
  treatment for, 92–93
  vasospasm in, 92–93
subdural hematoma, 98
substance abuse
  alcohol use disorder. *See* alcohol use disorder
  narcotics. *See* narcotic abuse
  in women, 1106
sucralfate
  for erosive gastropathies, 788
  for peptic ulcer disease, 787
sudden death, 57–60, 57*t*
suicide, 1064, 1066, 1088–1090*t*
sulfadiazine, for toxoplasmosis, 598
sulfadoxine-pyrimethamine, for malaria, 588*t*
sulfasalazine
  for enteropathic arthritis, 867
  for inflammatory bowel disease, 792
  for psoriatic arthritis, 859
  for reactive arthritis, 860
  for rheumatoid arthritis, 846
sulfhemoglobinemia, 145
sulfinpyrazone, for gout, 865
sulfonamides, for nocardiosis, 479
sulfonylureas, for diabetes mellitus, 906, 908*t*
sulindac
  for colon cancer prevention, 1100
  for colonic polyps, 327
sumatriptan
  for cluster headache, 219
  for migraine, 217*t*, 219*t*
summer grippe, 544
sunitinib
  for islet-cell tumors, 333
  for renal cancer, 335
superior vena cava syndrome, 110
supraventricular arrhythmia, in STEMI, 663
supraventricular tachycardia (SVT), 682*t*, 685*f*
suramin, for sleeping sickness, 596
surgical wound infections, 358, 359*t*
SVR (systemic vascular resistance), 663
swallowing studies, 164
Sweet's syndrome, 362
swimmer's ear, 250, 459
swimmer's itch, 417, 605
swinging flashlight test, 229
sympathectomy, digital, for systemic sclerosis, 848
sympathetic system, 989*f*, 990*t*
sympathomimetics, for allergic rhinitis, 838
synchronized intermittent mandatory ventilation (SIMV), 74, 75*t*
syncope, 222–225
  approach to, 222, 223*f*
  cardiac, 224*t*
  differential diagnosis of, 225
  etiology of, 222–224, 223–224*t*
  neurally mediated, 222, 223*t*

orthostatic hypotension, 224, 224*t*
treatment of, 225
vasodepressor, 222
vasovagal, 222, 223*t*
syndrome of inappropriate ADH (SIADH)
clinical manifestations of, 885
etiology of, 885, 885*t*
hyponatremia in, 4
paraneoplastic, 112, 351, 349*t*
treatment of, 116, 351, 886
syndrome X. *See* metabolic syndrome
synkinesis, 996
synovial fluid analysis, 205, 206*f*, 419, 864, 866
syphilis
clinical manifestations of, 403, 404*t*, 409–410
congenital, 410
diagnosis of, 410
endemic, 497
meningitis in, 1033*t*
microbiology and epidemiology of, 409
pathogenesis of, 409
phases of, 409–410
in pregnancy, 411*t*
tertiary, 1007
treatment of, 410–412, 411*t*
syringomyelia, 1006
systemic lupus erythematosus (SLE), 844–845
chorea and, 237
chronic meningitis in, 1039*t*
clinical manifestations of, 844
diagnosis of, 844
evaluation of, 844
glomerular disease in, 762, 768*t*
pathogenesis of, 844
treatment of, 845
systemic sclerosis (scleroderma), 165, 847–848
systemic vascular resistance (SVR), 663

T
T cell deficiency syndromes, 840, 841*t*, 842
T cell receptors, 840
T cells, 189
T_3 (triiodothyronine), 886
T_4 (thyroxine), 883*t*, 886
tabes dorsalis, 410, 1007
TAC (transient aplastic crisis), 542
tâche noire, 504
tachyarrhythmias, 679–686
clinical and ECG features of, 680–682*t*
treatment of, 685–686
tachycardia, 677
tacrine, 973
tacrolimus
for immunosuppression after renal transplantation, 758
for inflammatory bowel disease, 794
for inflammatory myopathy, 1059
for myasthenia gravis, 1053
tadalafil
for erectile dysfunction, 916
for pulmonary hypertension, 702
taeniasis asiatica, 606–607
taeniasis saginata, 606–607
taeniasis solium, 607
Takayasu arteritis, 851
Takayasu's disease, 696
tamoxifen
for breast cancer, 320, 321
for breast cancer prevention, 1100
endometrial cancer and, 340
for melanoma, 307
tapeworm infections, 606–610
tardive dyskinesia, 237, 1074
target cells, 265
target lesion, 255
tarsal tunnel syndrome, 1049*t*
TAVI (transcatheter aortic valve implantation), for aortic stenosis, 636
taxanes, for prostate cancer, 343
tazarotene, for psoriasis, 259
TB. *See* tuberculosis
TCAs. *See* tricyclic antidepressants
Td (tetanus and diphtheria toxoid) vaccine, 442, 1090*t*
teardrop cells, 265
tedizolid, for staphylococcal infections, 432*t*, 433*t*
telangiectasia, 257*t*
telavancin, for staphylococcal infections, 430
telbivudine, for chronic hepatitis B, 817, 818–819*t*
temazepam
for insomnia, 242
pharmacology of, 1075*t*
temozolomide, for melanoma, 307
temperature, 127
temporal (giant cell) arteritis, 231, 851
temsirolimus, for renal cancer, 335
tendinitis, 869–870

tendon reflexes, 233*t*
tendon xanthoma, 936
tenecteplase, for thrombotic disorders, 282
teneligliptin, for diabetes mellitus, 908*t*
tenofovir
  for chronic hepatitis B, 817, 818–819*t*
  for HIV infection, 561*t*, 566
tenosynovitis, 864
tension headache, 215*t*, 218
tension pneumothorax, 743
teratoma, 336
terazosin, for prostate hyperplasia, 342
terbinafine
  for dermatophyte infections, 262
  pharmacology of, 570
teriflunomide, for multiple sclerosis, 1018
teriparatide, for osteoporosis, 934
terminally ill patient
  care during last hours, 53, 54–56*t*
  clinical courses in last days, 53*f*
  constipation in, 50, 50*t*
  delirium in, 52, 52*t*, 56*t*
  depression in, 52
  dyspnea in, 51, 51*t*
  fatigue in, 51–52, 54*t*
  nausea and vomiting in, 51–52
  pain management in, 50
  physical symptoms of, 49–52, 49*t*
  psychological symptoms of, 49*t*
  withdrawal of care, 35
testicular cancer, 335–336, 337*f*
testosterone deficiency. *See* androgen deficiency
testosterone therapy
  for androgen deficiency, 914–915
  for hypopituitarism, 883*t*
tetanus, 469–471
tetanus and diphtheria toxoid (Td) vaccine, 442, 1090*t*
tetanus booster, 118
tetanus immune globulin, 470
tetracyclines
  for acne, 263
  for actinomycosis, 481
  for brucellosis, 464
  for *C. pneumoniae* infections, 513
  for *C. psittaci* infections, 516
  for donovanosis, 413
  for *H. pylori* eradication, 787*t*
  for human monocytotropic ehrlichiosis, 508
  for intestinal pseudoobstruction, 797
  for *Legionella* infections, 513
  for *M. pneumoniae* infections, 511
  for malaria, 588*t*
  for relapsing fever, 499
  for syphilis, 411*t*
Tetralogy of Fallot, 631
tetrathiomolybdate, for Wilson's disease, 946
thalassemia, 269, 271*t*, 273
thalidomide
  for leprosy, 492
  for multiple myeloma, 302
theophylline
  for asthma, 713
  for COPD, 720
  poisoning, 9
therapeutic hypothermia, 60
thermoregulatory sweat test (TST), 990–991
thiamine deficiency, 45*t*
thiamine therapy, for alcohol withdrawal, 1083
thiazides
  for heart failure, 688
  for hypertension, 651, 652*t*
  for nephrolithiasis, 781*t*
thiazolidinedione, for diabetes mellitus, 906
thienopyridines, for thrombotic disorders, 283
thigh, muscles and innervation of, 950*t*
thin basement membrane nephropathy, 766
thiocyanate toxicity, 690–691
thioridazine
  for delirium, 52*t*
  dosage and side effects of, 1076*t*
thiothixene, 1076*t*
thoracentesis, 27–28, 28*f*, 710–711
thoracic outlet syndrome, 212, 1048*t*
thoracic spine disease, chest pain in, 139*f*, 141
thoracic surgery, video-assisted (VATS), 711, 737
thrombocytopenia, 277–279, 278*f*
  drug-induced, 278, 280
  heparin-induced, 278
  refractory, 290*t*
  treatment of, 280
thrombocytopenic purpura
  idiopathic, 278
  thrombotic. *See* thrombotic thrombocytopenic purpura
thrombocytosis, 279, 293
thrombolytic therapy

for arterial embolism, 697
for stroke, 86, 86*t*
thrombophlebitis, superficial, 698
thrombotic disorders, 281–283
thrombotic thrombocytopenic purpura (TTP)
clinical manifestations of, 279
treatment of, 47, 280
thrush, 570
thumb, muscles and innervation of, 950*t*
thymectomy, for myasthenia gravis, 1053
thymoma, 353*t*
thymus, in myasthenia gravis, 1050
thyroid disease, 886–895
hypothyroidism. *See* hypothyroidism
neoplasms, 893–895, 894*f*
nontoxic goiter, 892–893
paraneoplastic syndromes in, 349*t*
sick euthyroid syndrome, 892
thyrotoxicosis. *See* thyrotoxicosis
toxic adenoma, 893
toxic multinodular goiter, 893
thyroid function tests, 889
thyroid nodule, 894*f*
thyroid storm (thyrotoxic crisis), 889, 891
thyroidectomy
for thyroid neoplasms, 894–895
for thyrotoxicosis, 891
for toxic multinodular goiter, 893
thyroiditis, 889, 891, 891*f*
thyroid-stimulating hormone (TSH)
deficiency of, 882, 883*t*
hypersecretion of, 881
production of, 877, 878*f*
thyrotoxic crisis (thyroid storm), 889, 891
thyrotoxicosis
amiodarone-induced, 892
clinical manifestations of, 889
diagnosis of, 889, 890*f*
etiology of, 886, 889
treatment of, 890–891
thyroxine (T_4), 883*t*, 886
TIA (transient ischemic attack), 82, 85*f*
tiagabine
for generalized anxiety disorder, 1068
for seizures, 965*t*, 967*t*
TIBC (total iron-binding capacity), 268, 268*f*, 270*t*
tic douloureux. *See* trigeminal neuralgia
ticagrelor, for UA/NSTEMI, 670, 671
ticarcillin-clavulanate
for mixed anaerobic infections, 476*t*
for *S. maltophilia* infections, 461*t*
tick, removal of, 123
tick bite, 122–123
tick paralysis, 123
tick-borne relapsing fever, 499
tick-borne spotted fevers, 500–505, 501*t*
ticlopidine, for thrombotic disorders, 283
tics, 238
TIGAR-O classification, of pancreatic disease, 808*t*
tigecycline
anaerobic infections, 476*t*
for *C. difficile* infections, 398
for enterococcal infections, 440
for *Klebsiella* infections, 456
for nontuberculous mycobacterial infections, 494
for staphylococcal infections, 430
tilt-table test, 990
TIMI Risk Score, 670*f*
tinea capitis, 261
tinea corporis, 261
tinea cruris, 256*f*, 261
tinea pedis, 256*f*, 261
tinea (pityriasis) versicolor, 258
tinea unguium, 261
tinidazole
for amebiasis, 397
for giardiasis, 391
for trichomoniasis, 401
tinnitus, 227
TINU (tubulointerstitial nephritis and uveitis syndrome), 772
TIPS (transjugular intrahepatic portosystemic shunt), 178, 188, 832
tirofiban
for thrombotic disorders, 283
for UA/NSTEMI, 670
tissue necrosis, 275
tissue plasminogen activator (tPA)
for stroke, 86, 86*t*
for thrombotic disorders, 282–283
for venous thromboembolism, 733
tizanidine, for multiple sclerosis, 1019
TMP-SMX. *See* trimethoprim-sulfamethoxazole

TMS (transcranial magnetic stimulation), for depression, 1065
TNM staging
  for breast cancer, 318–319, 318–319*t*
  for gastric carcinoma, 324*t*
  for lung cancer, 311, 312–313*t*
tobramycin
  for community-acquired pneumonia, 725*t*
  for health care–associated pneumonia, 727*t*
  for *P. aeruginosa* infections, 460–461*t*
  for sepsis/septic shock, 68*t*
tocilizumab, for rheumatoid arthritis, 847
toes, muscles and innervation of, 950*t*
tofacitinib, for rheumatoid arthritis, 847
tolcapone, for Parkinson's disease, 980*t*
tolfenamic acid, for migraine, 217*t*
tolnaftate, for dermatophyte infections, 262
Tolosa-Hunt syndrome, 1002
tolvaptan, for SIADH, 112, 886
tongue paralysis, 1001
tonic-clonic (grand mal) seizures, 956. *See also* seizures
topical antifungal agents, 570
topiramate
  for migraine prevention, 220*t*
  for seizures, 966*t*, 967*t*
torsades de pointes, 682*t*
torsemide
  for edema, 153*t*
  for heart failure, 688, 690*t*
torticollis, 237
tositumomab, for follicular lymphoma, 298
total iron-binding capacity (TIBC), 268, 268*f*, 270*t*
total lung capacity, 705, 705*f*
Tourette syndrome, 238
toxic adenoma, 893
toxic chemicals, 717–718
toxic granulations, 266
toxic shock syndrome (TSS)
  clostridial, 473, 474*t*
  staphylococcal, 428, 429*t*, 430
  streptococcal, 436*t*, 437, 437*t*
Toxocara canis infections, 600
toxoplasmosis, 596–598
  clinical manifestations of, 597
  congenital, 597
  diagnosis of, 597–598
  meningitis in, 1035*t*
  microbiology and epidemiology of, 596–597
  pathogenesis of, 597
  in pregnancy, 597
  prevention of, 598
  treatment of, 598
tPA. *See* tissue plasminogen activator
TR (tricuspid regurgitation), 616*t*, 638–639
tracheobronchitis, 141
trachoma, 408, 514–515
"tram tracks," 729
tramadol
  abuse, 1084
  for osteoarthritis, 862
  for pain, 39*t*
  for polyneuropathy, 1045*t*
trametinib, for melanoma, 307
trandolapril, for heart failure, 690*t*
transaminases, 183, 184*t*
transcatheter aortic valve implantation (TAVI), for aortic stenosis, 636
transcranial magnetic stimulation (TMS), for depression, 1065
transfusion therapy, 46–47
  autologous, 46
  complications of, 46, 47*t*
  plasma components, 47
  platelet, 47
  red blood cell, 46
  whole blood, 46
transient aplastic crisis (TAC), 542
transient ischemic attack (TIA), 82, 85*f*
transient monocular blindness, 230
transjugular intrahepatic portosystemic shunt (TIPS), 178, 188, 832
transplant recipient
  infections in, 366–369, 367*t*, 526–527, 758–759, 759*t*
  transfusion for, 46
  vaccination of, 369–370*t*
transsphenoidal surgery
  for acromegaly, 881
  for pituitary adenomas, 879, 896
transtubular potassium gradient (TTKG), 8, 10*f*, 13, 14*f*
transurethral microwave thermotherapy (TUMT), 342
transurethral resection of prostate (TURP), 342
tranylcypromine, 1073*t*
trastuzumab, for breast cancer, 320, 321

traveler's diarrhea, 389
trazodone
  dosage and side effects of, 1073*t*
  for insomnia, 242
  pharmacology of, 1071
  for PTSD, 1069
trematode infections, 604–606
tremor, 236–238
  coarse, 236
  essential, 236, 237*t*
  intention, 236
  parkinsonian, 236, 237*t*
  postural, 236
trench fever, 467*t*, 468
trench mouth, 475
Treponema pallidum, 409. *See also* syphilis
treponematosis, endemic, 497
treprostinil, for pulmonary hypertension, 702
triamterene
  for edema, 153*t*
  for hypertension, 652*t*
triazolam
  dosage and action of, 1075*t*
  for insomnia, 242
triazoles
  for coccidioidomycosis, 580
  for dermatophyte infections, 262
trichinellosis, 599–600
Trichomonas vaginalis infections, 399, 401
triclabendazole, for liver flukes, 606
tricuspid regurgitation (TR), 616*t*, 638–639
tricuspid stenosis (TS), 616*t*, 638
tricuspid valve endocarditis, 372
tricuspid valve prolapse, 616*t*
tricyclic antidepressants (TCAs), 1071. *See also* antidepressants
  dosage and side effects of, 1072*t*
  for irritable bowel syndrome, 796*t*
  for migraine prevention, 220*t*
  for narcolepsy, 244
  for polyneuropathy, 1044, 1045*t*
trientine, for Wilson's disease, 946
trifluoperazine, 1076*t*
trifluorothymidine, for HSV infections, 521*t*
trigeminal nerve (CN V)
  examination of, 948
  sensory divisions of, 996*f*
trigeminal neuralgia, 221, 995–996
trigeminal neuropathy, 996, 997*t*
trigger points, 995
triglycerides, 936. *See also* hypertriglyceridemia
trihexyphenidyl, for dystonia, 237
triiodothyronine (T_3), 886
trimethoprim, for *Pneumocystis* infections, 584*t*
trimethoprim-sulfamethoxazole (TMP-SMX)
  for ANCA-associated glomerulonephritis, 762
  for animal bite infections, 116*t*
  for *B. cepacia* infections, 461*t*
  for COPD exacerbations, 721
  for *Corynebacterium* infections, 443
  for cyclosporiasis, 392
  for cystoisosporiasis, 392
  for diverticulitis, 796
  for donovanosis, 414
  for extraintestinal *E. coli* infections, 454
  for glanders, 461*t*
  for HSCT patients, 367
  for listerial infections, 447
  for *M. catarrhalis*, 452
  for melioidosis, 461*t*
  for nephrolithiasis, 782*t*
  for nocardiosis, 479
  for osteomyelitis, 421*t*
  for peritonitis prevention, 382
  for pertussis, 451
  for plague, 466
  for *Pneumocystis* infections, 584, 584*t*
  for *Pneumocystis* prophylaxis, 585, 585*t*
  for *Proteus* infections, 457
  for Q fever, 509–510
  for *S. maltophilia* infections, 461*t*
  for salmonellosis, 394
  for snakebite, 117*t*
  for staphylococcal infections, 430, 433*t*
  for toxoplasmosis, 598
  for transplant recipients, 368
  for urinary tract infections, 777, 777*t*
  for Whipple's disease, 482
triolein breath test, 170
triple-H therapy, for subarachnoid hemorrhage with vasospasm, 93
triptans
  for migraine prophylaxis, 216
  for migraine treatment, 217*t*, 219*t*
Tropheryma whipplei, 481–482

trophozoite, 586
troponins, cardiac-specific, 668
Trousseau's sign, 928
trypanosomiasis, 594–596, 1035*t*
TS (tricuspid stenosis), 616*t*, 638
TSH. *See* thyroid-stimulating hormone
TSS. *See* toxic shock syndrome
TST (thermoregulatory sweat test), 990–991
TTKG (transtubular potassium gradient), 8, 10*f*, 13, 14*f*
TTP. *See* thrombotic thrombocytopenic purpura
tuberculin skin test, 489*t*, 490
tuberculosis (TB), 482–490
  vs. brucellosis, 463, 463*t*
  clinical manifestations of, 483–485
  diagnosis of, 485
  epidemiology of, 482–483
  extensively drug-resistant, 482
  extrapulmonary, 483–484
  gastrointestinal disease in, 484
  genitourinary disease in, 484
  HIV infection and, 485
  latent, 489*t*, 490
  meningitis in, 484, 1033*t*
  microbiology of, 482
  miliary disease in, 484
  multidrug-resistant, 482
  nosocomial, 361
  pathogenesis of, 483
  pericarditis in, 484
  pleural involvement in, 484
  prevention of, 490, 490*t*
  pulmonary, 483
  skeletal disease in, 484
  treatment of, 485–486, 487–488*t*, 489–490
tuberoeruptive xanthoma, 941
tuberous xanthoma, 936
tubulointerstitial disease. *See* renal tubular disease
tubulointerstitial nephritis and uveitis syndrome (TINU), 772
tularemia, 115, 464–465
tumor lysis syndrome, 113
tumor (skin lesion), 257*t*
TUMT (transurethral microwave thermotherapy), 342
Turcot's syndrome, 326*t*, 327
Turner's sign, 804
TURP (transurethral resection of prostate), 342
twitching, 951
two-point discrimination, 951
typhlitis, in cancer patients, 364
typhoid fever. *See* enteric fever
typhus
  epidemic (louse-borne), 502*t*, 506–507
  Kenya tick, 504
  murine (flea-borne), 502*t*, 505–506
  scrub, 503*t*, 507
Tzanck preparation, 258

U

UFH. *See* unfractionated heparin
ulcer, 257*t*
  cutaneous, 417
  genital, 403, 404*t*
  skin lesion, 257*t*
ulcerative colitis (UC), 791. *See also* inflammatory bowel disease
ulnar nerve entrapment, 1046, 1047*t*
ultrasonography (US)
  diagnostic, 25
  endoscopic, 322, 800*t*
  hepatobiliary, 185, 800*t*
  in pancreatitis, 804
  renal, 752
  in stroke, 88
  venous, 731
undecylenic acid, for dermatophyte infections, 262
underweight, 901*t*
unfractionated heparin (UFH)
  for STEMI, 662
  for thrombotic disorders, 281–282
  for UA/NSTEMI, 670
  for venous thromboembolism, 732–733
unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI)
  clinical manifestations of, 668
  diagnosis of, 668, 669*f*
  ECG in, 620, 621*t*, 668
  TIMI Risk Score for, 670*f*
  treatment of, 668, 669*f*, 670–671, 671*f*
upper respiratory infections (URIs), 247–254. *See also* respiratory tract infections
  ear infections. *See* ear infections
  epiglottitis, 254
  laryngitis, 253–254
  nonspecific, 247
  pharyngitis, 251–253
  sinusitis, 247–249
urate nephropathy, 864

urea breath test, 786, 786*t*
Ureaplasma infections, 399, 408–409
ureidopenicillin, for cholecystitis, 801
uremia, 199
uremic syndrome, 753. *See also* chronic kidney disease
ureteral obstruction, 784
ureterosigmoidostomy, 18*t*
urethral syndrome, 400
urethritis
  in men, 399–400
  in women, 400
uric acid nephrolithiasis, 864
uric acid stones, 780, 782*t*, 864
uricosuric drugs, for gout, 865
urinalysis, 777
urinary incontinence, in terminally ill patient, 55*t*
urinary retention, 342
urinary tract infections (UTI), 775–778
  in cancer patients, 364
  catheter-associated, 778
  clinical manifestations of, 776–777
  definition of, 775–776
  diagnosis of, 777
  epidemiology of, 776
  microbiology of, 776
    Corynebacterium, 443
    E. coli, 454
    Klebsiella, 456
    P. aeruginosa, 459, 461*t*
    Proteus, 456–457
    S. aureus, 428
  nosocomial, 358, 359*t*
  pathogenesis of, 776
  recurrent, prevention of, 778
  treatment of, 777–778, 777*t*
urinary tract obstruction (UTO), 782–784, 783*f*
urine abnormalities
  asymptomatic, 766–767, 767*t*
  of composition, 199–203
  of volume, 199
URIs. *See* upper respiratory infections
urokinase, for thrombotic disorders, 282
ursodeoxycholic acid
  for gallstones, 800
  for primary biliary cirrhosis, 829
  for primary sclerosing cholangitis, 803
urticaria
  classification of, 836, 836*t*
  clinical manifestations of, 264
  diagnosis of, 836–837
  pathogenesis of, 264
  treatment of, 837
US. *See* ultrasonography
ustekinumab, for psoriasis, 259
ustekinumab, for psoriatic arthritis, 859
UTI. *See* urinary tract infections
UTO (urinary tract obstruction), 782–784, 783*f*

V

vaccination. *See* immunization
vaccine-associated poliomyelitis, 544
vagotomy, for peptic ulcer disease, 788*t*
vagus nerve (CN X)
  disorders of, 1000
  examination of, 948
  stimulation of, 1065
valacyclovir
  for Bell's palsy, 997
  for genital HSV infections, 412, 415*t*
  for herpes zoster infections, 415*t*
  for HSCT patients, 367
  for HSV infections, 519, 520–522*t*
  for transplant recipients, 368
  for viral esophagitis, 165
  for viral meningitis, 1027
  for VZV infections, 524
valdecoxib, for pain, 38*t*
valganciclovir
  for cytomegalovirus infections, 527
  for viral esophagitis, 165
valproate/valproic acid
  for bipolar disorder, 1066
  dosage and side effects of, 1078*t*
  for migraine prevention, 220*t*
  for myoclonus, 238
  for posthypoxic myoclonus, 101
  for seizures, 966*t*, 967*t*
  for status epilepticus, 102*f*
Valsalva maneuver, 617*t*, 990
Valsalva ratio, 990
valsartan
  for heart failure, 690*t*
  for hypertension, 653*t*
  for STEMI, 662
valvotomy, for mitral stenosis, 632
valvular heart disease, 632–639
  aortic regurgitation, 637–638
  aortic stenosis. *See* aortic stenosis
  echocardiography in, 623, 624*f*, 626*t*
  mitral regurgitation. *See* mitral regurgitation

valvular heart disease (*Cont.*):
mitral stenosis. *See* mitral stenosis
mitral valve prolapse, 634, 636
murmurs in, 616*t*
tricuspid regurgitation, 638–639
tricuspid stenosis, 638
valvuloplasty, for mitral stenosis, 632
vancomycin
for anaerobic infections, 476*t*
for bacterial meningitis, 1024*t*, 1025*t*
for brain abscess, 1030
for *C. difficile* infections, 398
for clostridial infections, 474*t*
for *Corynebacterium* infections, 443
for health care–associated pneumonia, 727*t*
for infectious arthritis, 420
for infective endocarditis, 376–378*t*, 379
for MRSA infections, 416*t*
for necrotizing fasciitis, 416*t*
for osteomyelitis, 421*t*
for peritonitis, 383
for pneumococcal infections, 424
for pyomyositis, 418
for sepsis/septic shock, 68*t*
for staphylococcal infections, 430, 431–432*t*
for streptococcal infections, 439
vancomycin-resistant enterococci (VRE), 440
VAP. *See* ventilator-associated pneumonia
vardenafil, for erectile dysfunction, 916
varenicline, for smoking cessation, 720, 1103
varicella-zoster immune globulin, 524
varicella-zoster vaccine, 371*t*, 524, 1090*t*
varicella-zoster virus (VZV) infections, 519
chickenpox, 523
herpes zoster, 523–524
nosocomial, 361
prevention of, 524
varicocele, 915
vascular dementia, 970*t*, 971, 974, 975*f*
vascular disease
abdominal pain in, 155*t*
gastrointestinal, 797–798
headache in, 215*t*
malabsorption in, 173*t*
peripheral. *See* peripheral vascular disease
skin diseases, 263–264
vascular malformation, myelopathy in, 1006, 1007*f*
vascular shunting, anatomic, 145
vasculitis, 264
approach to, 852, 852*f*
conditions that mimic, 853*t*
cutaneous, 264
definition and pathogenesis of, 851
differential diagnosis of, 853
neuropathy in, 1046
primary syndromes, 851
secondary syndromes, 852
treatment of, 264, 853–854
urticarial, 264
vasoconstrictors, for allergic rhinitis, 838
vasodilators
for acute renal failure, 751
for aortic regurgitation, 638
for heart failure, 663–664, 664*t*, 690–691, 691*t*
for pulmonary hypertension, 702
for STEMI, 662
for STEMI complications, 667
vasopressin
for asystole, 60*f*
deficiency of, 883*t*
intraarterial, for gastrointestinal bleeding, 178
for shock, 64, 64*t*
for ventricular fibrillation, 59*f*
vasopressin antagonists, for hyponatremia, 4
vasospasm, in subarachnoid hemorrhage, 92–93
vasospastic disorders, 697–698
VATS (thoracic surgery, video-assisted), 711, 737
vemurafenib, for melanoma, 307
venlafaxine, 1071
dosage and side effects of, 39*t*, 1072*t*
for menopausal symptoms, 922
for migraine prevention, 220*t*
for narcolepsy, 245
for pain, 39*t*
for polyneuropathy, 1045*t*
venous disease, 698–699
venous insufficiency, chronic, 699
venous thromboembolism, 730. *See also* deep-vein thrombosis; pulmonary embolism
ventilation, disorders of, 744–745
ventilation/perfusion lung scan, 731

ventilation/perfusion mismatch, 708
ventilator-associated pneumonia (VAP)
diagnosis of, 358, 726
etiology of, 358, 726
P. aeruginosa, 458–459
pathophysiology of, 76, 726, 728*t*
prevention of, 359*t*, 728*t*
risk factors for, 358
treatment of, 726–727, 727*t*
ventilatory support
in ALS, 988
in ARDS, 72, 72*f*
for asthma exacerbations, 715
complications of, 76
during COPD exacerbations, 722
for cor pulmonale, 693
for hemoptysis, 149
modes of, 74, 75*t*
patient care, 32–34, 76
in respiratory failure, 73–76, 75*t*
weaning from, 33–34
ventricular aneurysm
pseudoaneurysm, 667
in STEMI, 667
ventricular fibrillation (VF)
clinical and ECG features of, 682*t*
management of, 59*f*
in STEMI, 662–663
ventricular premature beats, 681*t*
ventricular septal defect (VSD), 616*t*, 628–629
ventricular septal rupture, 667
ventricular tachycardia (VT)
clinical and ECG features of, 681*t*
vs. supraventricular tachycardia, 685*f*
pulseless, 59*f*
in STEMI, 662
verapamil
for aortic dissection, 695
for arrhythmias, 684*t*
for atrial fibrillation, 686
for chronic stable angina, 674
for cluster headache prevention, 219
for hypertension, 651, 653*t*
for hypertrophic cardiomyopathy, 643
for mitral stenosis, 632
for supraventricular arrhythmias, 663
for tachyarrhythmias, 680–681*t*
for UA/NSTEMI, 670
for Wolff-Parkinson-White syndrome, 686
verruca plana, 256*f*
verruca vulgaris, 256*f*
verrucous carcinoma, 308
verruga peruana, 467*t*, 469
vertebral disk herniation
acute, 1005
cervical disk, 212, 214
lumbar disk, 209
vertebral fracture, 210
vertebral metastasis, 210
vertigo, 226
benign positional, 227
central, 227*t*, 228
pathologic, 227
peripheral, 227, 227*t*
physiologic, 227
provocative tests to reproduce, 226
psychogenic, 227
treatment of, 228*t*, 229
vesicle (skin lesion), 257*t*, 416
vestibular function tests, 227
vestibular neuritis, 227, 228*t*, 229
vestibular schwannomas, 227
VF. *See* ventricular fibrillation
Vibrio cholerae infections, 387, 389
Vibrio parahaemolyticus infections, 389
vidarabine, for HSV infections, 521*t*
videonystagmography, 226
vilazodone, 1073*t*
vildagliptin, for diabetes mellitus, 908*t*
vinblastine
for bladder cancer, 334
for lung cancer, 313
Vincent's stomatitis, 475
vincristine
for ALL, 300
for Burkitt's lymphoma/leukemia, 301
for gastric carcinoma, 324
for idiopathic thrombocytopenic purpura, 280
for lymphoma, 299
for multiple myeloma, 302
vindesine, for lung cancer, 313
vinorelbine
for breast cancer, 321
for lung cancer, 313
VIPoma, 332*t*, 333
viral gastroenteritis, 389–390
viral hemorrhagic fever (VHF) syndrome, 551
viral infections
animal-borne, 546–548
arthropod- and rodent-borne, 548–552

viral infections (*Cont.*):
chronic meningitis in, 1037*t*
in HSCT patients, 367–368
lymphadenopathy and, 190*t*
respiratory. *See* respiratory tract infections
viridans streptococci, 439
virilization, 920
visceral abscess, 385
visceral larva migrans, 600
visceral leishmaniasis (kala-azar), 593–594
visceral pain, 36, 36*t*
visceral spasm, 155*t*
vismodegib, for basal cell carcinoma, 307
visual acuity, 229
visual field mapping, 229, 230*f*
visual loss
acute, approach to, 229
transient or sudden, 230–231
vitamin A deficiency, 45*t*
vitamin A supplementation
for head and neck cancer prevention, 1101
for measles, 539
vitamin B_{12} deficiency
anemia in, 269
in dementia, 971
leukopenia in, 276
in myelopathy, 1006
in polyneuropathy, 1044
in tapeworm infection, 610
treatment of, 273
vitamin C deficiency, 45*t*
vitamin C supplementation, for nephrolithiasis, 782*t*
vitamin D deficiency, 45*t*, 928, 935, 1105
vitamin D supplementation
for hypocalcemia, 929
in multiple sclerosis, 1018
for osteomalacia, 935
for osteoporosis, 934
for primary biliary cirrhosis, 829
for primary sclerosing cholangitis, 803
for psoriasis, 259
vitamin E deficiency, 45*t*, 983
vitamin E supplementation, for menopausal symptoms, 922
vitamin K deficiency
pathophysiology of, 279
treatment of, 45*t*, 281
vitamin K supplementation
for vitamin K deficiency, 281
for warfarin reversal, 282
vitamins. *See also specific vitamins*
for alcohol withdrawal, 1083
for alcoholic liver disease, 828
for ataxia, 984
vitiligo, 256*f*
vitreous detachment, 231
vitreous hemorrhage, 231
voglibose, for diabetes mellitus, 908*t*
Vogt-Koyanagi-Harada syndrome, 1038*t*
volume regulation, 1*t*
volume status, assessment of, 3*f*
vomiting. *See* nausea and vomiting
von Hippel-Lindau disease, 335
von Willebrand disease, 279, 281
voriconazole, 569
for aspergillosis, 574*t*
for candidiasis, 571
for fusariosis, 582
for scedosporiosis, 582
for sepsis/septic shock, 68*t*
vortioxetine, 1073*t*
VRE (vancomycin-resistant enterococci), 440
VSD (ventricular septal defect), 616*t*, 628–629
VT. *See* ventricular tachycardia
VZV infections. *See* varicella-zoster virus infections

W
Waldenström's macroglobulinemia, 768*t*
warfarin
for antiphospholipid antibody syndrome, 850
for atrial fibrillation, 686
for mitral stenosis, 632
for pulmonary hypertension, 702
for STEMI, 662
for venous thromboembolism, 733
warts
cutaneous, 262
genital, 413–414
wasp sting, 124–125
water requirements, 41
watery diarrhea, 386*t*
weakness, 131, 233–235
approach to, 233, 235*f*
causes of, 233*t*
diagnostic evaluation of, 1055*f*, 1056*f*
site of responsible lesion, 233, 233*t*

weaning, from mechanical ventilation, 33–34
Wegener's granulomatosis (granulomatosis with polyangiitis), 768*t*, 851, 1039*t*
weight, ideal, 42*t*
weight loss, 135–137
  clinical manifestations of, 135–137
  drug-induced, 136*t*
  etiology of, 135, 136*t*
  for hypertension, 651
  laboratory testing in, 137*t*
  in malnutrition, 41
  for metabolic syndrome, 658
  for obesity, 902–903
  for sleep apnea, 746
  treatment for, 137
Weil's syndrome, 498
Wenckebach AV block, 677, 679*f*
Wernicke-Korsakoff's syndrome, 1083
Wernicke's aphasia, 239*t*, 240–241
Wernicke's encephalopathy, 1082–1083
West Nile virus (WNV) encephalitis, 550, 1027, 1029
WFNS (World Federation of Neurosurgical Societies) Scale, for subarachnoid hemorrhage, 92*t*
wheal, 257*t*
whiplash injury, 212
Whipple's disease, 481–482, 867, 1034*t*
Whipple's triad, 107, 108*f*, 332
whitlow, herpetic, 518, 522*t*
WHO classification
  of AML, 284*t*
  of lymphoid malignancy, 294
whole blood transfusion, 46
whooping cough. *See* pertussis
widow spider bite, 123–124
Wilson's disease, 945–946
winking owl sign, 110
Winterbottom's sign, 596
Winter's formula, 15
withdrawal of care, 35
withdrawal syndrome, 1074
WNV (West Nile virus) encephalitis, 550, 1027, 1029
Wolbachia, 604
Wolff-Parkinson-White (WPW) syndrome, 621*t*, 679, 686
women's health, 1104–1106
  Alzheimer's disease, 1104
  autoimmune disease, 1105
  coronary heart disease, 1104–1105
  diabetes mellitus, 1105
  HIV infections, 1105
  hypertension, 1105
  nicotine addiction, 1106
  obesity, 1105
  osteoporosis, 1105
  pharmacology, 1105–1106
  psychiatric disease, 1106
  sleep disorders, 1106
  substance abuse, 1106
  violence, 1106
Wood's light examination, 258
World Federation of Neurosurgical Societies (WFNS) Scale, for subarachnoid hemorrhage, 92*t*
wound infections
  botulism, 472
  clostridial, 473
  surgical-site, 358, 359*t*
wrist, muscles and innervation of, 949*t*
Wuchereria bancrofti infections. *See* filariasis

X

xanthelasma, 256*f*, 936
xanthoma, 936, 940
XDR (extensively drug-resistant) tuberculosis, 482
xerostomia, 849
D-xylose absorption test, 170

Y

yaws, 497
yellow fever, 552
yellow jacket sting, 124–125
Yersinia pestis, 465–466
yersiniosis, 396

Z

zafirlukast, for urticaria/angioedema, 837
zaleplon, for insomnia, 242
zanamivir, for influenza, 532, 532*t*
zidovudine (AZT, azidothymidine)
  for adult T cell leukemia/lymphoma, 301
  for HIV infection, 560*t*
Zieve's syndrome, 826
zinc deficiency, 45*t*

zinc supplementation
for hepatic encephalopathy, 833
for Wilson's disease, 946
ziprasidone
dosage and side effects of, 1077*t*
for schizophrenia, 1067
zoledronate
for hypercalcemia, 112, 351, 927*t*
for osteoporosis, 934
Zollinger-Ellison syndrome
clinical manifestations of, 332, 332*t*, 789
diagnosis of, 789
differential diagnosis of, 789, 789*t*
treatment of, 789–790
zolmitriptan, for migraine, 217*t*, 219*t*
zolpidem, for insomnia, 242
zonisamide, for seizures, 966*t*, 967*t*
zoster ophthalmicus, 523

This page intentionally left blank

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS

I. MULTISYSTEM MANIFESTATIONS

Anaphylaxis
- Cephalosporins
- Dextran
- Insulin
- Iodinated drugs or contrast media
- Lidocaine
- Penicillins
- Procaine

Angioedema
- ACE inhibitors

Drug-induced lupus erythematosus
- Cephalosporins
- Hydralazine
- Iodides
- Isoniazid
- Methyldopa
- Phenytoin
- Procainamide
- Quinidine
- Sulfonamides
- Thiouracil

Fever
- Aminosalicylic acid
- Amphotericin B
- Antihistamines
- Penicillins

Hyperpyrexia
- Antipsychotics

Serum sickness
- Aspirin
- Penicillins
- Propylthiouracil
- Sulfonamides

II. ENDOCRINE MANIFESTATIONS

Addisonian-like syndrome
- Busulfan
- Ketoconazole

Galactorrhea (may also cause amenorrhea)
- Methyldopa
- Phenothiazines
- Tricyclic antidepressants

Gynecomastia
- Calcium channel antagonists
- Digitalis
- Estrogens
- Griseofulvin
- Isoniazid
- Methyldopa
- Phenytoin
- Spironolactone
- Testosterone

Sexual dysfunction
- Beta blockers
- Clonidine
- Diuretics
- Guanethidine
- Lithium
- Major tranquilizers
- Methyldopa
- Oral contraceptives
- Sedatives

Thyroid function tests, disorders of
- Acetazolamide
- Amiodarone
- Chlorpropamide
- Clofibrate
- Colestipol and nicotinic acid
- Gold salts
- Iodides
- Lithium
- Oral contraceptives
- Phenothiazines
- Phenylbutazone
- Phenytoin
- Sulfonamides
- Tolbutamide

III. METABOLIC MANIFESTATIONS

Hyperbilirubinemia
- Rifampin

Hypercalcemia
- Antacids with absorbable alkali
- Thiazides
- Vitamin D

Hyperglycemia
- Chlorthalidone
- Diazoxide
- Encainide
- Ethacrynic acid
- Furosemide

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

Glucocorticoids
Growth hormone
Oral contraceptives
Thiazides

Hypoglycemia
Insulin
Oral hypoglycemics
Quinine

Hyperkalemia
ACE inhibitors
Amiloride
Cytotoxics
Digitalis overdose
Heparin
Lithium
Potassium preparations including salt substitute
Potassium salts of drugs
Spironolactone
Succinylcholine
Triamterene

Hypokalemia
Alkali-induced alkalosis
Amphotericin B
Diuretics
Gentamicin
Insulin
Laxative abuse
Mineralocorticoids, some glucocorticoids
Osmotic diuretics
Sympathomimetics
Tetracycline
Theophylline
Vitamin B12

Hyperuricemia
Aspirin
Cytotoxics
Ethacrynic acid
Furosemide
Hyperalimentation
Thiazides

Hyponatremia
1. Dilutional
Carbamazepine
Chlorpropamide
Cyclophosphamide
Diuretics
Vincristine
2. Salt wasting
Diuretics
Enemas
Mannitol

Metabolic acidosis
Acetazolamide
Paraldehyde
Salicylates
Spironolactone

IV. DERMATOLOGIC MANIFESTATIONS

Acne
Anabolic and androgenic steroids
Bromides
Glucocorticoids
Iodides
Isoniazid
Oral contraceptives

Alopecia
Cytotoxics
Ethionamide
Heparin
Oral contraceptives (withdrawal)

Eczema
Captopril
Cream and lotion perservatives
Lanolin
Topical antihistamines
Topical antimicrobials
Topical local anesthetics

Erythema multiforme or Steven Johnson syndrome
Barbiturates
Chlorpropamide
Codeine
Penicillins
Phenylbutazone
Phenytoin
Salicylates
Sulfonamides
Sulfones

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

- Tetracyclines
- Thiazides

Erythema nodosum
- Oral contraceptives
- Penicillins
- Sulfonamides

Exfoliative dermatitis
- Barbiturates
- Gold salts
- Penicillins
- Phenylbutazone
- Phenytoin
- Quinidine
- Sulfonamides

Fixed drug eruptions
- Barbiturates
- Captopril
- Phenylbutazone
- Quinine
- Salicylates
- Sulfonamides

Hyperpigmentation
- Bleomycin
- Busulfan
- Chloroquine and other antimalarials
- Corticotropin
- Cyclophosphamide
- Gold salts
- Hypervitaminosis A
- Oral contraceptives
- Phenothiazines

Lichenoid eruptions
- Aminosalicylic acid
- Antimalarials
- Chlorpropamide
- Gold salts
- Methyldopa
- Phenothiazines

Photodermatitis
- Captopril
- Chlordiazepoxide
- Furosemide
- Griseofulvin
- Nalidixic acid
- Oral contraceptives
- Phenothiazines
- Sulfonamides
- Sulfonylureas
- Tetracyclines, particularly demeclocycline
- Thiazides

Purpura (see also thrombocytopenia)
- Allopurinol
- Ampicillin
- Aspirin
- Glucocorticoids

Rashes (nonspecific)
- Allopurinol
- Ampicillin
- Barbiturates
- Indapamide
- Methyldopa
- Phenytoin

Skin necrosis
- Warfarin

Toxic epidermal necrolysis (bullous)
- Allopurinol
- Barbiturates
- Bromides
- Iodides
- Nalidixic acid
- Penicillins
- Phenylbutazone
- Phenytoin
- Sulfonamides

Urticaria
- Aspirin
- Barbiturates
- Captopril
- Enalapril
- Penicillins
- Sulfonamides

V. HEMATOLOGIC MANIFESTATIONS

Agranulocytosis (see also Pancytopenia)
- Captopril
- Carbimazole
- Chloramphenicol
- Cytotoxics
- Gold salts
- Indomethacin
- Methimazole
- Oxyphenbutazone

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

Phenothiazines
Phenylbutazone
Propylthiouracil
Sulfonamides
Tolbutamide
Tricyclic antidepressants

Clotting abnormalities/ hypothrombinemia
Cefamandole
Cefoperazone
Moxalactam

Eosinophilia
Aminosalicylic acid
Chlorpropamide
Erythromycin estolate
Imipramine
L-Tryptophan
Methotrexate
Nitrofurantoin
Procarbazine
Sulfonamides

Hemolytic anemia
Aminosalicylic acid
Cephalosporins
Chlorpromazine
Dapsone
Insulin
Isoniazid
Levodopa
Mefenamic acid
Melphalan
Methyldopa
Penicillins
Phenacetin
Procainamide
Quinidine
Rifampin
Sulfonamides

Hemolytic anemias in G6PD deficiency
See Table 62-4

Leukocytosis
Glucocorticoids
Lithium

Lymphadenopathy
Phenytoin
Primidone

Megaloblastic anemia
Folate antagonists
Nitrous oxide
Oral contraceptives
Phenobarbital
Phenytoin
Primidone
Triamterene
Trimethroprim

Pancytopenia (aplastic anemia)
Carbamazepine
Chloramphenicol
Cytotoxics
Gold salts
Mephenytoin
Phenylbutazone
Phenytoin
Quinacrine
Sulfonamides
Trimethadione
Zidovudine (AZT)

Pure red cell aplasia
Azathioprine
Chlorpropamide
Isoniazid
Phenytoin

Thrombocytopenia (see also Pancytopenia)
Acetazolamine
Aspirin
Carbamazepine
Carbenicillin
Chlorpropamide
Chlorthalidone
Furosemide
Gold salts
Heparin
Indomethacin
Isoniazid
Methyldopa
Moxalactam
Phenylbutazone
Phenytoin and other hydantoins
Quinidine
Quinine
Thiazides
Ticarcillin

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

VI. CARDIOVASCULAR MANIFESTATIONS

Angina exacerbation
- Alpha blockers
- Beta blocker withdrawal
- Ergotamine
- Excessive thyroxine
- Hydralazine
- Methysergide
- Minoxidil
- Nifedipine
- Oxytocin
- Vasopressin

Arrhythmias
- Adriamycin
- Antiarrhythmic drugs
- Atropine
- Anticholinesterases
- Beta blockers
- Digitalis
- Emetine
- Lithium
- Phenothiazines
- Sympathomimetics
- Thyroid hormone
- Tricyclic antidepressants
- Verapamil

AV block
- Clonidine
- Methyldopa
- Verapamil

Cardiomyopathy
- Adriamycin
- Daunorubicin
- Emetine
- Lithium
- Phenothiazines
- Sulfonamides
- Sympathomimetics

Fluid retention or congestive heart failure
- Beta blockers
- Calcium antagonists
- Estrogens
- Indomethacin
- Mannitol
- Minoxidil
- Phenylbutazone
- Steroids

Hypertension
- Clonidine withdrawal
- Corticotropin
- Cyclosporine
- Glucocorticoids
- Monoamine oxidase inhibitors with sympathomimetics
- NSAIDs
- Oral contraceptives
- Sympathomimetics
- Tricyclic antidepressants with sympathomimetics

Hypotension
- Calcium antagonists
- Citrated blood
- Diuretics
- Levodopa
- Morphine
- Nitroglycerin
- Phenothiazines
- Protamine
- Quinidine

Pericarditis
- Emetine
- Hydralazine
- Methysergide
- Procainamide

Thromboembolism
- Oral contraceptives

VII. RESPIRATORY MANIFESTATIONS

Airway obstruction
- Beta blockers
- Cephalosporins
- Cholinergic drugs
- NSAIDs
- Penicillins
- Pentazocine
- Streptomycin
- Tartrazine (drugs with yellow dye)

Cough
- ACE inhibitors

Pulmonary edema
- Contrast media
- Heroin

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

- Methadone
- Propoxyphene

Pulmonary infiltrates

- Acyclovir
- Amiodarone
- Azathioprine
- Bleomycin
- Busulfan
- Carmustine (BCNU)
- Chlorambucil
- Cyclophosphamide
- Melphalan
- Methotrexate
- Methysergide
- Mitomycin C
- Nitrofurantoin
- Procarbazine
- Sulfonamides

VIII. GASTROINTESTINAL MANIFESTATIONS

Cholestatic jaundice

- Anabolic steroids
- Androgens
- Chlorpropamide
- Erythromycin estolate
- Gold salts
- Methimazole
- Nitrofurantoin
- Oral contraceptives
- Phenothiazines

Constipation or ileus

- Aluminum hydroxide
- Barium sulfate
- Calcium carbonate
- Ferrous sulfate
- Ion exchange resins
- Opiates
- Phenothiazines
- Tricyclic antidepressants
- Verapamil

Diarrhea or colitis

- Antibiotics (broad-spectrum)
- Colchicine
- Digitalis
- Magnesium in antacids
- Methyldopa

Diffuse hepatocellular damage

- Acetaminophen (paracetamol)
- Allopurinol
- Aminosalicylic acid
- Dapsone
- Erythromycin estolate
- Ethionamide
- Glyburide
- Halothane
- Isoniazid
- Ketoconazole
- Methimazole
- Methotrexate
- Methoxyflurane
- Methyldopa
- Monoamine oxidase inhibitors
- Niacin
- Nifedipine
- Nitrofurantoin
- Phenytoin
- Propoxyphene
- Propylthiouracil
- Pyridium
- Rifampin
- Salicylates
- Sodium valproate
- Sulfonamides
- Tetracyclines
- Verapamil
- Zidovudine (AZT)

Intestinal ulceration

- Solid KCl preparations

Malabsorption

- Aminosalicylic acid
- Antibiotics (broad-spectrum)
- Cholestyramine
- Colchicine
- Colestipol
- Cytotoxics
- Neomycin
- Phenobarbital
- Phenytoin

Nausea or vomiting

- Digitalis
- Estrogens
- Ferrous sulfate
- Levodopa
- Opiates

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

Potassium chloride
Tetracyclines
Theophylline

Oral conditions

1. Gingival hyperplasia
Calcium antagonists
Cyclosporine
Phenytoin

2. Salivary gland swelling
Bretylium
Clonidine
Guanethidine
Iodides
Phenylbutazone

3. Taste Disturbances
Biguanides
Captopril
Griseofulvin
Lithium
Metronidazole
Penicillamine
Rifampin

4. Ulceration
Aspirin
Cytotoxics
Gentian violet
Isoproterenol (sublingual)
Pancreatin

Pancreatitis
Azathioprine
Ethacrynic acid
Furosemide
Glucocorticoids
Opiates
Oral contraceptives
Sulfonamides
Thiazides

Peptic ulceration or hemorrhage
Aspirin
Ethacrynic acid
Glucocorticoids
NSAIDs

IX. RENAL/URINARY MANIFESTATIONS

Bladder dysfunction
Anticholinergics
Disopyramide
Monoamine oxidase inhibitors
Tricyclic antidepressants

Calculi
Acetazolamide
Vitamin D

Concentrating defect with polyuria (or nephrogenic diabetes insipidus)
Demeclocycline
Lithium
Methoxyflurane
Vitamin D

Hemorrhagic cystitis
Cyclophosphamide

Interstitial nephritis
Allopurinol
Furosemide
Penicillins, esp. methicillin
Phenindione
Sulfonamides
Thiazides

Nephropathies
Due to analgesics (e.g., phenacetin)

Nephrotic syndrome
Captopril
Gold salts
Penicillamine
Phenindione
Probenecid

Obstructive uropathy
Extrarenal: methysergide
Intrarenal: cytotoxics

Renal dysfunction
Cyclosporine
NSAIDS
Triamterene

Renal tubular acidosis
Acetazolamide
Amphotericin B
Degraded tetracycline

Tubular necrosis
Aminoglycosides
Amphotericin B
Colistin

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

- Cyclosporine
- Methoxyflurane
- Polymyxins
- Radioiodinated contrast medium
- Sulfonamides
- Tetracyclines

X. NEUROLOGIC MANIFESTATIONS

Exacerbation of myasthenia
- Aminoglycosides
- Polymyxins

Extrapyramidal effects
- Butyrophenones, e.g., haloperidol
- Levodopa
- Methyldopa
- Metoclopramide
- Oral contraceptives
- Phenothiazines
- Tricyclic antidepressants

Headache
- Ergotamine (withdrawal)
- Glyceryl trinitrate
- Hydralazine
- Indomethacin

Peripheral neuropathy
- Amiodarone
- Chloramphenicol
- Chloroquine
- Chlorpropamide
- Clofibrate
- Demeclocycline
- Disopyramide
- Ethambutol
- Ethionamide
- Glutethimide
- Hydralazine
- Isoniazid
- Methysergide
- Metronidazole
- Nalidixic acid
- Nitrofurantoin
- Phenytoin
- Polymyxin, colistin
- Procarbazine
- Streptomycin
- Tolbutamide
- Tricyclic antidepressants
- Vincristine

Pseudotumor cerebri (or intracranial hypertension)
- Amiodarone
- Glucocorticoids, mineralocorticoids
- Hypervitaminosis A
- Oral contraceptives
- Tetracyclines

Seizures
- Amphetamines
- Analeptics
- Isoniazid
- Lidocaine
- Lithium
- Nalidixic acid
- Penicillins
- Phenothiazines
- Physostigmine
- Theophylline
- Tricyclic antidepressants
- Vincristine

Stroke
- Oral contraceptives

XI. OCULAR MANIFESTATIONS

Cataracts
- Busulfan
- Chlorambucil
- Glucocorticoids
- Phenothiazines

Color vision alteration
- Barbiturates
- Digitalis
- Methaqualone
- Streptomycin
- Thiazides

Corneal edema
- Oral contraceptives

Corneal opacities
- Chloroquine
- Indomethacin
- Vitamin D

Glaucoma
- Mydriatics
- Sympathomimetics

Optic neuritis
- Aminosalicylic acid

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

- Chloramphenicol
- Ethambutol
- Isoniazid
- Penicillamine
- Phenothiazines
- Phenylbutazone
- Quinine
- Streptomycin

Retinopathy

- Chloroquine
- Phenothiazines

XII. EAR MANIFESTATIONS

Deafness

- Aminoglycosides
- Aspirin
- Bleomycin
- Chloroquine
- Erythromycin
- Ethacrynic acid
- Furosemide
- Nortriptyline
- Quinine

Vestibular disorders

- Aminoglycosides
- Quinine

XIII. Musculoskeletal manifestations

Bone disorders

1. Osteoporosis

- Glucocorticoids
- Heparin

2. Osteomalacia

- Aluminum hydroxide
- Anticonvulsants
- Glutethimide

Myopathy or myalgia

- Amphotericin B
- Chloroquine
- Clofibrate
- Glucocorticoids
- Oral contraceptives

Myositis

- Gemfibrozil
- Lovastatin

XIV. PSYCHIATRIC MANIFESTATIONS

Delirious or confusional states

- Amantadine
- Aminophylline
- Anticholinergics
- Antidepressants
- Cimetidine
- Digitalis
- Glucocorticoids
- Isoniazid
- Levodopa
- Methyldopa
- Penicillins
- Phenothiazines
- Sedatives and hypnotics

Depression

- Amphetamine withdrawal
- Beta blockers
- Centrally acting antihypertensives (reserpine, methyldopa, clonidine)
- Glucocorticoids
- Levodopa

Drowsiness

- Antihistamines
- Anxiolytic drugs
- Clonidine
- Major tranquilizers
- Methyldopa
- Tricyclic antidepressants

Hallucinatory states

- Amantadine
- Beta blockers
- Levodopa
- Meperidine
- Narcotics
- Pentazocine
- Tricyclic antidepressants

Hypomania, mania, or excited reactions

- Glucocorticoids
- Levodopa
- Monoamine oxidase inhibitors
- Sympathomimetics
- Tricyclic antidepressants

(*Continued*)

TABLE 206-1 CLINICAL MANIFESTATIONS OF ADVERSE REACTIONS TO DRUGS (*CONTINUED*)

Schizophrenic-like or paranoid reactions
- Amphetamines
- Bromides
- Glucocorticoids
- Levodopa
- Lysergic acid
- Monoamine oxidase inhibitors
- Tricyclic antidepressants

Sleep disturbances
- Anorexiants
- Levodopa
- Monoamine oxidase inhibitors
- Sympathomimetics

Source: Adapted from AJJ Wood: *HPIM-15*, pp. 432-436. For a more detailed discussion, see Roden DM: *Principles of Clinical Pharmacology,* Chap 5, p. 33, *HPIM-18*; Wood AJJ: Adverse Reactions to Drugs, Chap 71, p. 430, in *HPIM-15*.

GLOSSARY

JVP	jugular venous pressure
LA	left atrium
LAD	left axis deviation
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LLQ	left lower quadrant
LP	lumbar puncture
LUQ	left upper quadrant
LV	left ventricle
MI	myocardial infarction
MRI	magnetic resonance imaging
NPO	nothing by mouth
NSAIDs	nonsteroidal anti-inflammatory drugs
P_2	pulmonic second sound
Pao_2	partial pressure of O_2 in arterial blood
PAo_2	partial pressure of O_2 in alveolar blood
PCR	polymerase chain reaction
PFTs	pulmonary function tests
PMNs	polymorphonuclear cells or leukocytes
PO	by mouth
PPD	purified protein derivative, skin test for tuberculosis
prn	as needed
pt/pts	patient/patients
PT	prothrombin time
PTT	partial thromboplastin time
qAM	every morning
qd	every day
qh	every hour
qhs	every bedtime
qid	four times daily
qod	every other day
R	respiratory rate
RA	rheumatoid arthritis
RBBB	right bundle branch block
RBC	red blood (cell) count
RLQ	right lower quadrant
RUQ	right upper quadrant
RV	right ventricle
S1 . . . S4	heart sounds, 1st to 4th
SARS	severe acute respiratory syndrome
SC	subcutaneous
SL	sublingual
SLE	systemic lupus erythematosus
SVC	superior vena cava
TIA	transient ischemic attack
tid	three times daily
tiw	thrice a week
TLC	total lung capacity
TNF	tumor necrosis factor
UA	urinalysis
URI	upper respiratory infection
UTI	urinary tract infection
UV	ultraviolet
VDRL	test for syphilis
VPC	ventricular premature contractions
VZV	varicella-zoster virus
WBC	white blood (cell) count

POCKET NOTEBOOK

POCKET MEDICINE

SEVENTH EDITION

Marc S. Sabatine



The Massachusetts General Hospital Handbook of Internal Medicine



Wolters Kluwer

POCKET NOTEBOOK

Pocket MEDICINE

Seventh Edition

Edited by

MARC S. SABATINE, MD, MPH

Professor of Medicine

Harvard Medical School

The Massachusetts General Hospital Handbook of Internal Medicine

Wolters Kluwer

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Senior Acquisitions Editor: Sharon Zinner
Development Editor: Ashley Fischer
Production Project Manager: Sadie Buckallew
Editorial Coordinator: Ingrid Greenlee
Manufacturing Coordinator: Kathy Brown
Design Coordinator: Stephen Druding
Prepress Vendor: S4Carlisle Publishing Services

Copyright © 2020, 2017, 2014, 2011, 2008, 2004, 2000 by Wolters Kluwer

All rights reserved. This book is protected by copyright. No part of this book may be reproduced in any form by any means, including as photocopies or scanned-in or other electronic copies, or utilized by any information storage and retrieval system without written permission from the copyright owner, except for brief quotations embodied in critical articles and reviews. Materials appearing in this book prepared by individuals as part of their official duties as U.S. government employees are not covered by the above-mentioned copyright. To request permission, please contact Wolters Kluwer at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103, via email at permissions@ww.com, or via our website at shop.lww.com (products and services).

10 9 8 7 6 5 4 3 2 1

Printed in Mexico

Library of Congress Cataloging-in-Publication Data

ISBN-13: 978-1-975142-37-7
ISBN-10: 1-975142-37-3
eISBN: 978-1-975142-39-1

Library of Congress Control Number: 2019908668

This work is provided “as is,” and the publisher disclaims any and all warranties, express or implied, including any warranties as to accuracy, comprehensiveness, or currency of the content of this work.

This work is no substitute for individual patient assessment based upon healthcare professionals’ examination of each patient and consideration of, among other things, age, weight, gender, current or prior medical conditions, medication history, laboratory data and other factors unique to the patient. The publisher does not provide medical advice or guidance and this work is merely a reference tool. Healthcare professionals, and not the publisher, are solely responsible for the use of this work including all medical judgments and for any resulting diagnosis and treatments.

Given continuous, rapid advances in medical science and health information, independent professional verification of medical diagnoses, indications, appropriate pharmaceutical selections and dosages, and treatment options should be made and healthcare professionals should consult a variety of sources. When prescribing medication, healthcare professionals are advised to consult the product information sheet (the manufacturer’s package insert) accompanying each drug to verify, among other things, conditions of use, warnings and side effects and identify any changes in dosage schedule or contraindications, particularly if the medication to be administered is new, infrequently used or has a narrow therapeutic range. To the maximum extent permitted under applicable law, no responsibility is assumed by the publisher for any injury and/or damage to persons or property, as a matter of products liability, negligence law or otherwise, or from any reference to or use by any person of this work.

shop.lww.com

CONTENTS

Contributing Authors
Foreword
Preface

CARDIOLOGY

Rachel Frank, Shilpa Sharma, Nino Mihatov, Nilay Patel, Marc S. Sabatine, Michelle L. O'Donoghue

Electrocardiography
Chest Pain
Noninvasive Evaluation of CAD
Coronary Angiography and Revascularization
Acute Coronary Syndromes
PA Catheter and Tailored Therapy
Heart Failure
Cardiomyopathies
Valvular Heart Disease
Pericardial Disease
Hypertension
Aortic Aneurysms
Acute Aortic Syndromes
Arrhythmias
Atrial Fibrillation
Syncope
Cardiac Rhythm Management Devices
Cardiac Risk Assessment for Noncardiac Surgery
Peripheral Artery Disease

PULMONARY

Miranda Theodore, Jason Maley, Walter J. O'Donnell

Dyspnea
Pulmonary Function Tests
Asthma
Anaphylaxis
Chronic Obstructive Pulmonary Disease
Solitary Pulmonary Nodule
Hemoptysis
Bronchiectasis
Cystic Fibrosis
Interstitial Lung Disease
Pleural Effusion
Venous Thromboembolism
Pulmonary Hypertension
Respiratory Failure
Mechanical Ventilation
Acute Respiratory Distress Syndrome
Sepsis and Shock
Toxicology
Lung Transplant

GASTROENTEROLOGY

Stephanie M. Rutledge, Emily Walsh Lopes, Lawrence S. Friedman

Esophageal and Gastric Disorders
Gastrointestinal Bleeding
Diarrhea
Dysmotility & Nutrition
Disorders of the Colon
Inflammatory Bowel Disease
Intestinal Ischemia
Pancreatitis
Abnormal Liver Tests
Hepatitis
Acute Liver Failure
Cirrhosis
Hepatic Vascular Disease
Ascites
Biliary Tract Disease

NEPHROLOGY

Alexander Blair, Harish Seethapathy, Andrew S. Allegretti

Acid-Base Disturbances
Sodium and Water Homeostasis
Potassium Homeostasis
Renal Failure
Glomerular Disease
Urinalysis
Nephrolithiasis

HEMATOLOGY-ONCOLOGY

Melissa Lumish, Arielle Medford, Tanya E. Keenan, Harshabad Singh, Jean M. Connors, Daniel J. DeAngelo, David P. Ryan

Anemia
Disorders of Hemostasis
Platelet Disorders
Coagulopathies
Hypercoagulable States
Disorders of Leukocytes
Transfusion Therapy
Myelodysplastic Syndromes
Myeloproliferative Neoplasms
Leukemia
Lymphoma
Plasma Cell Dyscrasias
Hematopoietic Stem Cell Transplantation
Lung Cancer
Breast Cancer
Prostate Cancer
Colorectal Cancer
Pancreatic Tumors
Hepatocellular Carcinoma (HCC)
Oncologic Emergencies
Chemotherapy & Immunotherapy Side Effects

INFECTIOUS DISEASES

Alison C. Castle, Kristen Hysell, Kimon C. Zachary

Pneumonia
Fungal Infections
Infections in Immunosuppressed Hosts

Urinary Tract Infections
Soft Tissue and Bone Infections
Infections of the Nervous System
Bacteremia & Endocarditis
Tuberculosis
HIV/AIDS
Tick-Borne Diseases
Fever Syndromes

ENDOCRINOLOGY

Caitlin Colling, Armen Yerevanian, Michael Mannstadt

Pituitary Disorders
Thyroid Disorders
Adrenal Disorders
Calcium Disorders
Diabetes Mellitus
Lipid Disorders

RHEUMATOLOGY

Isaac D. Smith, Mazen Nasrallah, Robert P. Friday

Approach to Rheumatic Disease
Rheumatoid Arthritis
Adult-Onset Still's Disease & Relapsing Polychondritis
Crystal Deposition Arthritides
Seronegative Spondyloarthritis
Infectious Arthritis & Bursitis
Connective Tissue Diseases
Systemic Lupus Erythematosus
Vasculitis
IgG4-Related Disease
Cryoglobulinemia
Amyloidosis

NEUROLOGY

Omar Al-Louzi, Leeann Brigham Burton, Kristin Galetta, Morgan Prust, Michael P. Bowley

Change in Mental Status
Seizures
Alcohol Withdrawal
Dizziness
Stroke
Weakness & Neuromuscular Dysfunction
Headache
Back and Spinal Cord Disease

CONSULTS

Sarah J. Carlson, Jennifer F. Tseng, Katherine T. Chen, Stella K. Kim

Surgical Issues
Ob/Gyn Issues
Ophthalmic Issues

APPENDIX

ICU Medications & Treatment of Hypotension/Shock
Antibiotics
Formulae and Quick Reference

ABBREVIATIONS

INDEX

PHOTO INSERTS

Radiology
Echocardiography & Coronary Angiography
Peripheral Blood Smears & Leukemias
Urinalysis

ACLS

CONTRIBUTING AUTHORS

Andrew S. Allegretti, MD, MSc
Director of ICU Nephrology, Attending Physician, Nephrology Division, and Principal Investigator, Kidney Research Center, Massachusetts General Hospital
Instructor of Medicine, Harvard Medical School

Omar Al-Louzi, MD
Neurology Resident, Partners Neurology Residency

Alexander Blair, MD
Internal Medicine Resident, Massachusetts General Hospital

Michael P. Bowley, MD, PhD
Instructor in Neurology, Massachusetts General Hospital
Associate Program Director, Partners Neurology Residency Program

Leeann Brigham Burton, MD
Neurology Resident, Partners Neurology Residency

Sarah J. Carlson
Assistant Professor of Surgery, Boston University of Medicine
Attending Surgeon, Boston Veterans Affairs Healthcare

Alison C. Castle, MD
Internal Medicine Resident, Massachusetts General Hospital

Katherine T. Chen, MD, MPH
Vice-Chair of Ob/Gyn Education, Career Development, and Mentorship
Professor of Obstetrics, Gynecology, and Reproductive Science
Professor of Medical Education
Icahn School of Medicine at Mount Sinai, New York

Caitlin Colling, MD
Internal Medicine Resident, Massachusetts General Hospital

Jean M. Connors, MD
Medical Director, Anticoagulation Management Services
Hematology Division, Brigham and Women's Hospital & Dana-Farber Cancer Institute
Associate Professor of Medicine, Harvard Medical School

Daniel J. DeAngelo, MD, PhD
Chief of the Division of Leukemia, Dana-Farber Cancer Institute
Professor of Medicine, Harvard Medical School

Rachel Frank, MD
Internal Medicine Resident, Massachusetts General Hospital

Robert P. Friday, MD, PhD
Chief, Division of Rheumatology, Newton-Wellesley Hospital
Affiliate Physician, Rheumatology Unit, Massachusetts General Hospital
Instructor in Medicine, Harvard Medical School

Lawrence S. Friedman, MD
The Anton R. Fried, MD, Chair, Department of Medicine, Newton-Wellesley Hospital

Assistant Chief of Medicine, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School
Professor of Medicine, Tufts University School of Medicine

Kristin Galetta, MD
Neurology Resident, Partners Neurology Residency

Kristen Hysell, MD
Infectious Disease Fellow, Massachusetts General Hospital

Tanya E. Keenan, MD, MPH
Hematology-Oncology Fellow, Dana-Farber/Partners CancerCare

Stella K. Kim, MD
Joe M. Green Jr. Professor of Clinical Ophthalmology
Ruiz Department of Ophthalmology and Visual Sciences
Robert Cizik Eye Clinic
University of Texas McGovern School of Medicine

Emily Walsh Lopes, MD
Gastroenterology Fellow, Massachusetts General Hospital

Melissa Lumish, MD
Internal Medicine Resident, Massachusetts General Hospital

Jason Maley, MD
Pulmonary Fellow, Massachusetts General Hospital

Michael Mannstadt, MD
Chief, Endocrine Unit, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School

Arielle Medford, MD
Internal Medicine Resident, Massachusetts General Hospital

Nino Mihatov, MD
Cardiology Fellow, Massachusetts General Hospital

Mazen Nasrallah, MD, MSc
Rheumatology Fellow, Massachusetts General Hospital

Walter J. O'Donnell, MD
Staff Physician, Pulmonary/Critical Care Unit, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School

Michelle L. O'Donoghue, MD, MPH
Senior Investigator, TIMI Study Group
Associate Physician, Cardiovascular Division, Brigham and Women's Hospital
Affiliate Physician, Cardiology Division, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School

Nilay Patel, MD
Cardiology Fellow, Massachusetts General Hospital

Morgan Prust, MD
Neurology Resident, Massachusetts General Hospital

Stephanie M. Rutledge, MBBCh, BAO, MRCPI
Internal Medicine Resident, Massachusetts General Hospital

David P. Ryan, MD

Clinical Director, Massachusetts General Hospital Cancer Center
Chief of Hematology/Oncology, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

Marc S. Sabatine, MD, MPH
Chairman, TIMI Study Group
Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine, Brigham and Women's Hospital
Affiliate Physician, Cardiology Division, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

Harish Seethapathy, MBBS
Nephrology Fellow, BWH/MGH Joint Nephrology Fellowship Program

Shilpa Sharma, MD
Internal Medicine Resident, Massachusetts General Hospital

Harshabad Singh, MBBS
Instructor, Gastrointestinal Cancer Treatment Center, Dana-Farber Cancer Institute

Isaac D. Smith, MD
Internal Medicine Resident, Massachusetts General Hospital

Miranda Theodore, MD
Internal Medicine Resident, Massachusetts General Hospital

Jennifer F. Tseng, MD, MPH
Utley Professor and Chair, Boston University School of Medicine
Surgeon-in-Chief, Boston Medical Center

Armen Yerevanian, MD
Endocrinology Fellow, Massachusetts General Hospital

Kimon C. Zachary, MD
Assistant Professor of Medicine, Infectious Disease Division, Massachusetts General Hospital

FOREWORD

To the 1st Edition

It is with the greatest enthusiasm that I introduce *Pocket Medicine.* In an era of information glut, it will logically be asked, "Why another manual for medical house officers?" Yet, despite enormous information readily available in any number of textbooks, or at the push of a key on a computer, it is often that the harried house officer is less helped by the description of differential diagnosis and therapies than one would wish.

Pocket Medicine is the joint venture between house staff and faculty expert in a number of medical specialties. This collaboration is designed to provide a rapid but thoughtful initial approach to medical problems seen by house officers with great frequency. Questions that frequently come from faculty to the house staff on rounds, many hours after the initial interaction between patient and doctor, have been anticipated and important pathways for arriving at diagnoses and initiating therapies are presented. This approach will facilitate the evidence-based medicine discussion that will follow the workup of the patient. This well-conceived handbook should enhance the ability of every medical house officer to properly evaluate a patient in a timely fashion and to be stimulated to think of the evidence supporting the diagnosis and the likely outcome of therapeutic intervention. *Pocket Medicine* will prove to be a worthy addition to medical education and to the care of our patients.

DENNIS A. AUSIELLO, MD
Physician-in-Chief, Massachusetts General Hospital
Jackson Professor of Clinical Medicine, Harvard Medical School

PREFACE

To my parents, Matthew and Lee Sabatine, to their namesake grandchildren Matteo and Natalie, and to my wife Jennifer

Written by residents, fellows, and attendings, the mandate for *Pocket Medicine* was to provide, in a concise a manner as possible, the key information a clinician needs for the initial approach to and management of the most common inpatient medical problems.

The tremendous response to the previous editions suggests we were able to help fill an important need for clinicians. With this seventh edition come several major improvements. We have updated every topic thoroughly. In particular, we have included the newest diagnostic algorithms and pharmacotherapy for acute coronary syndromes, the revolutionary data for transcatheter aortic valve replacement (TAVR), and distilled the most recent guidelines for the classification and treatment of hypertension. We have added a dedicated section for the management of cystic fibrosis and updated the treatment of sepsis and shock. We continue to revise the approach to malignancies based on molecular classification and the corresponding biologic therapies, including dedicated sections on immunotherapy. We have incorporated the paradigm-shifting data for diabetes medications that lower cardiovascular risk and cover the newest classes of lipid-lowering therapies. As always, we have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Medicine* went to press. We welcome any suggestions for further improvement.

This edition builds on the work of the many contributors to prior editions of *Pocket Medicine*. In addition, we appreciate the advice on specific topics from additional attendings including Dr. Adam Sperling.

Of course, medicine is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Medicine* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as possible, medicine is both a science and an art. As always, sound clinical judgement must be applied to every scenario.

I am grateful for the support of the house officers, fellows, and attendings at the Massachusetts General Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I always look back on my time there as Chief Resident as one of my best experiences. I am grateful to several outstanding clinical mentors, including Hasan Bazari, Larry Friedman, Nesli Basgoz, Eric Isselbacher, Mike Fifer, and Roman DeSanctis, as well as the late Charlie McCabe, Mort Swartz, and Peter Yurchak.

This edition would not have been possible without the help of Melinda Cuerda and Abby Cange, my academic coordinators. They shepherded every aspect of the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be.

Lastly, special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

I hope that you find *Pocket Medicine* useful throughout the arduous but incredibly rewarding journey of practicing medicine.

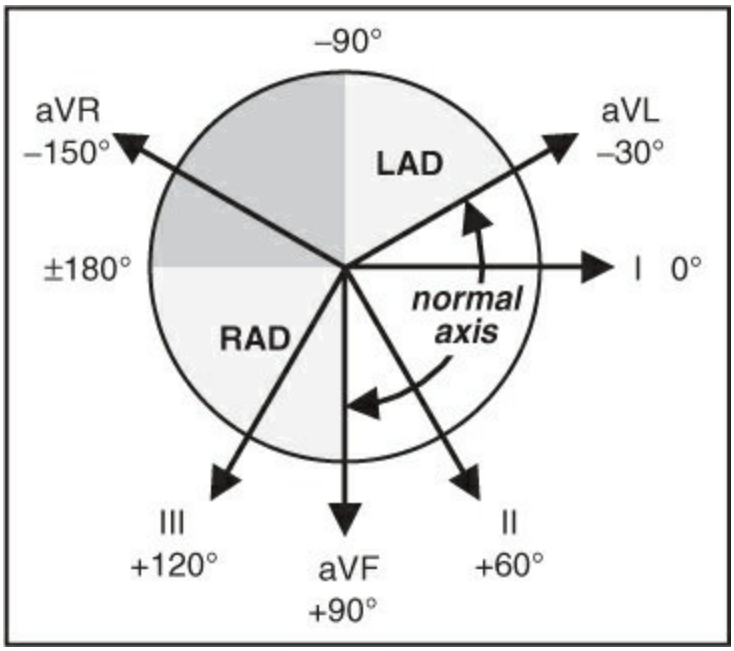
MARC S. SABATINE, MD, MPH

ELECTROCARDIOGRAPHY

Approach (a systematic approach is vital)

- Rate (? tachy or brady) and rhythm (? P waves, regularity, P & QRS relationship)
- Intervals (PR, QRS, QT) and axis (? LAD or RAD)
- Chamber abnormality (? LAA and/or RAA, ? LVH and/or RVH)
- QRST changes (? Q waves, poor R-wave progression V_1–V_6, ST ↑/↓ or T-wave Δs)

Figure 1-1 QRS axis



Left axis deviation (LAD)

- Definition: axis beyond –30° (S > R in lead II)
- Etiologies: LVH, LBBB, inferior MI, WPW
- Left anterior fascicular block (LAFB): LAD (–45 to –90°) *and* qR in aVL *and* QRS <120 msec *and* no other cause of LAD (eg, IMI)

Right axis deviation (RAD)

- Definition: axis beyond +90° (S > R in lead I)
- Etiologies: RVH, PE, COPD (usually not > +110°), septal defects, lateral MI, WPW
- Left posterior fascicular block (LPFB): RAD (90–180°) *and* rS in I & aVL *and* qR in III & aVF *and* QRS <120 msec *and* no other cause of RAD

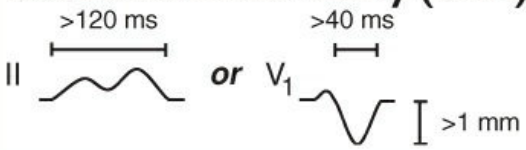
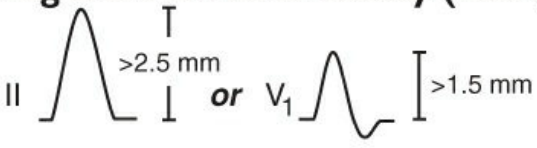
Bundle Branch Blocks (*Circ* 2009;119:e235)		
Normal		Initial depol. left to right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).
RBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. rSR' in R precordial leads (V_1,V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads
LBBB		1. QRS ≥120 msec (110–119 msec = IVCD or "incomplete") 2. Broad, slurred, monophasic R in I, aVL, V_5–V_6 (± RS in V_5–V_6 if cardiomegaly) 3. Absence of Q in I, V_5, and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. ± PRWP, LAD, Qw's in inferior leads

Bifascicular block: RBBB + LAFB/LPFB. "Trifascicular block": bifascicular block + 1° AVB.

Prolonged QT interval (*NEJM* 2008;358:169; www.torsades.org)

- Measure QT from start of QRS to end of Tw (use longest QT, often V2-V3, omit U wave)
- QT varies w/ HR → corrected w/ Bazett formula: QTc = QT/$\sqrt{RR}$ (RR in sec), overcorrects at high HR, undercorrects at low HR (nl QTc <450 msec ♂, <460 msec ♀)
- Fridericia's formula preferred at very high or low HR: QTc = QT/$\sqrt[3]{RR}$
- QT prolongation a/w ↑ risk TdP (espec >500 msec); establish baseline QT and monitor if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:

  Antiarrhythmics: class Ia (procainamide, disopyramide), class III (amio, sotalol, dofet)
  Psych drugs: antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA
  Antimicrobials: macrolides, quinolones, azoles, pentamidine, atazanavir
  Other: antiemetics (droperidol, 5-HT_3 antagonists), alfuzosin, methadone, ranolazine
  Electrolyte disturbances: hypoCa (nb, hyperCa a/w ↓ QT), ± hypoK, ? hypoMg
  Autonomic dysfxn: ICH (deep TWI), Takotsubo, stroke, CEA, neck dissection
  Congenital (long QT syndrome): K, Na, & Ca channelopathies (*Circ* 2013;127:126)
  Misc: CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia, BBB

ECG P-wave criteria	Left Atrial Abnormality (LAA)	Right Atrial Abnormality (RAA)
		

Left ventricular hypertrophy (LVH) (*Circ* 2009;119:e251)

- Etiologies: HTN, AS/AI, HCM, coarctation of aorta
- Criteria (all w/ Se <50%, Sp >85%; accuracy affected by age, sex, race, BMI)

Sokolow-Lyon: S in V_1 + R in V_5 or V_6 ≥35 mm or R in aVL ≥11 mm (↓ Se w/ ↑ BMI)

Cornell: R in aVL + S in V_3 >28 mm in men or >20 mm in women

Romhilt-Estes point-score system (4 points = probable; 5 points = diagnostic): ↑ volt: limb lead R or S ≥20 mm *or* S in V_1 or V_2 ≥30 mm *or* R in V_5 or V_6 ≥30 mm (3 pts)

ST displacement opposite to QRS deflection: w/o dig (3 pts); w/ dig (1 pt)

LAA (3 pts); LAD (2 pts); QRS duration ≥90 msec (1 pt)

Intrinsicoid deflection (QRS onset to peak of R) in V_5 or V_6 ≥50 msec (1 pt)

If LAFB present: S in III + max (R+S) in any lead ≥30 mm in men or ≥28 mm in women

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251; *JACC* 2014;63:672)

- Etiologies: cor pulmonale, congenital (tetralogy of Fallot, TGA, PS, ASD, VSD), MS, TR
- Criteria [all insensitive, but specific (except in COPD); all w/ poor PPV in general population]

  R > S in V_1, R in V_1 ≥6 mm, S in V_5 ≥10 mm, S in V_6 ≥3 mm, R in aVR ≥4 mm

  RAD ≥110° (LVH + RAD *or* prominent S in V_5 or V_6 → consider *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular abnl: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCM; Duchenne's
- Myocardial injury: posterior MI (anterior R wave = posterior Q wave; often with IMI)
- Abnormal depolarization: RBBB (QRS >120 msec, rSR′); WPW (↓ PR, δ wave, ↑ QRS)
- Other: dextroversion; counterclockwise rotation; lead misplacement; nl variant

Poor R wave progression (PRWP) (*Am Heart J* 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V_1–V_3); R wave in V_3 ≤3 mm
- Possible etiologies (nonspecific):

  old anteroseptal MI (usually w/ R wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3)

  LVH (delayed RWP w/ ↑ left precordial voltage), RVH, COPD (may also have RAA, RAD, limb lead QRS amplitude ≤5 mm, $S_IS_{II}S_{III}$ w/ R/S ratio <1 in those leads)

  LBBB; WPW; clockwise rotation of the heart; lead misplacement; CMP; PTX

Pathologic Q waves

- Definition: ≥30 msec (≥20 msec V_2–V_3) or >25% height of R wave in that QRS complex
- Small (septal) q waves in I, aVL, V_5 & V_6 are nl, as can be isolated Qw in III, aVR, V_1
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative dis., HCM, COPD, PTX, WPW

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e262)

- Acute MI: upward convexity STE (ie, a "frown") ± TWI (or prior MI w/ persistent STE)
- Coronary spasm: Prinzmetal's angina; transient STE in a coronary distribution
- Pericarditis: diffuse, upward concavity STE (ie, a "smile"); a/w PR ↓; Tw usually upright
- HCM, Takotsubo CMP, ventricular aneurysm, cardiac contusion

- Pulmonary embolism: occ. STE V_1–V_3; classically a/w TWI V_1–V_4, RAD, RBBB, $S_1Q_3T_3$
- Repolarization abnormalities:
  LBBB (↑ QRS duration, STE discordant from QRS complex; see "ACS" for dx MI in LBBB)
  LVH (↑ QRS amplitude); Brugada syndrome (rSR′, downsloping STE V_1–V_2); pacing
  Hyperkalemia (↑ QRS duration, tall Ts, no P's); epsilon waves (late afterdepol.) in ARVC
- aVR: STE >1 mm a/w ↑ mortality in STEMI; STE aVR > V_1 a/w left main disease
- Early repolarization: most often seen in V_2–V_5 in young adults (*Circ* 2016;133:1520)
  1–4 mm elev of peak of notch or start of slurred downstroke of R wave (ie, J point); ± up concavity of ST & large Tw (∴ ratio of STE/T wave <25%; may disappear w/ exercise)
  ? early repol in inf leads may be a/w ↑ risk of VF (*NEJM* 2009;361:2529; *Circ* 2011;124:2208)

ST depression (STD)

- Myocardial ischemia (± Tw abnl)
- Acute true posterior MI: posterior STE appearing as anterior STD (± ↑ R wave) in V_1–V_3
  ✔ posterior ECG leads; manage as a STEMI with rapid reperfusion (see "ACS")
- Digitalis effect (downsloping ST ± Tw abnl; does *not* correlate w/ dig levels)
- Hypokalemia (± U wave)
- Repolarization abnl a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL)

T wave inversion (TWI; generally ≥1 mm; deep if ≥5 mm) (*Circ* 2009;119:e241)

- Ischemia or infarct; *Wellens' sign* (deep, symm precordial TWI) → critical prox LAD lesion
- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWI V_1–V_4)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"); BBB; nl variant if QRS predom. ⊖
- Posttachycardia or postpacing ("memory" T waves)
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH/core temp Δ's, intracranial bleed ("cerebral Tw")

Low voltage

- QRS amplitude (R + S) <5 mm in all limb leads & <10 mm in all precordial leads
- Etiol: COPD, pericard./pleural effusion, myxedema, ↑ BMI, amyloid, diffuse CAD

Electrolyte abnormalities

- ↑ K: tented Tw, ↓ QT, ↑ PR, AVB, wide QRS, STE; ↓ K: flattened Tw, U waves, ↑ QT
- ↑ Ca: ↓ QT, flattened Tw & Pw, J point elevation; ↓ Ca: ↑ QT; Tw Δs

ECG in young athletes (*JACC* 2017;69:805)

- Normal patterns may incl. LVH, RVH, early repol
- Evaluate if: arrhythmias, HR <30, prolonged QT, ε/δ waves, LBBB, Brugada pattern, QRS >140 ms, PR >400 ms, Mobitz II, 3° AVB, ST depression, TWI

CHEST PAIN

Disorder	Typical Characteristics & Diagnostic Studies
	Cardiac Causes
ACS (15–25% of chest pain in ED)	Substernal "pressure" (! LR 1.3) → neck, jaw, arm (! LR 1.3–1.5) Sharp, pleuritic, positional, or reprod. w/ palp all w/ ⊕ LR ≤0.35 Diaphoresis (⊕ LR 1.4), dyspnea (⊕ LR 1.2), a/w exertion (⊕ LR 1.5–1.8) ≈ prior MI (⊕ LR 2.2); ↓ w/ NTG/rest (but not reliable; *Annals EM* 2005;45:581) ± ECG Δs: STE, STD, TWI, Qw. ± ↑ Troponin.
Pericarditis & myo- pericarditis	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myocarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.
Aortic dissection	Sudden severe tearing pain (absence ⊖ LR 0.3). ± Asymm (>20 mmHg) BP or pulse (⊕ LR 5.7), focal neuro deficit (⊕ LR >6), AI, widened mediast. on CXR (absence ⊖ LR 0.3); false lumen on imaging. (*JAMA* 2002;287:2262)
	Pulmonary Causes
Pneumonia	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
Pleuritis	Sharp, pleuritic pain. ± Pleuritic friction rub.
PTX	Sudden onset, sharp pleuritic pain. Hyperresonance, ↓ BS. PTX on CXR.
PE	Sudden onset pleuritic pain. ↑ RR & HR, ↓ S_aO_2, ECG Δs (sinus tach, RAD, RBBB, $S_IQ_{III}T_{III}$, TWI V_1–V_4, occ STE V_1–V_3), + CTA or V/Q, ± ↑ Tn.
Pulm HTN	Exertional pressure, DOE. ↓ S_aO_2, loud P_2, RV heave, right S_3 and/or S_4.
	GI Causes
Esophageal reflux	Substernal burning, acid taste in mouth, water brash. ↑ by meals, recumbency; ↓ by antacids. EGD, manometry, pH monitoring.
Esoph spasm	Intense substernal pain. ↑ by swallowing, ↓ by NTG/CCB. Manometry.
Mallory-Weiss	Esoph tear precipitated by vomiting. ± Hematemesis. Dx w/ EGD.
Boerhaave	Esoph rupture. Severe pain, ↑ w/ swallow. Mediastinal air palpable & on CT.
PUD	Epigastric pain, relieved by antacids. ± GIB. EGD, ± *H. pylori* test.
Biliary dis.	RUQ pain, N/V. ↑ by fatty foods. RUQ U/S; ↑ LFTs.
Pancreatitis	Epigastric/back discomfort. ↑ amylase & lipase; abd CT.
	Musculoskeletal and Miscellaneous Causes
Costochond	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
Zoster	Intense unilateral pain. Pain may precede dermatomal rash.
Anxiety	"Tightness," dyspnea, palpitations, other somatic symptoms

(*Braunwald's Heart Disease*, 11th ed, 2018; *JAMA* 2015;314:1955)

Initial approach

- Focused history: quality, severity, location, radiation; provoking/palliating factors; intensity at onset; duration, freq, & pattern; setting; assoc sx; cardiac hx & risk factors
- Targeted exam: VS (incl. BP in both arms); gallops, murmurs, rubs; signs of vascular dis.

(carotid/femoral bruits, ↓ pulses) or CHF; lung & abd. exam; chest wall for reproducibility

- 12-lead ECG: obtain w/in 10 min; comp to priors & obtain serial ECGs; consider *posterior leads* (V_7–V_9) to ✔ for posterior STEMI if: hx c/w ACS but stnd ECG unrevealing; ST ↓ V_1–V_3 (ant ischemia vs. post STEMI) w/ refractory angina; or R/S >1 in V_1–V_2
- CXR; other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing
- Troponin: *>99th %ile w/ rise and/or fall in approp. setting is dx of AMI* (*Circ* 2018;138:e618)
  Detectable 1–6 h after injury, peaks 24 h, may be elevated for 7–14 d in STEMI ✔ at presentation & 3–6 h later; repeat if clinical or ECG Δs; ? sex-specific cutpoints If high-sens Tn (hsTn) assay, can ✔ at presentation & 1 h later; assess level & Δ
- Causes for ↑ Tn other than plaque rupture (= "type 1 MI"): (1) Supply-demand mismatch not due to Δ in CAD (= "type 2 MI"; eg, ↑↑ HR, shock, HTN crisis, spasm, severe AS), (2) non-ischemic injury (myocarditis/toxic CMP, cardioversion, cardiac contusion) or (3) multifactorial (PE, sepsis, severe HF, renal failure, Takotsubo, infilt dis.)
- CK-MB: less Se & Sp than Tn (other sources: skel. muscle, intestine, etc.); CK-MB/CK ratio >2.5 → cardiac source. Limited utility: ? higher bar for post-revasc MI; early reMI.

Early noninvasive imaging

- Low prob of ACS (eg, ⊖ ECG & Tn) & stable → outPt or inPt noninv. fxnal or imaging test (qv)
- CCTA w/ high NPV, low PPV. ↓ LOS c/w fxnal testing (*NEJM* 2012;366:1393). In stable outPt w/ CP, CCTA added to standard of care ↑ early but not overall angiography/revasc; ↑ use of preventive med Rx, and ↓ coronary death/MI at 5 y (*NEJM* 2018;379:924).
- "Triple r/o" CT angiogram sometimes performed to r/o CAD, PE, AoD if dx unclear

NONINVASIVE EVALUATION OF CAD

Stress testing (*JACC* 2012;60:1828; *J Nucl Cardiol* 2016; 23:606)

- Indications: dx obstructive CAD, evaluate Δ in clinical status in Pt w/ known CAD, risk stratify after ACS, evaluate exercise tolerance, localize ischemia (imaging required)
- Contraindications (*Circ* 2002;106:1883; & 2012;126:2465)
  - Absolute: AMI w/in 48 h, high-risk UA, acute PE, severe sx AS, uncontrolled HF, uncontrolled arrhythmias, myopericarditis, acute aortic dissection
  - Relative (discuss with stress lab): left main CAD, mod symptomatic valvular stenosis, severe HTN, HCMP, high-degree AVB, severe electrolyte abnl

Exercise tolerance test (w/ ECG alone)

- Generally preferred if Pt can meaningfully exercise; ECG Δs w/ Se ~65%, Sp ~80%
- Typically via treadmill w/ Bruce protocol (modified Bruce or submax if decond. or recent MI)
- Hold anti-isch. meds (eg, nitrates, βB) if dx'ing CAD but give to assess adequacy of meds

Pharmacologic stress test (nb, requires imaging because ECG not interpretable)

- Use if unable to exercise, low exercise tolerance, or recent MI. Se & Sp ≈ exercise.
- Preferred if LBBB, WPW or V-paced, because higher prob of false ⊕ imaging with exercise
- *Coronary vasodilator:* diffuse vasodilation → relative "coronary steal" from vessels w/ fixed epicardial dis. Reveals CAD, but *not* if Pt *ischemic w/ exercise.* Regadenoson (↓ side effects), dipyridamole, adenosine. Side effects: flushing, ↓ HR, AVB, SOB, bronchospasm.
- *Chronotropes/inotropes* (dobuta): more physiologic, but longer test; may precip arrhythmia

Imaging for stress test

- Use if uninterpretable ECG (V-paced, LBBB, resting ST ↓ >1 mm, digoxin, LVH, WPW), after indeterminate ECG test, or if pharmacologic test
- Use when need to localize ischemia (often used if prior coronary revasc)
- Radionuclide myocardial perfusion imaging w/ images obtained at rest & w/ stress
  - SPECT (eg, ^{99m}Tc-sestamibi): Se ~85%, Sp ~80%
  - PET (rubidium-82): Se ~90%, Sp ~85%; requires pharmacologic stress, not exercise
  - ECG-gated imaging allows assessment of regional LV fxn (sign of ischemia/infarction)
- Echo (exercise or dobuta): Se ~85%, Sp ~85%; no radiation; operator dependent
- Cardiac MRI (w/ pharmacologic stress) another option with excellent Se & Sp

Test results

- HR (must achieve ≥85% of max pred HR [220-age] for *exer.* test to be dx), BP response, peak double product (HR × BP; nl >20k), HR recovery ($HR_{peak} - HR_{1\ min\ later}$; nl >12)

- Max exercise capacity achieved (METS or min); occurrence of symptoms
- ECG Δs: *downsloping* or *horizontal* ST ↓ (≥1 mm) 60–80 ms after QRS predictive of CAD (but does *not* localize ischemic territory); however, STE highly predictive & localizes
- Duke treadmill score = exercise min – (5 × max ST dev) – (4 × angina index) [0 none, 1 nonlimiting, 2 limiting]; score ≥5 → <1% 1-y mort; –10 to + 4 → 2–3%; ≤–11 → ≥5%
- Imaging: radionuclide defects or echocardiographic regional wall motion abnormalities
  reversible defect = ischemia; fixed defect = infarct; transient isch dilation → ? severe 3VD
  false ⊕: breast → ant defect; diaphragm → inf defect. False ⊖: balanced (3VD) ischemia.

High-risk test results (PPV ~50% for LM or 3VD, ∴ consider coronary angio)

- ECG: ST ↓ ≥2 mm *or* ≥1 mm in stage 1 *or* in ≥5 leads *or* ≥5 min in recovery; ST ↑; VT
- Physiologic: ↓ or fail to ↑ BP, <4 METS, angina during exercise, Duke score ≤–11; ↓ EF
- Radionuclide: ≥1 lg or ≥2 mod. reversible defects, transient LV cavity dilation, ↑ lung uptake

Myocardial viability (*Circ* 2008;117:103; *Eur Heart J* 2011;31:2984 & 2011;32:810)

- Goal: identify hibernating myocardium that could regain fxn after revascularization
- Options: MRI (Se ~85%, Sp ~75%), PET (Se ~90%, Sp ~65%), dobutamine stress echo (Se ~80%, Sp ~80%); SPECT/rest-redistribution (Se ~85%, Sp ~60%)
  In Pts w/ LV dysfxn, viabil. doesn't predict ↑ CABG benefit vs. med Rx (*NEJM* 2011;364:1617)

Coronary CT/MR angio (*NEJM* 2008;359:2324; *Circ* 2010;121:2509; *Lancet* 2012;379:453)

- Pts w/ CP: CCTA 100% Se, 54% Sp for ACS, ∴ NPV 100%, PPV 17% (*JACC* 2009;53:1642). ↓ LOS, but ↑ cath/PCI, radiation vs. fxnal study (*NEJM* 2012;367:299; *JACC* 2013;61:880).
- Sx outPt: CCTA vs. fxnal testing → ↑ radiation, cath/PCI early; by 5 y, ↓ CHD death/MI w/ similar rates of cath/PCI (*NEJM* 2018;379:924)
- Unlike CCTA, MR does not require iodinated contrast or radiation, and can assess LV fxn

Coronary artery calcium score (*NEJM* 2012;366:294; *JAMA* 2012;308:788)

- Quantifies extent of calcium; thus, *estimates* plaque burden (but *not* % coronary stenosis)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD
- May provide incremental value to clinical scores for risk stratification (*JAMA* 2004;291:210). ACC/AHA guidelines note CAC assessment is reasonable in asx Pts w/ intermed risk (7.5– <20% 10-y risk) and selected borderline risk (5– <7.5% 10-y risk) (*Circ* 2019;139:e1082).

CORONARY ANGIOGRAPHY AND REVASCULARIZATION

Indications for coronary angiography in stable CAD, asx Pts, and others

- CCS class III–IV angina despite med Rx, angina + systolic dysfxn, or unexplained low EF
- High-risk stress test findings (qv) or uncertain dx after noninv testing (& info will Δ mgmt)
- Occupational need for definitive dx (eg, pilot) or inability to undergo noninvasive testing
- Survivor of SCD, polymorphic VT, sustained monomorphic VT
- Suspected spasm; nonathero cause of ischemia (eg, anomalous coronary; CCTA preferred)
- Preop workup in select Pts undergoing organ transplant eval (CCTA reasonable)

Precath checklist & periprocedural pharmacotherapy

- Peripheral arterial exam (radial, femoral, DP, PT pulses; bruits); ✔ palmar arch intact (eg, w/ pulse oximetry & plethysmography). ✔ can lie flat, NPO >6 h.
- ✔CBC, PT, Cr; hold ACEI/ARB if renal dysfxn (see "CIAKI"). Blood bank sample.
- ASA 325 mg × 1. Timing of $P2Y_{12}$ inhib debated. ASAP for STEMI. ? preRx NSTEACS if clopi (*JAMA* 2012;308:2507) or ticagrelor, not prasugrel. Cangrelor (IV $P2Y_{12}$ inhib) ↓ peri-
  PCI events vs. clopi w/o PreRx (*NEJM* 2013;368:1303). ? statin preRx (*Circ* 2011;123:1622).

Coronary revascularization in stable CAD (*NEJM* 2016;374:1167; *JACC* 2017;69:2212)

- Optimal med Rx (OMT): preferred 1st line if stable disease w/o critical anatomy & w/ nl EF
- PCI: ↓ angina; no Δ exercise time (*Lancet* 2018;391:31) or D/MI (*NEJM* 2015;373:1204);
  if ≥1 stenosis w/ FFR (qv) ≤0.8, ↓ urg revasc & MI c/w OMT (*NEJM* 2018;379:250)
- CABG (*NEJM* 2016;374:1954): in older studies, ↓ mort. c/w OMT if 3VD, LM, 2VD w/ crit. prox LAD, esp. if ↓ EF; recently confirmed if multivessel dis. & EF <35% (*NEJM* 2016;374:1511); radial artery ↑ patency & ↓ MACE vs. saphenous vein grafts (*NEJM* 2018;378:2069); less complete revasc & possibly ↑ mort. w/ off vs. on-pump (*NEJM* 2016;375:2359 & 377:623)
- If revasc deemed necessary, *PCI* if limited # of discrete lesions, nl EF, no DM, poor operative candidate; *CABG* if extensive or diffuse disease, ↓ EF, DM or valvular disease; SYNTAX score II: ID Pts w/ ↑ benefit w/ CABG (*Lancet* 2013;381:639); if multivessel disease w/ high complexity or DM, CABG ↓ mortality (*Lancet* 2018;391:939); if LM disease, PCI ≈ CABG, but ↑ repeat revasc w/ PCI (*JAMA Cardiol.* 2017;2:1079)

PCI and peri-PCI interventions

- Access: radial ↓ bleed/vasc comp (? ↓ death in ACS) vs. fem (*Circ CV Interv* 2018;11:e000035)
- Fractional flow reserve (FFR): ratio of max flow (induced by adenosine) distal vs. prox to stenosis to ID hemodyn. signif. lesions (≤0.80). Instantaneous wave-free ratio (iFR)

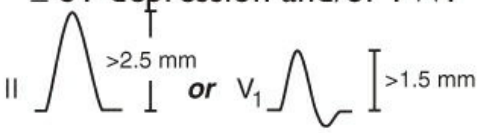
similar to FFR, doesn't require vasodilator; iFR threshold ≤0.89 (*NEJM* 2017;376:1813 & 1824).

- Balloon angioplasty by itself rare b/c elastic recoil; reserved for lesions too narrow to stent
- Bare metal stents (BMS): ↓ restenosis & repeat revasc c/w angioplasty alone
- Drug-eluting stents (DES): latest DES ↓ cardiac death or MI, repeat revasc, and stent thrombosis vs. BMS (*Lancet* 2019;393:2503)
- Antiplt Rx: DAPT (ASA 81 + $P2Y_{12}$ inhib) in SIHD for 4 wk (BMS) or ≥6 mo (DES); in *ACS* (qv) for 12 mo and possibly beyond (*JAMA Cards* 2016;1:627). Data emerging for DAPT for just 1 mo, followed by $P2Y_{12}$ inhib for 11 mo (*Lancet* 2018;392:940; *JAMA* 2019;321:2414 & 2428).
- If need long-term oral anticoag, consider clopi+DOAC and consider stopping ASA (? after ~1 wk) as ↓ bleed, but trend small ↑ ischemic risk (*Lancet* 2013;381:1107 & *NEJM* 2019;380:1509)

Post-PCI complications (*NEJM* 2017;377:1513)

- Postprocedure ✔ vascular access site, distal pulses, ECG, CBC, Cr
- Bleeding: if hematoma/overt bleeding → manual compression, reverse/stop anticoag.
  Retroperitoneal bleed: may p/w ↓ Hct ± back pain; ↑ HR & ↓ BP late; Dx w/ abd/pelvic CT (I^-); Rx: reverse/stop anticoag (d/w interventionalist), IVF/PRBC/plts as required.
- Vascular damage (~1% of dx angio, ~5% of transfemoral PCI; *Circ* 2007;115:2666)
  Pseudoaneurysm: triad of pain, expansile mass, systolic bruit; Dx: U/S; Rx (if pain or >2 cm): manual or U/S-directed compression, thrombin injection, or surgical repair
  AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair if large or sx
  LE ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: pulse volume recording (PVR), angio; Rx: percutaneous or surgical repair
- Peri-PCI MI: >5× ULN of Tn/CK-MB + either sx or ECG/angio Δs; Qw MI in <1%
- Contrast-induced AKI: w/in 48 h, peak 3–5 d; pre-hydration reasonable (see "CIAKI")
- Cholesterol emboli syndrome (typically in middle-aged & elderly and w/ Ao atheroma)
  renal failure (late and progressive, ± eos in urine); mesenteric ischemia (abd pain, LGIB, pancreatitis); intact distal pulses but livedo pattern and toe necrosis
- Stent thrombosis: mins-yrs after PCI, typically p/w AMI. Due to mech prob. (stent underexpansion or unrecognized dissection, typically presents early) or d/c of antiplt Rx; espec if d/c both ASA & $P2Y_{12}$ inhib (*JAMA* 2005;293:2126).
- In-stent restenosis: mos after PCI, typically p/w gradual ↑ angina (10% p/w ACS).
  Due to combination of elastic recoil and neointimal hyperplasia; ↓ w/ DES vs. BMS.

ACUTE CORONARY SYNDROMES

Spectrum of Acute Coronary Syndromes			
Dx	**UA**	**NSTEMI**	**STEMI**
Coronary thrombosis	Subtotal occlusion		Total occlusion
History	Angina that is new-onset, crescendo or at rest; usually <30 min		Angina at rest
ECG	± ST depression and/or TWI 		ST elevations 
Troponin/CK-MB	⊖	⊕	⊕ ⊕

Ddx (causes of myocardial ischemia/infarction other than atherosclerotic plaque rupture)

- Nonatherosclerotic coronary artery disease (*JACC* 2018;72:2231)
  - Spasm: Prinzmetal's variant, cocaine-induced (6% of chest pain + cocaine use r/i for MI)
  - Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (PCI, surgery, trauma)
  - Embolism (*Circ* 2015;132:241): AF, thrombus/myxoma, endocard., prosth valve thrombosis
  - Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA
  - Congenital: anomalous origin from aorta or PA, myocardial bridge (intramural segment)
- Ischemia w/o plaque rupture ("type 2" MI): ↑ demand (eg, ↑ HR), ↓ supply (eg, HoTN)
- Direct myocardial injury: myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

Clinical manifestations (*JAMA* 2015;314:1955)

- Typical angina: retrosternal pressure/pain/tightness ± radiation to neck, jaw, arms; precip. by exertion, relieved by rest/ NTG. In ACS: new-onset, crescendo or at rest.
- Associated symptoms: dyspnea, diaphoresis, N/V, palpitations or light-headedness
- Many MIs (~20% in older series) are initially unrecognized b/c silent or atypical sx
- Atypical sxs (incl N/V & epig pain) ? more common in ♀, elderly, diabetes, inferior ischemia

Physical exam

- Signs of ischemia: S_4, new MR murmur 2° pap. muscle dysfxn, paradoxical S_2, diaphoresis
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S_3, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP, carotid or femoral bruits, ↓ distal pulses

Diagnostic studies (*NEJM* 2017;376:2053)

- ECG: ST ↓/↑, TWI, new LBBB, hyperacute Tw; Qw/PRWP may suggest prior MI & ∴ CAD
  - ✔ ECG w/in 10 min of presentation, with any Δ in sx & at 6–12 h; compare w/ baseline
  - STEMI dx w/ old LBBB: ≥1 mm STE *concordant* w/ QRS (Se 73%, Sp 92%), STD ≥1 mm V_1–V_3 (Se 25%, Sp 96%), STE ≥5 mm *discordant* w/ QRS (Se 31%, Sp 92%)

Localization of MI		
Anatomic Area	ECG Leads w/ STE	Coronary Artery
Septal	V_1–V_2 ± aVR	Proximal LAD
Anterior	V_3–V_4	LAD
Apical	V_5–V_6	Distal LAD, LCx, or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF ± aVR	RCA (~85%), LCx (~15%)
RV	V_1–V_2 & V_4R (most Se)	Proximal RCA
Posterior	ST *depression* V_1–V_3 (= STE V_7–V_9 posterior leads, ✔ if clinical suspicion)	RCA or LCx

If ECG non-dx & suspicion high, ✔ leads V_7–V_9 to assess distal LCX/RCA territory. ✔ R-sided precordial leads in IMI to help detect RV involvement (STE in V_4R most Se). STE in III > STE in II and lack of STE in I or aVL suggest RCA rather than LCX culprit in IMI. STE in aVR suggests LM or prox LAD occlusion or diffuse ischemia.

- Cardiac biomarkers: ✔ Tn (pref. over CK-MB) at presentation & 3–6 h (? 1hr if hsTn); repeat if clinical or ECG Δs; >99th %ile w/ rise and/or fall in appropriate clinical setting dx of AMI (see "Chest Pain"); in CKD, ↑ Tn still portends poor prognosis (*NEJM* 2002;346:2047)
- If low prob, stress test, CT angio to r/o CAD; new wall motion abnl on TTE suggests ACS
- Coronary angio gold standard for epicardial CAD

Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (*but* MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Angiography: nonobstructive CAD (spasm can be provoked during cath but rarely done)
- Treatment: high-dose CCB & standing nitrates (+SL prn), ? α-blockers/statins; d/c smoking; avoid high-dose ASA (can inhibit prostacyclin and worsen spasm), nonselect βB, triptans
- Cocaine-induced vasospasm: CCB, nitrates, ASA; ? avoid βB, but labetalol appears safe

Likelihood of ACS (*Circ* 2007;116:e148)			
Feature	**High** (any of below)	**Intermediate** (no high features, any of below)	**Low** (no high/inter. features, may have below)
History	Chest or L arm pain like prior angina, h/o CAD (incl MI)	Chest or arm pain, age >70 y, male, diabetes	Atypical sx (eg, pleuritic, sharp or positional pain)
Exam	HoTN, diaphoresis, HF, transient MR	PAD or cerebrovascular disease	Pain reproduced on palp.
ECG	New STD (≥1 mm) TWI in mult leads	Old Qw, STD (0.5–0.9 mm), TWI (>1 mm)	TWF/TWI (<1 mm) in leads w/ dominant R wave
Biomarkers	⊕ Tn or CK-MB	Normal	Normal

Approach to triage

- If hx, initial ECG & Tn non-dx, repeat ECG q15–30min × 1 h & Tn 3–6 h (? 1hr if hs) later
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If remain nl, have ruled out MI, *but* if high suspicion for ACS based on hx, then still need to r/o UA w/ stress test to assess for inducible ischemia (or CTA to r/o epicardial CAD);
  if low risk (eg, age ≤70; ∅ prior CAD, CVD, PAD; ∅ rest angina) can do before d/c from ED or as outPt w/in 72 h (0% mortality, <0.5% MI; *Ann Emerg Med* 2006;47:427)
  if not low risk, admit and initiate Rx for possible ACS and consider stress test or cath

Acute Anti-Ischemic and Analgesic Treatment	
Nitrates (SL or IV) 0.3–0.4 mg SL q5min × 3, then consider IV if still sx	Use for relief of sx, Rx for HTN or HF. No clear ↓ in mortality. *Caution* if preload-sensitive (eg, HoTN, AS, sx RV infarct); contraindicated if recent PDE5 inhibitor use.
β-blockers eg, metop 25–50 mg PO q6h titrate slowly to HR 50–60 IV only if HTN and no HF	↓ ischemia & progression of UA to MI (*JAMA* 1988;260:2259) STEMI: ↓ arrhythmic death & reMI, but ↑ cardiogenic shock early (espec if signs of HF) (*Lancet* 2005;366:1622). *Contraindic.* PR >0.24 sec, HR <60, 2°/3° AVB, severe bron-chospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
CCB (nondihydropyridines)	If cannot tolerate βB b/c bronchospasm
Morphine	Relieves pain/anxiety; venodilation ↓ preload. Do not mask refractory sx. May delay antiplt effects of $P2Y_{12}$ inhib.
Oxygen	Use prn for resp distress or to keep S_aO_2 >90%; no mortality benefit if S_aO_2 ≥90% (*NEJM* 2017;377:1240)

Other early adjunctive therapy

- High-intensity statin therapy (eg, atorva 80 mg qd; PROVE-IT TIMI 22, *NEJM* 2004;350:1495); ↓ ischemic events w/ benefit emerging w/in wks (*JAMA* 2001;285:1711 & *JACC* 2005;46:1405); ↓ peri-PCI MI (*JACC* 2010;56:1099); ? ↓ contrast-induced nephropathy (*NEJM* 2019;380:2156)
- Ezetimibe: ↓ CV events when added to statin (IMPROVE-IT, *NEJM* 2015;372:1500)

- ACEI/ARB: start once hemodynamics and renal function stable
  - Strong indication for ACEI if heart failure, EF <40%, HTN, DM, CKD; ~10% ↓ mortality, greatest benefit in ant. STEMI or prior MI (*Lancet* 1994;343:1115 & 1995;345:669)
  - ARB appear ≈ ACEI (*NEJM* 2003;349:20); give if contraindic to ACEI
- IABP: can be used for refractory angina when PCI not available

NSTE-ACS (*CIRC* 2014;130:e344)

Key issues are antithrombotic regimen and invasive vs. conservative strategy

Antiplatelet Therapy	
Aspirin 162–325 mg × 1, then 81 mg qd (non–enteric-coated, chewable)	50–70% ↓ D/MI (*NEJM* 1988;319:1105) Low dose (~81 mg) pref long term (*NEJM* 2010;363:930) If allergy, use clopi and/or desensitize to ASA
$P2Y_{12}$ (ADP receptor) inhibitor (choose one of the following in addition to ASA). Timing (on presentation or at angiography) remains controversial. Some data for upstream clopidogrel (*JAMA* 2012;308:2507). See below for specific recommendations.	
• Ticagrelor (preferred over clopi) 180 mg × 1 → 90 mg bid Reversible, but wait 3–5 d prior to surg. Antidote being developed (*NEJM* 2019;380:1825). Use only with ASA <100 mg qd	More rapid and potent plt inhib c/w clopi 16% ↓ CVD/MI/stroke & 21% ↓ CV death c/w clopi; ↑ non-CABG bleeding (*NEJM* 2009;361;1045) Given upstream or at time of PCI Dyspnea (but S_aO_2 & PFTs nl) & ventricular pauses
• Prasugrel (preferred over clopi) 60 mg × 1 if undergoing PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery	More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs. clopi, but ↑ bleeding (*NEJM* 2007;359:2001), incl fatal bleeds In NSTE-ACS, should be given at time of PCI and not upstream due to ↑ bleeding (*NEJM* 2013;369:999) Contraindic. if h/o TIA/CVA; ? avoid if >75 y
• Clopidogrel* 300–600 mg × 1 → 75 mg qd Requires ~6 h to steady state	ASA+clopi → 20% ↓ CVD/MI/stroke vs. ASA alone ↑ benefit if given hrs *prior* to PCI (*JAMA* 2012;308:2507), but if require CABG, need to wait >5 d after d/c clopi
• Cangrelor Only IV $P2Y_{12}$ inhibitor Rapid onset/offset; t½ 3–5 min	22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs. clopi 300 mg at time of PCI; no significant ↑ bleeding (*NEJM* 2013;368:1303) Consider for rapidly reversible $P2Y_{12}$ inhibition during PCI or as bridge to surgery in high-risk Pts who need to stop $P2Y_{12}$
GP IIb/IIIa inhibitors (GPI) abciximab; eptifibatide; tirofiban Infusions given ≤24 h peri & post PCI; shorter (~2 h) as effective w/ ↓ bleeding (*JACC* 2009;53:837)	No clear benefit for routinely starting prior to PCI and ↑ bleeding (*NEJM* 2009;360:2176) Consider if refractory ischemia despite optimal Rx while awaiting angio or in high-risk Pts (eg, large clot burden) at time of PCI, espec if using clopi and no preRx.

*~30% pop has ↓ fxn *CYP2C19* → ↑ CV events if PCI on clopi (*NEJM* 2009;360:354)

Anticoagulant Therapy (choose one)	
UFH: 60 U/kg IVB (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of	24% ↓ D/MI (*JAMA* 1996;276:811) Titrate to aPTT 1.5–2× control (~50–70 sec) Hold until INR <2 if already on warfarin

PCI	
Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2–8 d or until PCI	~10% ↓ D/MI vs. UFH (*JAMA* 2004;292:45,89). Can perform PCI on enox (*Circ* 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.
Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	No diff in bleeding, MI, or death c/w UFH (*NEJM* 2017;377:1132). Use instead of UFH if HIT.
Fondaparinux (Xa inh) 2.5 mg SC qd	Rarely used; must supplement w/ UFH if PCI.

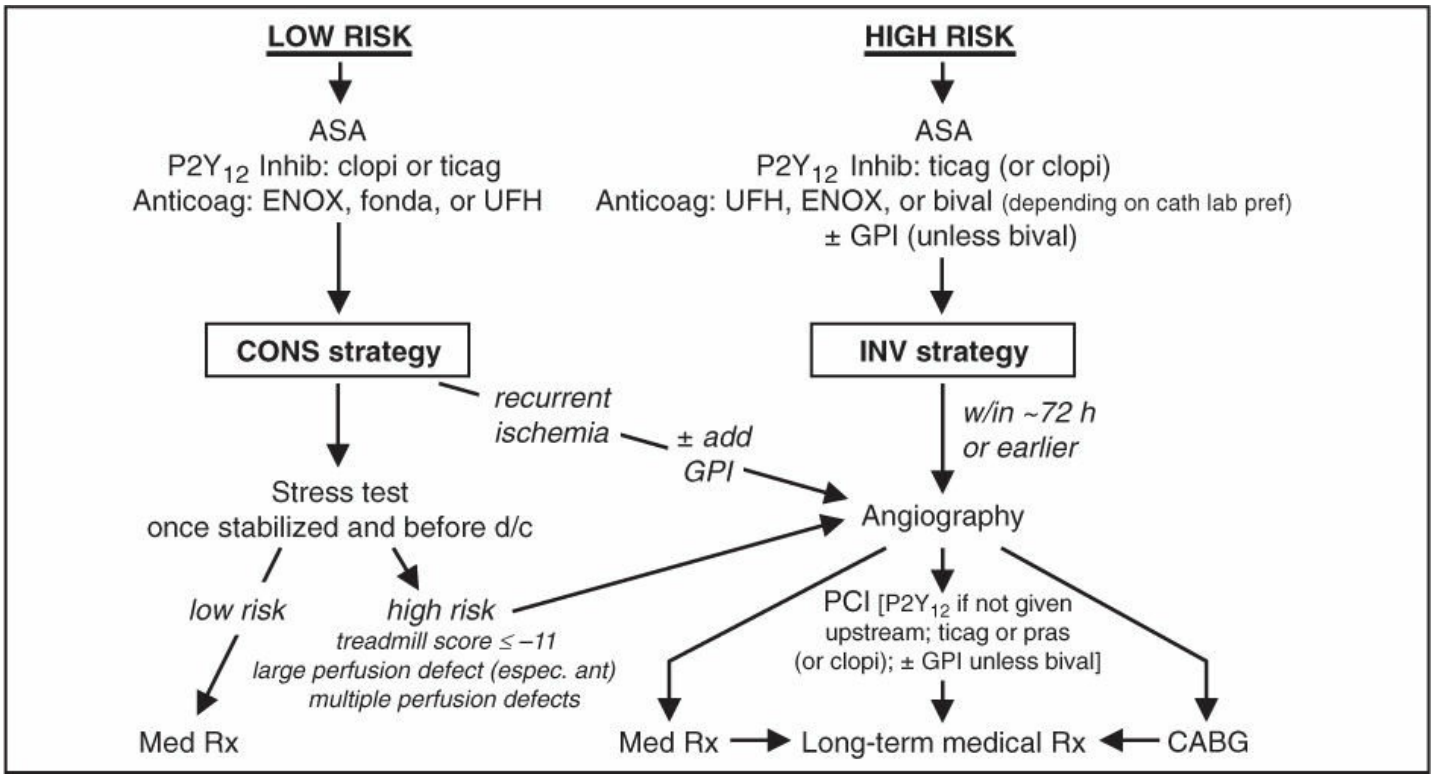
Coronary angiography (*Circ* 2014;130:e344)

- Immediate/urgent coronary angiography (w/in 2 h) if refractory/recurrent angina or hemodynamic or electrical instability
- Invasive (INV) strategy = routine angiography w/in 72 h
  - *Early (w/in 24 h) if:* ⊕ Tn, ST Δ, GRACE risk score (www.outcomes-massmed.org/grace) >140 (*NEJM* 2009;360:2165; *Circ* 2018;138:2741)
  - *Delayed (ie, w/in 72 h) acceptable if w/o above features but w/:* diabetes, EF <40%, GFR <60, post-MI angina, TRS ≥3, GRACE score 109–140, PCI w/in 6 mo, prior CABG
  - 32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mortality c/w cons. (*JAMA* 2008;300:71).
  - ↑ peri-PCI MI counterbalanced by ↓↓ in spont. MI. Mortality benefit seen in some studies, likely only if cons. strategy w/ low rate of angio.
- Conservative (CONS) strategy = selective angio. Med Rx w/ pre-d/c stress test; angio only if recurrent ischemia or strongly ⊕ ETT. *Indicated for:* low TIMI Risk Score, Pt or physician pref in absence of high-risk features, or low-risk women (*JAMA* 2008;300:71).

TIMI Risk Score (TRS) for UA/NSTEMI (*JAMA* 2000;284:835)

Calculation of Risk Score		**Application of Risk Score**	
Characteristic	**Point**	**Score**	**D/MI/UR by 14 d**
Historical		0–1	5%
Age ≥65 y	1	2	8%
≥3 Risk factors for CAD	1	3	13%
Known CAD (stenosis ≥50%)	1	4	20%
ASA use in past 7 d	1	5	26%
Presentation		6–7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors and early angiography (*JACC* 2003;41:89S)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		
RISK SCORE = Total points	**(0–7)**		

Figure 1-2 Approach to UA/NSTEMI



STEMI

Requisite STE (at J point)

- ≥2 contiguous leads w/ ≥1 mm (except for V_2–V_3: ≥2 mm in ♂ and ≥1.5 mm in ♀), or
- New or presumed new LBBB w/ compelling H&P, or
- True posterior MI: ST depression V_1–V_3 ± tall Rw w/ STE on posterior leads (V_7–V_9)

Reperfusion ("time is muscle")

- In PCI-capable hospital, goal should be primary PCI w/in 90 min of 1st medical contact
- In non–PCI-capable hospital, consider *transfer* to PCI-capable hospital (see below), o/w fibrinolytic therapy w/in 30 min of hospital presentation
- Do not let decision regarding *method* of reperfusion delay *time* to reperfusion

Primary PCI (*JACC* 2013;61:e78 & 2016;67:1235)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- Indic: STE + sx onset w/in <12 h; ongoing ischemia 12–24 h after sx onset; shock
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↓ ICH (*Lancet* 2003;361:13)
- *Transfer* to center for 1° PCI superior to lysis (*NEJM* 2003;349:733), see below
- Routine thrombus aspiration: no benefit, ↑ stroke (*Lancet* 2015;387:127; 2015;372:1389)
- Consider PCI of non-culprit lesions at time of primary PCI or planned staged procedure because appears to ↓ MACE vs. culprit alone (*NEJM* 2013;369:1115; *JACC* 2015;65:963); but may harm if cardiogenic shock (*NEJM* 2018;379:1699)

Fibrinolysis vs. Hospital Transfer for Primary PCI: Assess Time and Risk
1. Time required for transport to skilled PCI lab: door-to-balloon <120 min & [door- to-balloon]–[door-to-needle] <1 h favors transfer for PCI

2.	high-risk Pts (eg, shock) fare better with mechanical reperfusion
3.	Time to presentation: efficacy of lytics ↓ w/ ↑ time from sx onset, espec >3 h
4.	Risk of fibrinolysis: if high risk of ICH or bleeding, PCI safer option

Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529)

Fibrinolysis

- Indic: STE/LBBB + sx <12 h (& >120 min before PCI can be done); benefit if sx >12 h less clear; reasonable if persist. sx & STE, hemodynamic instability or large territory at risk
- Mortality ↓ ~20% in anterior MI or LBBB and ~10% in IMI c/w ⌀ reperfusion Rx
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (*JAMA* 2000;283:2686)
- ~1% risk of ICH; high risk incl elderly (~2% if >75 y), ♀, low wt. ∴ PCI more attractive

Contraindications to Fibrinolysis	
Absolute Contraindications	Relative Contraindications
• Any prior ICH • Intracranial neoplasm, aneurysm, AVM • Ischemic stroke or closed head trauma w/in 3 mo; head/spinal surg. w/in 2 mo • Active internal bleeding or known bleeding diathesis • Suspected aortic dissection • Severe uncontrollable HTN • For SK, SK Rx w/in 6 mo	• H/o severe HTN, SBP >180 or DBP >110 on presentation (? absolute if low-risk MI) • Ischemic stroke >3 mo prior • CPR >10 min; trauma/major surg. w/in 3 wk • Internal bleed w/in 2–4 wk; active PUD • Noncompressible vascular punctures • Pregnancy • Current use of anticoagulants • For SK, prior SK exposure

Nonprimary PCI

- Rescue PCI if shock, unstable, failed reperfusion, or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (*NEJM* 2009;360:2705);
  ∴ *if lysed at non-PCI-capable hosp., consider transfer to PCI-capable hosp. ASAP espec if hi-risk (eg, ant. MI, IMI w/ ↓ EF or RV infarct, extensive STE/LBBB, HF, ↓ BP or ↑ HR)*
- *Late* PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy	
Aspirin 162–325 mg × 1 (crushed/chewed) then 81 mg qd	23% ↓ in death (*Lancet* 1988;ii:349) Should not be stopped if CABG required
$P2Y_{12}$ inhibitor Give ASAP (do not wait for angio) b/c onset inhib delayed in STEMI pts Ticagrelor or prasugrel (if PCI) as detailed above Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd	*Lysis:* clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (*NEJM* 2005;352:1179; *Lancet* 2005;366:1607); no data for pras or ticag w/ lytic *PCI:* prasugrel and ticagrelor ↓ CV events c/w clopi (*Lancet* 2009;373:723 & *Circ* 2010;122:2131) Prehospital ticagrelor may be safe & ? ↓ rate of stent thrombosis (*NEJM* 2014;371:1016)
GP IIb/IIIa inhibitors	*Lysis:* no indication (*Lancet* 2001;357:1905)

abciximab, eptifibatide, tirofiban	*Peri-PCI:* 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

Adapted from ACC/AHA 2013 STEMI Guidelines Update (*Circ* 2013;127:529); *Lancet* 2013;382:633

Anticoagulant Therapy (choose one)	
UFH 60 U/kg IVB (max 4000 U) 12 U/kg/h (max 1000 U/h initially)	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics Titrate to aPTT 1.5–2× control (~50–70 sec)
Enoxaparin *Lysis:* 30 mg IVB → 1 mg/kg SC bid (adjust for age >75 & CrCl) *PCI:* 0.5 mg/kg IVB	*Lysis:* 17% ↓ D/MI w/ ENOX × 7 d vs. UFH × 2 d (*NEJM* 2006;354:1477) *PCI:* ↓ D/MI/revasc and ≈ bleeding vs. UFH (*Lancet* 2011;378:693)
Bivalirudin 0.75 mg/kg IVB → 1.75 mg/kg/hr IV	*PCI:* similar bleeding, ± ↑ MI, ↑ stent thromb (*Lancet* 2014;384:599; *NEJM* 2017;377:1132)

Fondaparinux can be used (if CrCl >30 mL/min) in setting of lysis, where superior to UFH w/ less bleeding (*JAMA* 2006;295:1519). Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529; *Lancet* 2013;382:633)

LV failure (occurs in ~25%)

- Diurese to achieve PCWP ~14 → ↓ pulmonary edema, ↓ myocardial O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand. Can use IV NTG or nitroprusside (although risk of coronary steal) → short-acting ACEI.
- Inotropes if HF despite diuresis & ↓ afterload; use dopamine, dobutamine, or milrinone
- Cardiogenic shock (~7%) = MAP <60 mmHg, CI <2.2 L/min/m^2, PCWP >18 mmHg.
  - If not done already, coronary revasc (*NEJM* 1999;341:625)
  - Support w/ inotropes or mechanical circulatory support to keep CI >2
    - Intraaortic balloon pump (IABP) counterpulsation offers ~0.5 L/min CO and ↑ coronary perfusion, but no survival benefit if early revasc (*NEJM* 2012;367:1287)
    - Axial flow pumps (eg, Impella) offer up to 3–5 L/min CO, but no data that improves clinical outcomes (*JACC* 2017;69:278)

IMI complications (*Circ* 1990;81:401; *NEJM* 1994;330:1211; *JACC* 2003;41:1273)

- Heart block: ~20%, occurs in part because RCA typically supplies AV node
  - 40% on present., 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly
  - Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- RV infarct: proximal RCA occlusion → ↓ flow to RV marginals
  - Angiographically present in 30–50% of cases, but only ~$^1/_2$ clinically significant
  - HoTN; ↑ JVP, ⊕ Kussmaul's; ≥1 mm STE in V_4R; RA/PCWP ≥0.8; RV dysfxn on TTE
  - Rx: optimize preload (RA goal 10–14 mmHg; *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (IABP or RVAD); pulmonary vasodilators (eg, inhaled NO)

Mechanical complications (incid. <1% for each; typically occur a few days post-MI)

- Free wall rupture: ↑ risk w/ lysis, large MI, ↑ age, ♀, HTN; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, surgery
- VSD: large MI in elderly; AMI → apical VSD, IMI → basal septum; 90% w/ harsh

murmur ± thrill (*NEJM* 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP, surgery, perc. closure

- Papillary muscle rupture: more common after IMI (PM pap m. supplied by PDA alone) than AMI (AL supplied by OMs & diags); 50% w/ new murmur; ↑ *v* wave in PCWP tracing; asymmetric pulmonary edema on CXR. Rx: diuretics, vasodilators, IABP, surgery.

Arrhythmias post-MI (treat all per ACLS protocols if unstable or symptomatic)

- AF (10–16% incidence): βB or amio, ± digoxin (particularly if HF), heparin
- VT/VF: lido or amio × 6–24 h, then reassess; ↑ βB as tol., replete K & Mg, r/o ischemia; VT <48 h post-MI does *not* worsen prognosis; >48 h, consider ICD (see below)
- Accelerated idioventricular rhythm (AIVR): slow VT (<100 bpm), often seen after successful reperfusion; typically asx, self-terminates, and does not require treatment
- Backup transcutaneous *or* transvenous pacing if: 2° AVB type II; BBB + AVB
- Transvenous pacing if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB

Other Post-MI Complications		
Complication	Clinical Features	Treatment
LV thrombus	~30% incid. (espec lg antero-apical MI)	Anticoagulate × 3–6 mo
Ventricular aneurysm	Noncontractile outpouching of LV; 8–15% incid. (espec ant); persist STE	Surgery or perc repair if HF, thromboemboli, arrhythmia
Ventricular pseudoaneurysm	Rupture (narrow neck) → sealed by thrombus and pericardium (esp in inf).	Urgent surgery (or percutaneous repair)
Pericarditis	10–20% incid.; 1–4 d post-MI ⊕ pericardial rub; ECG Δs rare	High-dose ASA, colchicine, narcotics; minimize anticoag
Dressler's syndrome	<4% incid.; 2–10 wk post-MI fever, pericarditis, pleuritis	High-dose aspirin, NSAIDs

Prognosis

- In registries, in-hospital mortality is 6% w/ reperfusion Rx (lytic or PCI) and ~20% w/o
- TIMI Risk Score for STEMI (includes age, time to Rx, anterior MI or LBBB, Killip class, tachycardia, HoTN) defines 30-d mortality after STEMI (*JAMA* 2001;286:1356)

CHECKLIST AND LONG-TERM POST-ACS MANAGEMENT

Risk stratification

- Stress test if anatomy undefined; consider stress if signif residual CAD post-PCI of culprit
- Assess LVEF prior to d/c; EF ↑ ~6% in STEMI over 6 mo (*JACC* 2007;50:149)

Medications (barring contraindications)

- Aspirin: 81 mg daily (no clear benefit to higher doses)
- $P2Y_{12}$ inhib (ticagrelor or prasugrel preferred over clopi): treat for *at least* 12 mo

  Prolonged Rx >12 mo → ↓ MACE & CV death, ↑ in bleeding, but no ↑ ICH. Beyond 1st 12 mo, ticag 60 bid preferred to 90, b/c better tolerability (*NEJM* 2015;372:1791; *EHJ* 2016;37:390).

  PPIs ↓ GI complic; some PPIs ↓ antiplt effect, but no clear ↑ in CV risk (*NEJM* 2010;363:1909)

- **β**-blocker: 23% ↓ mortality after MI
- LDL-C management: benefit with lowering LDL-C to <<40 mg/dl (*Lancet* 2017;390:1962)
  Statin: high-intensity (eg, atorva 80 mg, PROVE-IT TIMI 22, *NEJM* 2004;350:1495)
  Ezetimibe: ↓ CV events when added to statin (IMPROVE-IT, *NEJM* 2015;372:1500)
  PCSK9 inhibitor: ↓ CV events when added to statin (*NEJM* 2017;376:1713; 2018;379:2097)
- ACEI: lifelong if HF, ↓ EF, HTN, DM; 4–6 wk or at least until hosp. d/c in all STEMI
  ? long-term benefit in CAD w/o HF (*NEJM* 2000;342:145 & 2004;351:2058; *Lancet* 2003;362:782)
- Aldosterone antag: 15% ↓ mort. if EF <40% & either s/s of HF or DM (*NEJM* 2003;348:1309)
- Nitrates: standing if symptomatic; SL NTG prn for all
- Ranolazine: ↓ recurrent ischemia, no impact on CVD/MI (*JAMA* 2007;297:1775)
- Oral anticoag: if needed (eg, AF, LV thrombus), consider DOAC instead of warfarin; some data for reduced-dose DOAC but unclear if ischemic stroke prevention adeq. (*NEJM* 2016; 375:2423 & 2017;377:1513). Clopi (not ticag or pras). Stopping ASA (? after ~1 wk) ↓ bleed risk by 40–50%, but trend small ↑ MI & stent thromb. (*Lancet* 2013;381:1107; *NEJM* 2019;379:1509).
- In Pts w/o indic. for anticoag, once DAPT completed, rivaroxaban 2.5 bid + ASA ↓ MACE & CV death and ↑ bleeding vs. ASA monoRx (*NEJM* 2017;377:1319)

ICD (*NEJM* 2008;359:2245; *Circ* 2014;130:94)

- Sust. VT/VF >2 d post-MI w/o revers. isch; ? ↓ death w/ *wearable* defib (*NEJM* 2018;379:1205)
- 1° prevention of SCD if post-MI EF ≤30–40% (NYHA II–III) or ≤30–35% (NYHA I); wait 40 d after MI (*NEJM* 2004;351:2481 & 2009;361:1427)

Risk factors and lifestyle modifications (*Circ* 2014;129(Suppl 2):S1 & S76)

- Low chol. (<200 mg/d) & fat (<7% saturated) diet; ? Ω-3 FA.
- LDL-C at least <70 mg/dl (& ≥50% ↓ in LDL-C) (*Circ* 2019;139:e1082)
- BP <130/80 (*JACC* 2018;71:e127); quit smoking
- If diabetic, tailor HbA1c goal based on Pt (avoid TZDs and saxa if HF); GLP1-RA & SGLT2i ↓ MACE & SGLT2i ↓ hospitalization for HF (*Lancet* 2019;393:31 & *Circ* 2019;139:2022)
- Exercise (30–60′ 5–7×/wk) 1–2 wk after revasc; cardiac rehab; BMI goal 18.5–24.9 kg/m^2
- Influenza & *S. pneumo* vaccines (*JAMA* 2013;310:1711; *NEJM* 2018;378:345); ✔ for depression

PA CATHETER AND TAILORED THERAPY

Rationale

- Cardiac output (CO) = SV × HR; optimize SV (and thereby CO) by manipulating preload/ LVEDV (w/ IVF, diuretics), contractility (w/ inotropes), & afterload (w/ vasodilators)
- Balloon at catheter tip inflated → floats into "wedge" position. Column of blood extends from tip of catheter, through pulm venous circulation to a point just prox to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
  (1) Catheter tip not in West lung zone 3 (and ∴ PCWP = alveolar pressure ≠ LA pressure); clues include lack of *a* & *v* waves and if PA diastolic pressure < PCWP
  (2) PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
  (3) Mean LA pressure > LVEDP (eg, MR, MS)
  (4) Δ LVEDP-LVEDV relationship (ie, abnl compliance, ∴ "nl" LVEDP may not be optimal)

Indications (*Circ* 2009;119:e391; *NEJM* 2013;369:e35)

- Diagnosis and evaluation
  Ddx of shock (cardiogenic vs. distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs. not; espec if trial of diuretic failed or is high risk)
  Evaluation of CO, intracardiac shunt, pulm HTN, MR, tamponade, cardiorenal syndrome
  Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)
- Therapeutics (*Circ* 2006;113:1020)
  Tailored therapy to optimize PCWP, SV, $S_{MV}O_2$, RAP, PVR in heart failure or shock
  Guide to vasodilator therapy (eg, inhaled NO, nifedipine) in PHT, RV infarction
  Guide periop mgmt in some high-risk Pts, candidacy for mech circ support & transplant
- Contraindications
  Absolute: right-sided endocarditis, thrombus/mass or mechanical valve; proximal PE
  Relative: coagulopathy (reverse), recent PPM or ICD (place under fluoroscopy), LBBB (~5% risk of RBBB → CHB, place under fluoro), bioprosthetic R-sided valve

Efficacy concerns (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine PAC use in high-risk surgery, sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~$^1/_2$ of *clinical* CO & PCWP estimates incorrect; CVP & PCWP not well correl.; ∴ use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

Placement (*NEJM* 2013;369:e35)

- Insertion site: R internal jugular or L subclavian veins for "anatomic" flotation into PA
- Inflate balloon (max 1.5 mL) when advancing and to measure PCWP
- Use resistance to inflation and pressure tracing to avoid overinflation & risk of PA rupture
- Deflate the balloon when withdrawing and at all other times
- CXR should be obtained after placement to assess for catheter position and PTX
- If catheter cannot be floated (i.e., severe TR, RV dilatation), consider fluoroscopic guidance

Complications

- Central venous access: pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- Advancement: atrial or ventricular arrhythmias (3% VT; 20% NSVT and >50% PVC), RBBB (5%), catheter knotting, cardiac perforation/tamponade, PA rupture
- Maintenance: infection (espec if catheter >3 d old), thrombus, pulm infarction (≤1%), valve/chordae damage, PA rupture/pseudoaneurysm (espec w/ PHT), balloon rupture

Intracardiac pressures

- Transmural pressure (≈ preload) = measured intracardiac pressure – intrathoracic pressure
- Intrathoracic pressure (usually slightly ⊖) is transmitted to vessels and heart
- Always measure intracardiac pressure at end-expiration, when intrathoracic pressure closest to 0 ("high point" in spont. breathing Pts; "low point" in Pts on ⊕ pressure vent.)
- If ↑ intrathoracic pressure (eg, PEEP), measured PCWP *overestimates* true transmural pressures. Can approx by subtracting ~1/2 PEEP (× ¾ to convert cm H_2O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulmonary edema from avg PCWP

Cardiac output

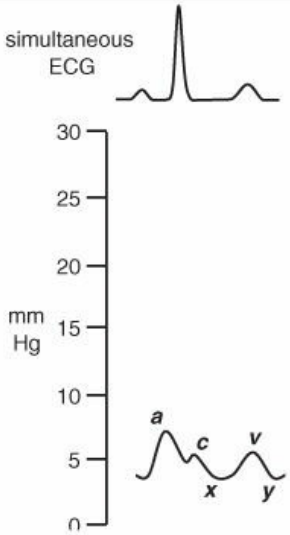
- Thermodilution: saline injected in RA or prox thermal filament. Δ in temp over time measured at thermistor (in PA) used to calc CO. Inaccurate if ↓ CO, sev TR, or shunt.
- Fick method: O_2 consumption $\dot{V}O_2$ (L/min) = CO (L/min) × Δ arteriovenous O_2 content

  ∴ CO = $\dot{V}O_2$ / C(a-v)O_2

  $\dot{V}O_2$ ideally measured (esp. if ↑ metab demands), but freq estimated (125 mL/min/m^2)

  C(a-v)O_2 = [10 × 1.36 mL O_2/g of Hb × Hb g/dL × (S_aO_2 – $S_{MV}O_2$)]. *$S_{MV}O_2$ is key var that Δs.*

  If $S_{MV}O_2$ >80%, consider if the PAC is "wedged" (ie, pulm vein sat), L→R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), ↑↑ FiO_2.

PA Catheter Waveforms				
Location	**RA**	**RV**	**PA**	**PCWP**
Distance	~20 cm	~30 cm	~40 cm	~50 cm
Normal Pressure (mmHg)	mean ≤6	syst 15–30 diast 1–8	syst 15–30 mean 9–18 diast 6–12	mean ≤12
Waves				
Comment	*a* = atrial contraction, occurs in PR interval *c* = bulging of TV back into RA at start of systole *x* = atrial relaxation and descent of base of heart *v* = blood entering RA, occurs mid T wave *y* = blood exiting RA after TV opens at start of diastole	RVEDP occurs right before upstroke and ≥ mean RA pressure unless there is TS or TR	Waveform should contain notch (closure of pulmonic valve). Peak *during* T wave. PA systolic = RV systolic unless there is a gradient (eg, PS). PA diastolic ≈ PCWP unless ↑ trans-pulm gradient (eg, ↑ PVR).	Similar to RA except *dampened* and *delayed*. *a* wave *after* QRS, ± distinct *c* wave, *v* wave *after* T (helps distinguish PCWP w/ large *v* waves 2° MR from PA).

PCWP waveform abnormalities: large *a* wave → ? mitral stenosis; large *v* wave → ? mitral regurgitation; blunted *y* descent → ? tamponade; steep *x* & *y* descents → ? constriction.

Hemodynamic Profiles of Various Forms of Shock (*NEJM* 2013;369:1726)				
Type of Shock	**RA**	**PCWP**	**CO**	**SVR**
Hypovolemic	↓	↓	↓	↑
Cardiogenic	nl or ↑	↑	↓	↑
RV infarct/massive PE	↑	nl or ↓	↓	↑
Tamponade	↑	↑	↓	↑
Distributive	variable	variable	usually ↑ (can be ↓ in sepsis)	↓

Surrogates: RA ≈ JVP (1 mmHg = 1.36 cm H_2O); pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2–3 sec) implies ↑ SVR

Tailored therapy in cardiogenic shock (*Circ* 2009;119:e391)

- Goals: optimize both MAP and CO while ↓ risk of pulmonary edema

MAP = CO × SVR; CO = HR × SV (which depends on preload, afterload, and contractility)
pulmonary edema when PCWP >20–25 (↑ levels may be tolerated in chronic HF)
hepatic and renal congestion when CVP/RAP >15 mmHg

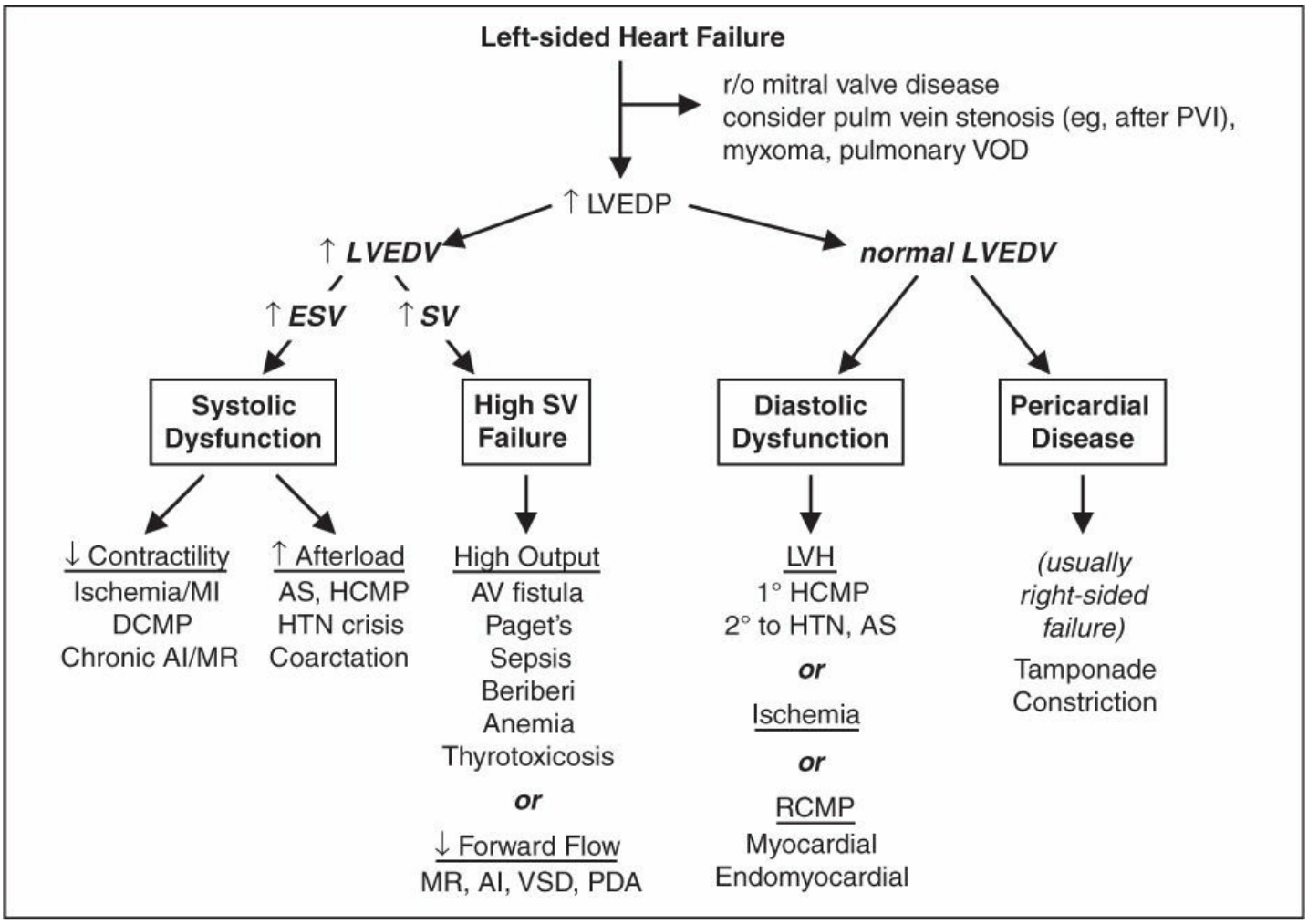
- Optimize preload = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (*NEJM* 1973;289:1263)
  goal PCWP ~14–18 in acute MI, ≤14 in acute decompensated HF
  optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve
  ↑ by giving NS (albumin w/o clinical benefit over NS; PRBC if significant anemia)
  ↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics
- Optimize afterload ≈ wall stress during LV ejection = [(~SBP × radius) / (2 × wall thick.)] and ∴ ∝ MAP and ∝ SVR = (MAP – CVP / CO); goals: MAP >60, SVR 800–1200
  MAP >60 & SVR ↑: vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors
  MAP <60 & SVR ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below)
  MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α] or vasopressin [V_1] if refractory); better outcomes w/ norepi than dopa even in cardiogenic shock (*NEJM* 2010;362:779)
- Optimize contractility ∝ CO for given preload & afterload; goal CI = (CO / BSA) >2.2
  if too low despite optimal preload & vasodilators (as MAP permits):
  ⊕ *inotropes:* eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl pulm), both proarrhythmic, or epi (strong inotrope & pressor)
  mech circulatory support (L/min): IABP (0.5), Impella (2–5), TandemHeart (5), VAD (L-sided, R-sided or both; temp or perm; 10) or ECMO (6) (*JACC* 2015;65:e7 & 2542)

HEART FAILURE

Definitions (*Braunwald's Heart Disease*, 11th ed., 2019)

- Failure of heart to pump blood forward at rate sufficient to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output (↓ cardiac output) vs. high output (↑ stroke volume ± ↑ cardiac output)
- Left-sided (pulmonary edema) vs. right-sided (↑ JVP, hepatomegaly, peripheral edema)
- Backward (↑ filling pressures, congestion) vs. forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs. diastolic (failure to relax and fill normally)
- Reduced (HFrEF, EF <40%), mid-range (HFmrEF, EF 40–49%), & preserved (HFpEF, EF >50%); combination of systolic and diastolic dysfxn may occur regardless of EF

Figure 1-3 Approach to left-sided heart failure



History

- Low output: fatigue, weakness, exercise intolerance, Δ MS, anorexia
- Congestive: left-sided → dyspnea, orthopnea, paroxysmal nocturnal dyspnea
  right-sided → peripheral edema, RUQ discomfort, bloating, satiety

Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity; class III: sx w/ minimal activity; class IV: sx at rest

Physical exam ("2-minute" hemodynamic profile; *JAMA* 1996;275:630 & 2002;287:628)

- Congestion ("dry" vs. "wet"): ↑ JVP (~80% of the time JVP >10 → PCWP >22)
  - ⊕ hepatojugular reflux: ≥4 cm ↑ in JVP for ≥15 sec w/ abdominal pressure Se/Sp 73/87% for RA >8 and Se/Sp 55/83% for PCWP >15 (*AJC* 1990;66:1002)
  - Abnl Valsalva response: square wave (↑ SBP w/ strain), no overshoot (no ↑ BP after strain)
  - S_3 (in Pts w/ HF → ~40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;345:574)
  - rales, dullness at base 2° pleural effus. (*often absent* in chronic HF due to lymphatic compensation) ± hepatomegaly, ascites and jaundice, peripheral edema
- Perfusion ("warm" *vs.* "cold")
  - narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; *JAMA* 1989;261:884);
  - soft S_1 (↓ dP/dt), pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- ± Other: Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S_4 (diast. dysfxn), murmur (valvular dis., ↑ MV annulus, displaced papillary muscles)

Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines; lung U/S better than CXR (PPV & NPV 92% vs. 77%; *Chest* 2015;148:202)
- BNP/NT-proBNP can help exclude HF; levels ↑ w/ age, renal dysfxn, AF; ↓ w/ obesity Se ≥95%, Sp: ~50%, PPV ~65%, NPV ≥ 94% for HF in Pts p/w SOB (*BMJ* 2015;350:h910)
- Evidence of ↓ organ perfusion: ↑ Cr, ↓ Na, abnl LFTs
- Echo (see inserts): ↓ EF & ↑ chamber size → systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler → ? diastolic dysfxn; abnl valves or pericardium; ↑ estimated RVSP
- PA catheterization: ↑ PCWP, ↓ CO, and ↑ SVR (in low-output failure)

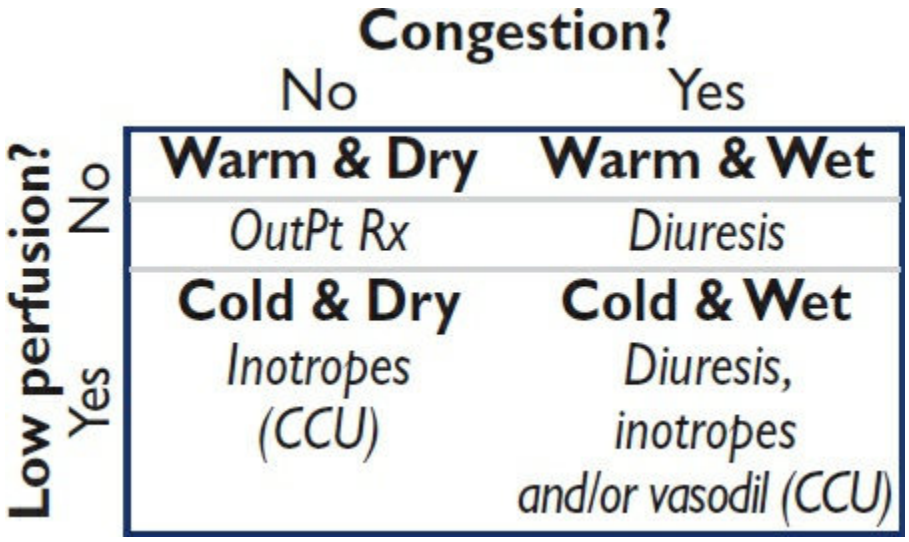
Evaluation for the potential causes of heart failure

- ECG: evidence for CAD, LVH, LAE, heart block or low voltage (? infiltrative CMP/DCMP)
- TTE: LV & RV size & fxn, valve abnl (cause or consequence?), infiltrative or pericardial dis.
- Cardiac MRI: distinguishes ischemic vs. nonischemic and can help determine etiol. of latter
- Coronary angio (or noninvasive imaging, eg, CT angio); if no CAD, w/u for NICM

Precipitants of acute heart failure

- Dietary indiscretion or medical nonadherence (~40% of cases)

- Myocardial ischemia or infarction (~10–15% of cases); myocarditis
- Renal failure (acute, progression of CKD, or insufficient dialysis) → ↑ preload
- Hypertensive crisis (incl. from RAS), worsening AS → ↑ left-sided afterload
- Drugs (βB, CCB, NSAIDs, TZDs), chemo (anthracyclines, trastuzumab), or toxins (EtOH)
- Arrhythmias; acute valvular dysfxn (eg, endocarditis), espec mitral or aortic regurgitation
- COPD/PE → ↑ right-sided afterload; extreme stress; anemia; systemic infxn; thyroid dis.



Rx of acute decompens. HF (*NEJM* 2017;377:1964)

- Assess degree of congestion & adequacy of perfusion
- For congestion: "LMNOP"
  - Lasix IV; total daily dose 2.5× usual daily PO dose → ↑ UOP, but transient ↑ in Cr vs. 1× usual dose; ∅ clear diff between contin. gtt vs. q12h (*NEJM* 2011;364:797)
  - Morphine (↓ sx, venodilator, ↓ afterload)
  - Nitrates (venodilator)
  - Oxygen ± noninvasive vent (↓ sx, ↑ P_aO_2; no Δ mortality; see "Mechanical Ventilation")
  - Position (sitting up & legs dangling over side of bed → ↓ preload)
- For low perfusion, see below
- Adjustment of oral meds
  - ACEI/ARB: hold if HoTN, consider Δ to hydralazine & nitrates if renal decompensation
  - βB: reduce dose by at least $^1/_2$ if mod HF, d/c if severe HF and/or need inotropes

Treatment of acute advanced heart failure (*Circ* 2009;119:e391)

- Consider PAC if not resp to Rx, unsure re: vol status, HoTN, ↑ Cr, need inotropes
- Tailored Rx w/ PAC (qv); goals of MAP >60, CI >2.2 (MVO_2 >60%), SVR <800, PCWP <18
- IV vasodilators: NTG, nitroprusside (risk of coronary steal if CAD)
- Inotropes (properties in addition to ↑ inotropy listed below)

dobutamine: vasodilation at doses ≤5 μg/kg/min; mild ↓ PVR; desensitization over time
dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrictor at ≥5 μg/kg/min
milrinone: prominent systemic & pulmonary vasodilation; ↓ dose by 50% in renal failure

- Mechanical circulatory support (also see "Tailored Therapy;" *JACC* 2015;65:e7 & 2542)
  Temporary: bridge to recovery, transplant, or durable MCS; periprocedural support
  Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to ↓ impedance to LV ejection, ↓ myocardial O_2 demand & ↑ coronary perfusion. +0.5 L/min CO
  Axial flow pumps (eg, Impella): Archimedes screw principle in LV; +2.5–5 L/min
  Extracorporeal centrifugal pumps: TandemHeart (+5 L/min, percutaneous) & CentriMag (10 L/min, surgical)
  Extracorporeal membrane oxygenation (ECMO): 6 L/min (*JACC HF* 2018;6:503)
  Durable: surgically placed LVAD ± RVAD as bridge to sufficient recovery (in 5–50% of niCMP; *JACC* 2017;69:1924), to transplant or as destination Rx (>50% ↓ 1-y mort. vs. med Rx; *NEJM* 2001;345:1435 & 2009;361:2241). Fully magnetically levitated centrifugal flow pump (HeartMate 3) ↓ stroke or re-op vs. axial flow HeartMate II (*NEJM* 2019;380:1618); HeartWare LVAD another centrifugal option (*NEJM* 2017;376:451).
- Cardiac transplantation: ~2500/yr in U.S. 10% mort. in 1st y, median survival ~10 y

Recommended Chronic Therapy by HF Stage (*Circ* 2009;119:e391)		
Stage (not NYHA Class)		Therapy
A	At risk for HF (eg, HTN, FHx CMP); but asx & w/o struct. heart dis.	Rx HTN, lipids, DM. Stop smoking, EtOH. ↑ exercise. ACEI/ARB if HTN/DM/CAD/PAD
B	⊕ Struct. heart dis. (eg, CMP, LVH), but asx	As per stage A + ACEI/ARB & βB if MI/CAD or ↓ EF. ? ICD.
C	⊕ Struct. heart dis. ⊕ Any h/o Sx of HF	As per stage A + diuretics, ↓ Na. If ↓ EF: ACEI, ARB or ARNI; βB; aldo antag; ICD; ? CRT; nitrate/hydral; dig.
D	Refractory HF requiring specialized interventions	All measures for stages A–C. Consider IV inotropes, VAD, transplant, end-of-life care (4-y mortality >50%)

- Utility of BNP-guided Rx (inPt and outPt) remains debated (*Eur Heart J* 2014;35:16)
- Implantable PA pressure sensor in NYHA III → ~33% ↓ risk of hosp (*Lancet* 2016;387:453)

Treatment of Chronic HF with Reduced EF (*JACC* 2017;70:776)	
Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
BP	Goal <130/80 (*JACC* 2018;71:127)
ACEI	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20–30% in asx but ↓ EF (*NEJM* 1992;327:685; *Lancet* 2000;355:1575) High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, K binders), cough, angioedema.
ATII receptor blockers (ARBs)	*Consider as alternative if cannot tolerate ACEI (eg, b/c cough)* Noninferior to ACEI (*Lancet* 2000;355:1582 & 2003;362:772) As with ACEI, higher doses more efficacious (*Lancet* 2009;379:1840)

	Adding to ACEI → ↑ risk of ↑ K and ↑ Cr (*BMJ* 2013;346:f360)
ARNI (ARB + neprilysin inhib) *(do not use w/ ACEI, allow 36-h washout)*	*Preferred RAAS inhib in NYHA II-IV*. Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides, bradykinin & angiotensins. Valsartan + sacubitril (NEPi) ↓ CV mort & HF hosp c/w ACEi; ↑ HoTN, AKI (*NEJM* 2014;371:993 & 2019;380:539). Contraindicated if h/o angioedema.
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in blacks w/ class III/IV* 25% ↓ mort. (*NEJM* 1986;314:1547); infer. to ACEI (*NEJM* 1991;325:303) 40% ↓ mort. in blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)
β-blocker (data for carvedilol, metoprolol, bisoprolol)	*EF will transiently ↓, then ↑. Contraindic. in decompensated HF.* 35% ↓ mort. & 40% ↓ rehosp. in NYHA II–IV (*JAMA* 2002;287:883) Carvedilol superior to low-dose metop in 1 trial (*Lancet* 2003;362:7), but meta-analysis suggests no diff between βB (*BMJ* 2013;346:f55).
Aldosterone antagonists	*Consider if adeq. renal fxn and w/o hyperkalemia; watch for ↑ K* 25–30% ↓ mort. in NYHA II–IV & EF ≤35% (*NEJM* 2011;364:11) 15% ↓ mort. in HF post-MI, EF ≤40% (EPHESUS, *NEJM* 2003;348:1309)
Cardiac resynch therapy (CRT, qv)	*Consider if EF ≤35%, LBBB (QRS ≥130 ms) and symptomatic HF* 36% ↓ mort. & ↑ EF in NYHA III–IV (CARE-HF, *NEJM* 2005;352:1539) 41% ↓ mort. if EF ≤30%, LBBB and NYHA I/II (*NEJM* 2014;370:1694)
ICD (see "Cardiac Rhythm Mgmt Devices")	*For 1° prevention if EF ≤30–35%* or *2° prevention; not if NYHA IV* ↓ mort. in ischemic CMP but perhaps only SCD in modern era in niCMP (*NEJM* 2005;352:225 & 2016;375:1221)
Diuretics	Loop ± thiazides diuretics (sx relief; no mortality benefit)
Digoxin	23% ↓ HF hosp., no Δ mort (*NEJM* 1997;336:525); ? ↑ mort w/ ↑ levels (*NEJM* 2002;347:1403); optimal 0.5–0.8 ng/mL (*JAMA* 2003;289:871)
Ivabradine (I_f blocker w/o ⊖ ino)	*Consider if EF ≤35%, NYHA II or III, HR ≥70, NSR on max βB.* 18% ↓ CV mort or HF hosp (*Lancet* 2010;376:875)
Iron supplementation	*? IV (not PO) if NYHA II/III, EF ≤40%, Fe-defic* (ferritin <100 or 100–300 & TSAT <20%). ↑ QoL independent of Hct (*NEJM* 2009;361:2436).
Anticoagulation	*If AF, VTE, LV thrombus*, ± *if large akinetic LV segments.* In SR w/ rEF, ↓ isch stroke, but ↑ bleed (*NEJM* 2012;366:1859 & 2018;379:1332).
Heart rhythm	If AF & NYHA II-IV w/ EF <35%, catheter ablation ↓ D/HF hosp vs. med Rx (rate or rhythm; *NEJM* 2018;378:417)
Other	SGLT2i ↓ death/HF hosp in DM (*Lancet* 2019;393:31)
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs

(*Circ* 2013;128:e240 & 2016;134:e282; *EHJ* 2016;37:2129)

Heart failure with preserved EF (HFpEF; "Diastolic HF") (*NEJM* 2016;375:1868)

- Epidemiology: ~$^1/_2$ of Pts w/ HF have normal or only min. impaired systolic fxn (EF ≥40%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mortality ≈ to those w/ systolic dysfxn.
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCMP, infiltrative CMP, RCMP, aging, hypothyroidism
- Precipitants of pulmonary edema: *volume overload* (poor compliance of LV → sensitive to even modest ↑ in volume); *ischemia* (↓ relaxation); *tachycardia* (↓ filling time in diastole), *AF* (loss of atrial boost to LV filling); *HTN* (↑ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic fxn. Dx supported by evidence of diast dysfxn:
  (1) echo: abnl MV inflow (E/A reversal and Δs in E wave deceleration time) & ↓

myocardial relax. (↑ isovol relax. time & ↓ early diastole tissue Doppler vel)
(2) exercise-induced ↑ PCWP (± ↓ response chronotropic & vasodilator reserve)

- Treatment: diuresis for vol overload, BP control, prevention of tachycardia and ischemia; no benefit to: ACEI/ARB (*NEJM* 2008;359:2456) or PDE5 inhib (*JAMA* 2013;309:1268); spironolactone ? ↓ CV death & HF hosp (at least in Americas) (*NEJM* 2014;370:1383); ARNi (*JACC Heart Fail* 2017;5:471) under study; transcatheter interatrial shunt reduces PCWP during exercise, ? whether improves sx/outcomes (*Circ* 2017;137:364)

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

DILATED CARDIOMYOPATHY (DCM)

Definition and epidemiology (*Circ* 2013;128:e240; *JACC* 2013;62:2046)

- Ventricular dilatation and ↓ contractility ± ↓ wall thickness *in the absence of myocardial disease caused by ischemia/infarct, valvular disease or hypertension*
- Incidence: 5–8/100,000/y; prevalence: 1/2500. Most common reason for heart transplant.

Etiologies (*JACC* 2011;57:1641; *Circ Res* 2012;111:131)

- Familial (~35%): Pt & ≥2 closely related family members w/ otherwise unexplained DCM; ~30 genes identified to date, encoding structural & nuclear proteins
- Idiopathic (<20%): ? undiagnosed infectious, alcoholic, or genetic cause
- Infectious myocarditis (10–15%; *Lancet* 2012;379:738; *JACC* 2012;59:779)
  - Viruses (parvoB19 & HHV6 > Coxsackie, adeno, echo, CMV, HCV): from subacute (dilated LV, mild–mod dysfxn) to fulminant (nondil., thick, edematous LV, sev dysfxn)
  - Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB)
  - HIV: ~8% of asx HIV ⊕; due to HIV, other virus *or* antiretrovirals; also premature CAD
  - Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*Lancet* 2018;391:82)
- Toxic: alcohol (~20%) typ. 7–8 drinks/d × >5 y, but variable; cocaine; XRT (usu RCMP); anthracyclines (risk ↑ >550 mg/m^2, may manifest late), cyclophosphamide, trastuzumab
- Infiltrative (5%): often mix of DCMP + RCMP (qv) with thickened wall
  amyloidosis, sarcoidosis, hemochromatosis, tumor
- Autoimmune: *collagen vasc. dis.* (3%): PM, SLE, scleroderma, PAN, RA, GPA;
  peripartum (last month → 5 mo postpartum; *EHJ* 2015;36:1090): ~1:3000 preg. ↑ risk w/ multiparity, ↑ age, Afr Am; stnd HF Rx (if preg, no ACEi or spironolact.); ? bromocriptine to ↓ prolactin; 72% normalize EF (*JACC* 2015;66:905); ~30% recur w/ next preg
  - Idiopathic giant cell myocarditis (GCM): avg age 42, fulminant, AVB/VT (*Circ HF* 2013;6:15)
  - Eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; STE, effusion, severe HF)
- Stress-induced (Takotsubo = apical ballooning): typically postmenopausal ♀; mimics MI (chest pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis; ? Rx w/ βB, ACEI; usu. improves over wks (*JAMA* 2011;306:277). In-hosp morb/mort similar to ACS (*NEJM* 2015;373:929).
- Arrhythmogenic right ventricular cardiomyopathy (ACM/ARVC): fibrofatty

replacement of RV → dilation (dx w/ MRI); ECG: ± RBBB, TWI V_1–V_3, ε wave; risk VT (*NEJM* 2017;376:61)
- Tachycardia: likelihood ∝ rate/duration; often resolves w/ rate cntl (*Circ* 2005;112:1092)
- LV noncompaction (*Lancet* 2015;386:813): prominent trabeculae, arrhythmias, cardioemboli
- Metab/other: hypothyroid, acromegaly, pheo, OSA, Vit B_1, selenium or carnitine defic.

Clinical manifestations
- Heart failure: both congestive & poor forward flow sx; signs of L- & R-sided HF
  diffuse, laterally displaced PMI, S3, ± MR or TR (annular dilat., displaced pap. muscle)
- Embolic events (~10%), supraventricular/ventricular arrhythmias, & palpitations
- Chest pain can be seen w/ some etiologies (eg, myocarditis)

Diagnostic studies and workup (*JACC* 2016;67:2996)
- CXR: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- ECG: may see PRWP, Q waves, or BBB; low-voltage; AF (20%); may be normal
- Echocardiogram: LV dilatation, ↓ EF, *regional or global* LV HK ± RV HK, ± mural thrombi
- Cardiac MRI: up to 76% Se, 96% Sp for myocarditis or infiltrative dis. (*JACC Imaging* 2014;7:254); extent of midwall fibrosis correlated w/ mortality in niCMP (*JAMA* 2013;309:896) and may identify Pts w/ EF >40% who benefit from ICD (*Circ* 2017;135:2106)
- Labs: TFTs, Fe panel, HIV, SPEP, ANA; viral sero *not* recommended; others per suspicion
- Family hx (20–35% w/ familial dis.), genetic counseling ± genetic testing (*JAMA* 2009;302:2471)
- Stress test: useful to r/o ischemia (low false ⊖ rate), high false ⊕ rate, even w/ imaging
- Coronary angiography to r/o CAD if risk factors, h/o angina, Qw MI on ECG, equivocal ETT; consider CT angiography (*JACC* 2007;49:2044)
- ? Endomyocardial biopsy (*JACC* 2007;50:1914): yield 10%; of these, 75% myocarditis (for which no proven Rx) & 25% systemic disease; 40% false ⊖ rate (patchy dis.) & false ⊕ (necrosis → inflammation); ∴ biopsy if: acute & hemodyn compromise (r/o GCM, ANEM); arrhythmia or RCMP features (r/o infiltrative); or suspect toxic, allergic, tumor

Treatment (see "Heart Failure" for standard HF Rx)
- Possibility of reversibility of CMP may temper implantation of devices
- Immunosuppression: for giant cell myocarditis (prednisone + AZA), collagen vascular disease, peripartum (? IVIg), & eosinophilic; no proven benefit for viral myocarditis
- Prognosis differs by etiology (*NEJM* 2000;342:1077): postpartum (best), ischemic/GCM (worst)

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Definition and epidemiology
- LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1/500; 50% sporadic, 50% familial, most asymptomatic

- Ddx: LVH 2° to HTN, AS, elite athletes (wall usually <13 mm & symmetric and nl/↑ rates tissue Doppler diastolic relaxation; *Circ* 2011;123:2723), Fabry dis. (↑ Cr, skin findings)

Pathology

- Autosomal dominant mutations in cardiac sarcomere genes (eg, β-myosin heavy chain)
- Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
- Many morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical

Pathophysiology

- LV outflow tract obstruction (LVOTO) in ≥70%: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable, or nonexistent) and papillary muscle displacement. Gradient (∇) worse w/ ↑ contractility (digoxin, β-agonists, exercise, PVCs), ↓ preload (eg, Valsalva maneuver) or ↓ afterload.
- Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and/or abnl mitral leaflets and papillary muscles (pansystolic, ant.-directed regurg. jet)
- Diastolic dysfunction: ↑ chamber stiffness + impaired relaxation
- Ischemia: small vessel dis., perforating artery compression (bridging), ↓ coronary perfusion
- Syncope: Δs in load-dependent CO, arrhythmias

Clinical manifestations (70% are asymptomatic at dx)

- Dyspnea (90%): due to ↑ LVEDP, MR, and diastolic dysfunction
- Angina (25%) even w/o epicardial CAD; microvasc. dysfxn (*NEJM* 2003;349:1027)
- Arrhythmias (AF in 20–25%; VT/VF): palpitations, syncope, sudden cardiac death

Physical exam

- Sustained PMI, S_2 paradoxically split if severe outflow obstruction, ⊕ S_4 (occ. palpable)
- Systolic murmur: crescendo-decrescendo; LLSB; ↑ w/ Valsalva & standing (↓ preload)
- ± mid-to-late or holosystolic murmur of MR at apex
- Bifid carotid pulse (brisk rise, decline, then 2nd rise); JVP w/ prominent *a* wave
- Contrast to AS, which has murmur that ↓ w/ Valsalva and ↓ carotid pulses

Diagnostic studies (*EHJ* 2014;35:2733)

- CXR: cardiomegaly (LV and LA)
- ECG: LVH, anterolateral TWI and inferior pseudo-Qw, ± apical giant TWI (apical variant)
- Echo: any LV wall segment ≥15 mm (or ? even ≥13 if ⊕ HFx), often but not necessarily involving septum; other findings include dynamic outflow obstruction, SAM, MR
- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure ∇; *Brockenbrough sign* = ↓ pulse pressure post-PVC (in contrast to AS, in which pulse pressure ↑ post-PVC); spike & dome Ao pressure pattern
- ? Genotyping for family screening, but pathogenic mutation ID'd in <$^1/_2$ (*Circ* 2011;124:2761)

Treatment (*EHJ* 2014;35:2733; *NEJM* 2018;379:655)

- Heart failure
  - ⊖ inotropes/chronotropes: β-blockers, CCB (verapamil), disopyramide

Careful use of diuretics, because may further ↓ preload. If LVOTO, *avoid vasodilators*. Avoid digoxin b/c ↑ contractility and ∴ outflow obstruction.

If sx refractory to drug Rx + *obstructive* physiology (∇ ≥50 mmHg):

(a) Surgical myectomy: long-term ↓ symptoms in 90% (*Circ* 2014;130:1617)

(b) Alcohol septal ablation (*JACC* 2018;72:3095): ∇ ↓ by ~80%, only 5–20% remain w/ NYHA III–IV sx; 14% require repeat ablation or myectomy. Good alternative for older Pts, multiple comorbidities. Complic: transient (& occ. delayed) 3° AVB w/ 10–20% req. PPM; VT due to scar formation.

No clear benefit of dual-chamber pacing (*JACC* 1997;29:435; *Circ* 1999;99:2927)

If refractory to drug therapy and there is *nonobstructive* pathophysiology: transplant

- Acute HF: can be precip. by dehydration or tachycardia; Rx w/ fluids, βB, phenylephrine
- AF: rate control w/ βB, maintain SR w/ disopyramide or amio; low threshold to anticoag
- ICD if VT/VF. Consider for SCD prevention if: NSVT, ⊕ FHx SCD, unexplained syncope, LV wall ≥30 mm, failure of SBP to ↑ or fall from peak ≥20 mmHg w/ exercise, ? extensive MRI delayed enhancement. EPS *not* useful. HCM Risk-SCD Score (*EHJ* 2014;35:2010): consider ICD if high risk (≥6%/y), may consider if intermediate (4–<6%/y).
- Counsel to avoid dehydration, extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;16:1736)
- 1st-degree relatives: screen w/ TTE q12–18m as teen or athlete then q5y as adult, ECG (because timing of HCMP onset variable). Genetic testing if known mutation.

RESTRICTIVE CARDIOMYOPATHY (RCM)

Definition (*Circ* 2006;113:1807)

- Impaired ventricular filling with ↓ compliance in nonhypertrophied, nondilated ventricles; normal or ↓ diastolic volumes, normal or near-normal EF; must r/o pericardial disease

Etiology (*JACC* 2010;55:1769 & 2016;68:411)

- Myocardial processes

Autoimmune (scleroderma, polymyositis-dermatomyositis)

Infiltrative diseases (see primary entries for extracardiac manifestations, Dx, Rx)

Amyloidosis (*Circ* 2011;124:1079): age at presentation ~60 y; ♂:♀ = 3:2

AL (eg, MM, etc.); familial (transthyretin, ATTR); AA/senile (dep. of TTR, ANP)

ECG: ↓ QRS amplitude (50%), pseudoinfarction pattern (Qw), AVB (10–20%), hemiblock (20%), BBB (5–20%)

Echo: biventricular wall thickening (*yet w/ low voltage on ECG*), granular sparkling (30%), biatrial enlargement (40%), valve thickening, small effusions

Nl voltage/septal thickness has NPV ~90%

Labs: ✔ SPEP/UPEP, serum free light chain ratio (<0.25 or >1.65 κ-to-λ ratio)

MRI: distinct late gadolinium enhancement pattern (*JACC* 2008;51:1022)

Sarcoidosis (can also be DCM): presents at age ~30 y; ↑'d in blacks, N. Europe, ♀ 5% w/ systemic sarcoid have overt cardiac involvement; cardiac w/o systemic in

10%
ECG: AVB (75%), RBBB (20–60%), VT; PET: ↑ FDG uptake in affected area
Echo: regional WMA (particularly basal septum) w/ thinning or mild hypertrophy
Gallium or FDG uptake at areas of inflam.; sestaMIBI w/ non-cor. perfusion defects
Cardiac MRI: T2 early gad (edema); fibrosis/scar in basal septum; LGE prognostic
Cardiac bx low-yield b/c patchy
Hemochromatosis: in middle-aged men (espec N. European); 15% p/w cardiac sx
Diabetes; storage diseases: Gaucher's, Fabry, Hurler's, glycogen storage diseases

- Endomyocardial processes
  Chronic eosinophilic: Löffler's endocarditis (temperate climates; ↑ eos; mural thrombi that embolize); endomyocardial fibrosis (tropical climates; var. eos; mural thrombi)
  Toxins: radiation (also p/w constrictive pericarditis, valvular dis, ostial CAD), anthracyclines
  Serotonin: carcinoid, serotonin agonists, ergot alkaloids. Metastatic cancer.

Pathology & pathophysiology

- Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
- ↓ myocardial compliance → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (*Circ* 2000;101:2490)

- Right-sided > left-sided heart failure with peripheral edema > pulmonary edema
- Diuretic "refractoriness"; thromboembolic events
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP not ↓ w/ inspir., classically seen in *constrict. pericarditis*)
- Cardiac: ± S_3 and S_4, ± murmurs of MR and TR
- Congestive hepatomegaly, ± ascites and jaundice, peripheral edema

Diagnostic studies

- CXR: normal ventricular chamber size, enlarged atria, ± pulmonary congestion
- ECG: low voltage, pseudoinfarction pattern (Qw), ± arrhythmias
- Echo: ± symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit. w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- Cardiac catheterization
  Atria: M's or W's (prominent *x* and *y* descents)
  Ventricles: dip & plateau (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  Concordance of LV & RV pressure peaks during respiratory cycle (vs. discordance in constrictive pericarditis; *Circ* 1996;93:2007)
- Endomyocardial biopsy if suspect infiltrative process; fat pad bx for amyloid
- Restrictive cardiomyopathy vs. constrictive pericarditis: see "Pericardial Disease"

Treatment (in addition to Rx'ing underlying disease)

- Gentle diuresis. May not tolerate CCB or other vasodilators.
- Control HR (but can ↓ CO); maintain SR (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Anticoagulation (particularly with AF or low CO)
- Transplantation for refractory cases
- Tafamidis (TTR binder) ↓ death and CV hosp for TTR amyloid CM (*NEJM* 2018;379:1007)

VALVULAR HEART DISEASE

AORTIC STENOSIS (AS)

Etiology

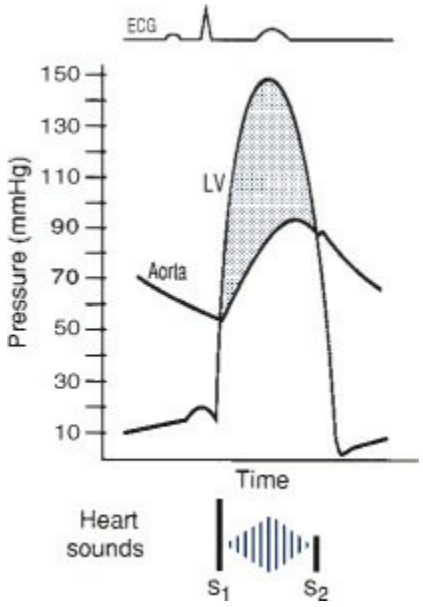
- Calcific: predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- Congenital (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- Rheumatic heart disease (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP, subAo membrane) or supravalvular stenosis

Clinical manifestations (usually indicates AVA <1 cm2 or concomitant CAD)

- Angina: ↑ O_2 demand (hypertrophy) + ↓ O_2 supply (↓ cor perfusion pressure) ± CAD
- Syncope (*exertional*): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- Heart failure: outflow obstruct + diastolic dysfxn → pulm. edema, esp. if ↑ HR/AF (↓ LV fill.)
- Acquired vWF disease (~20% of sev. AS): destruction of vWF; GI angiodysplasia
- Natural hx: usually slowly progressive (AVA ↓ ~0.1 cm^2/y, but varies; *Circ* 1997;95:2262), until sx develop; mean survival based on sx: angina = 5 y; syncope = 3 y; CHF = 2 y

Physical exam

- Midsystolic crescendo-decrescendo murmur at RUSB, harsh, high-pitched, radiates to carotids, apex (holosystolic = Gallavardin effect), ↑ w/ passive leg raise, ↓ w/ standing & Valsalva. Dynamic outflow obstruction (HCM) is the reverse.
- Ejection click after S_1 sometimes heard with *bicuspid* AoV
- Signs of severity: *late-peaking* murmur, paradoxically split S_2 or inaudible A_2, small and delayed carotid pulse ("*pulsus parvus et tardus*"), LV heave, ⊕ S_4 (occasionally palpable)



Pathophys Heart Dis., 6th ed., 2015, for this et al.

Diagnostic studies

- ECG: may see LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- Echo: valve morphology, jet velocity, estim pressure gradient (∇) & calculate AVA, LVEF
- Cardiac cath: usually to *r/o CAD* (in ~$^1/_2$ of calcific AS); for hemodyn. if disparity between exam & echo: ✔ pressure gradient (∇) across AoV, calc AVA (underestim. if mod/sev AR)
- Dobutamine challenge (echo or cath): if low EF and mean ∇ <40, use to differentiate:
  Afterload mismatch: 20% ↑ SV & ∇, no Δ AVA (implies contractile reserve, ↑ EF post-AVR)
  Pseudostenosis: 20% ↑ SV, no Δ in ∇, ↑ AVA (implies low AVA *artifact* of LV dysfxn)
  Limited contractile reserve: no Δ SV, ∇ or AVA (implies EF prob. will not improve w/ AVR)

Classification of Aortic Stenosis (*Circ* 2014;129:e521)						
Stage	**Sx**	**Severity**	**Max Jet Vel (m/s)**	**Mean Grad (mmHg)**	**AVA (cm^2)[a]**	**LVEF**
n/a	N	Normal	1	0	3–4	nl
A	N	At risk	<2	<10	3–4	nl
B	N	Mild	2–2.9	<20	>1.5	nl
		Moderate	3–3.9	20–39	1–1.5	nl
C1	N	Severe	≥4	≥40	≤1.0	nl
		Very severe	≥5	≥60	≤0.8	nl
C2		Severe + ↓ EF	≥4	≥40	≤1.0	↓
D1	Y	Severe	≥4	≥40	≤1.0	nl
D2		Severe + low flow/∇ + ↓ EF[b]	<4	<40	≤1.0	↓
D3		Severe + low flow/∇ + nl EF[c]	<4	<40	≤1.0	nl

[a]AVA indexed to BSA <0.6 cm^2/m^2 also severe; [b]DSE → max jet vel ≥4 & AVA ≤1.0; [c]small LV w/ ↓ stroke vol.

Treatment (*Circ* 2014;129:e521; *Lancet* 2016;387:1312; *JACC* 2017; 69:1313)

- Based on *symptoms:* once they develop, AVR needed.
- AVR: indicated in sx (stage D1); asx severe + EF <50% (stage C2); or severe (stage C1) *and* undergoing other cardiac surgery.
  Reasonable if:
  Asx severe (stage C1) *but* either sx or ↓ BP w/ exercise (can *carefully* exercise asx AS to uncover sx; do *not* exercise sx AS) or very severe
  Sx severe w/ low flow/∇ w/ low EF & response to dobuta (stage D2) or normal EF but AS felt to be cause of sx (stage D3)
  Asx moderate AS (stage B) *and* undergoing cardiac surgery
- Transcatheter AoV replacement (TAVR, see below) attractive alternative to surgery
- Medical (if not AVR candidate or to temporize): careful diuresis prn, control HTN, maintain SR; digoxin if ↓ EF & HF or if AF; *avoid* venodilators (nitrates) & ⊖ inotropes (βB/CCB) if severe AS; avoid vigorous physical exertion once AS mod–severe;
  ? nitroprusside (w/ PAC) in HF w/ sev. AS, ↓ EF/CO, & HTN (*Circ* 2013;128:1349)
- IABP: stabilization, bridge to surgery
- Balloon valvotomy: ↑ AVA, *but* risk of stroke/AR & restenosis; ∴ bridge to AVR or palliation

TAVR (transcatheter AoV replacement) (*JACC* 2017;135:e1159)

- Valves: balloon-expandable or self-expanding. Most commonly deployed retrograde via perc. transfemoral access (best outcomes); also retrograde via axillary art. or ascend. Ao (via small sternotomy & aortotomy). Alternatively, antegrade transapical via small thoracotomy & LV puncture (if narrow iliofemoral artery or calcified Ao).
- Peri- & postprocedural complic.: low CO; annular rupture or coronary occlusion (both rare); stroke; local vascular; paravalvular leaks; CHB (? higher w/ self-expanding valve).
- Post op: lifelong ASA 75–100 mg + clopidogrel 3–6 mo

- Outcomes w/ TAVR. In *nonoperative Pts* (ie, vs. med Rx): 44% ↓ mortality but still ~20% annual mortality in TAVR group (*NEJM* 2012;366:1696; *JACC* 2014;63:1972).
  High-risk Pts (STS predicted 30d surg. mort. >8%) vs. surgical AVR (SAVR): ≈ mortality & ↑ early risk of stroke w/ balloon-expand.; 20–30% ↓ in death or stroke w/ self-expand. (*Lancet* 2015;385:2477; *JACC* 2016;67:2565)
  Medium-risk Pts (predicted 30d-mort. ~4–8%): ≈ death/stroke (? ↓ w/ balloon-expandable via transfemoral) (*NEJM* 2016;374:1609 & 2017;376:1321)
  Low-risk Pts (predicted 30d-mort. <4%): ↓ death or stroke (*NEJM* 2019;380:1695 & 1706)
  TAVR w/ ↑ vasc. complic. but ↓ bleeding, AKI, AF; need for PPM in ~25% w/ self-expand.
  Mod/severe paravalvular AI in 5–10% at 2 y, ~14% at 5 y (may be lower in lower risk Pts). Repositionable valve has rate <1% at 1 y, but ~40% rate of PPM (*JAMA* 2018;319:27).

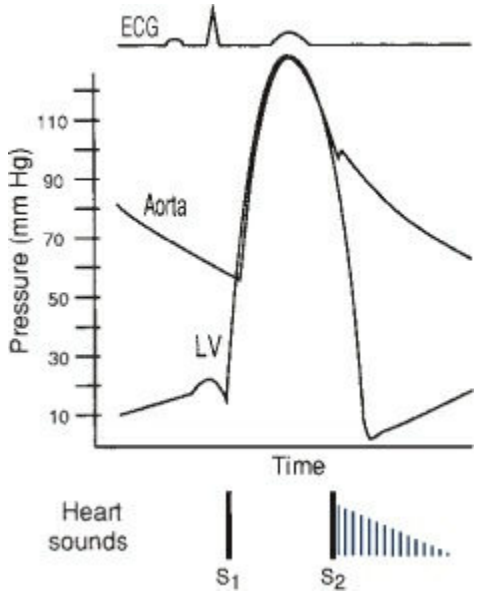
AORTIC REGURGITATION (AR)

Etiology (*Circ* 2006;114:422)

- Valve disease (43%): rheumatic heart disease (usually mixed AS/AR + MV disease); bicuspid AoV (natural hx: $^1/_3$ → normal, $^1/_3$ → AS, $^1/_6$ → AR, $^1/_6$ → endocarditis → AR); infective endocarditis; valvulitis (RA, SLE, certain anorectics & serotonergics, XRT)
- Root disease (57%): HTN, aortic aneurysm/dissection, annuloaortic ectasia (ie, Marfan), aortic inflammation (GCA, Takayasu's, ankylosing spond., reactive arthritis, syphilis)

Clinical manifestations

- Acute: sudden ↓ forward SV and ↑ LVEDP (noncompliant ventricle) → pulmonary edema ± hypotension and cardiogenic shock
- Chronic: clinically silent while LV dilates (to ↑ compliance to keep LVEDP low) more than it hypertrophies → chronic volume overload → LV decompensation → CHF
- Natural hx: *variable* progression (unlike AS, can be fast or slow); once decompensation begins, prognosis poor w/o AVR (mortality ~10%/y)



Physical exam

- Early diastolic decrescendo murmur at LUSB (RUSB if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); *Austin Flint murmur:* mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- Wide pulse pressure due to ↑ stroke volume, hyper-dynamic pulse; pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- PMI diffuse and laterally displaced; soft S_1 (early closure of MV); ± S_3 (≠ ↓ EF but rather just volume overload in AR)

Classic Eponymous Signs in Chronic AR (*South Med J* 1981;74:459)	
Sign	Description
Corrigan's pulse	"water hammer" pulse (ie, rapid rise/fall or distention/collapse)
Hill's sign	(popliteal SBP – brachial SBP) >60 mmHg
Duroziez's sign	to-and-fro murmur heard over femoral artery w/ light compression
Pistol shot sounds	pistol shot sound heard over femoral artery
Traube's sound	double sound heard over femoral artery when compressed distally
de Musset's sign	head-bobbing with each heartbeat (low Se)
Müller's sign	systolic pulsations of the uvula
Quincke's pulses	subungual capillary pulsations (low Sp)

Diagnostic studies

- ECG: can see LVH, LAD, abnl repol; CXR: cardiomegaly ± ascending Ao dilatation
- Echo: severity of AR (severe = regurg jet width ≥65% LVOT, regurg fraction ≥50%, effective regurg orifice ≥0.3 cm^2, holodiastolic flow reversal in descend. Ao; moderate = jet width 25–64%, regurg fraction 30–49%, regurg orifice 0.1–0.29 cm^2); LV size & fxn

Treatment (*Circ* 2014;129:e521; *Lancet* 2016;387:1312)

- Acute decompensation (consider endocarditis as possible acute precipitant):

surgery usually urgently needed for acute severe AR, which is poorly tolerated by LV
IV afterload reduction (nitroprusside) and inotropic support (dobutamine)
± chronotropic support (↑ HR → ↓ diastole → ↓ time for regurgitation)
pure vasoconstrictors and IABP contraindicated

- In chronic AR, management decisions based on *LV size and fxn* (and before sx occur)
- Surgery (AVR, replacement or repair if possible):
  Severe and sx (if equivocal, consider stress test)
  Asx *and* either EF ≤50% or LV dilation [LVESD >50 mm or LVESDi (indexed to BSA) ≥20 or 25 mm/m^2 (*JACC* 2019;73:1741)] or undergoing cardiac surg
- Transcatheter AoV replacement (TAVR) being explored (*JACC* 2013;61:1577 & 2017;70:2752)
- Medical therapy: vasodilators (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & not operative candidate or to improve hemodynamics before AVR; no clear benefit in asx severe AR w/ mild LV dilation & nl LV fxn (*NEJM* 2005;353:1342)

MITRAL REGURGITATION (MR)

Etiology (*Lancet* 2009;373:1382; *NEJM* 2010;363:156)

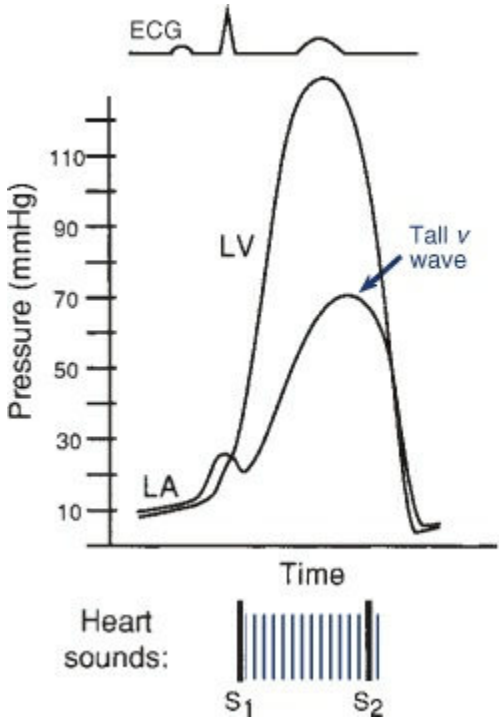
- Primary (degeneration of valve apparatus)
  Leaflet abnl: myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs (phen-fen), XRT
  Chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma
  Papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied predominantly by PDA) vs. anterolateral (suppl. by diags & OMs)]
- Secondary (functional): inferoapical papillary muscle displacement due to ischemic LV remodeling or DCM; HCM (*JACC* 2015;65:1231)

Clinical manifestations

- Acute: pulmonary edema, hypotension, cardiogenic shock (*NEJM* 2004;351:1627)
- Chronic: typically asx for yrs, then as LV fails → progressive DOE, fatigue, AF, PHT
- Prognosis: 5-y survival w/ medical therapy is 80% if asx, but only 45% if sx

Physical exam

- High-pitched, blowing, holosystolic murmur at apex; radiates to axilla; ± thrill; ↑ w/ handgrip (Se 68%, Sp 92%),
  ↓ w/ Valsalva (Se 93%) (*NEJM* 1988;318:1572)
  ant. leaflet abnl → post. jet heard at spine
  post. leaflet abnl → ant. jet heard at sternum
- ± diastolic rumble b/c ↑ flow across valve
- Lat. displ. hyperdynamic PMI, obscured S_1, widely split S_2 (A_2 early b/c ↓ LV afterload, P_2 late if PHT); ± S_3
- Carotid upstroke brisk (vs. diminished and delayed in AS)



Diagnostic studies (*NEJM* 2005;352:875)

- ECG: may see LAE, LVH, ± atrial fibrillation
- CXR: dilated LA, dilated LV, ± pulmonary congestion
- Echo: MV anatomy (ie, etiol); MR severity: jet area, jet width at origin (vena contracta) or effective regurgitant orifice (ERO; predicts survival); LV fxn (EF should be *supranormal* if compensated, ∴ EF <60% w/ sev. MR = LV dysfxn)
- TEE or cardiac MR if TTE not sufficiently informative
- Cardiac cath: prominent PCWP *c-v* waves (not spec. for MR), LVgram for MR severity & EF

Classification of Primary Mitral Regurgitation

Severity	Regurg. Fraction	Jet Area (% of LA)	Jet Width (cm)	ERO (cm^2)	Angio*
Mild	<30%	<20	<0.3	<0.2	1+
Moderate	30–49%	20–40	0.3–0.69	0.2–0.39	2+
Severe†	≥50%	>40	≥0.70	≥0.40	3/4+

*1+ = LA clears w/ each beat; 2+ = LA does not clear, faintly opac. after several beats; 3+ = LA & LV opac. equal.

†For secondary MR, because ERO underestimated & likely progressive LV dysfxn, ERO ≥0.20 is severe

Treatment (*Lancet* 2016;387:1324; *Circ* 2017;135:e1159; *JACC* 2017;70:2421)

- Acute severe MR: consider ischemia & endocarditis as precipitants; IV afterload reduction (nitroprusside), relieve congestion (diuresis & NTG), ± inotropes (dobuta), IABP, avoid vasoconstrictors; *surgery* usually needed b/c prognosis poor w/o (*JAMA* 2013;310:609)
- Chronic severe primary MR: surgery (repair [preferred if feasible] vs. replacement) if sx & EF >30%; asx & either EF 30–60% or LVESD ≥40 mm; ? asx, EF >60%, LVESD

<40, but EF ↓ or LVESD ↑; MV repair reasonable if asx & either EF >60% + LVESD <40 mm or new AF or PHT; if AF, concomitant surgical ablation ↓ AF recurrence, ∅ Δ stroke; consider for sx cntl or if planning no anticoag (*NEJM* 2015;372:1399)

- *Secondary MR:* if mod-sev MR (ideally ERO ≥0.40), EF 20–50%, sx despite optimized GDMT, transcatheter MV repair w/ edge-to-edge clips appears to ↓ mortality and HF hosp (*NEJM* 2018:379;2297 & 2307)
- For primary (degenerative) MR, surgery superior to percutaneous repair (*NEJM* 2011;364:1395)
- Balloon-expandable bioprosthetic valve in severe MR w/ severe mitral annular calcification under study (*JACC* 2018;71:1841)
- If sx & EF<60% but not operative candidate: HF Rx (βB, ACEI, ± aldo antag); ↓ preload w/ diuretics, NTG (espec. if ischemic MR) for sx relief ± ↓ ERO; maintain SR
- Asymptomatic: ∅ proven benefit of medical therapy; βB ↑ LV fxn (*JACC* 2012;60:833)

MITRAL VALVE PROLAPSE (MVP)

Definition and Etiology

- Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
- Primary: sporadic or familial myxomatous proliferation of spongiosa of MV apparatus
- Secondary: trauma, endocarditis, congenital, CTD (eg, Marfan's, OI, Ehlers-Danlos)

Clinical manifestations (usually asymptomatic)

- MR, endocarditis, emboli, arrhythmias (rarely SCD from VT from papillary muscle)
- High-pitched, midsystolic click (earlier w/ ↓ preload) ± mid-to-late systolic murmur
- No Rx *per se* [endocarditis Ppx not rec. (*Circ* 2007;116:1736)]; Rx MR as above

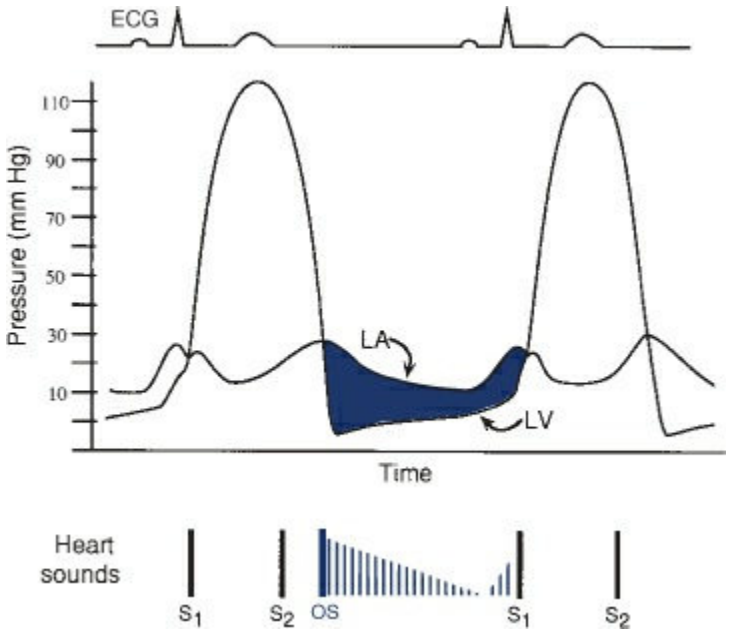
MITRAL STENOSIS (MS)

Etiology (*Lancet* 2012;379:953)

- Rheumatic heart disease (RHD): *fusion of commissures* → "fish-mouth" valve
  from autoimmune rxn to β strep infxn; seen largely in developing world today
- Mitral annular calcification: encroachment upon leaflets → fxnal MS; espec in ESRD
- Congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus
- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

Clinical manifestations (*Lancet* 2009;374:1271)

- Dyspnea and pulmonary edema (if due to RHD, sx usually begin in 30s)
  precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- Atrial fibrillation: onset often precipitates heart failure in Pts w/ MS
- Embolic events: commonly cerebral, espec in AF or endocarditis
- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve



Physical exam

- Low-pitched mid-diastolic rumble at apex w/ presystolic accentuation (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to *duration* (not intensity) of murmur; loud S_1
- Opening snap (high-pitched early diastolic sound at apex) from fused leaflet tips; MVA proportional to S_2–OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S_1 (unless MV calcified and immobile)

Diagnostic studies

- ECG: LAE ("P mitrale"), ± AF, ± RVH
- CXR: dilated LA (flat L heart border, R double density, displaced L mainstem bronchus)
- Echo: estimate pressure gradient (∇), RVSP, valve area, valve echo score (0–16, based on leaflet mobility & thick, subvalvular thick., Ca++); exer. TTE (to assess Δ RVSP and ∇) if sx & severity of MS at rest discrepant; TEE to assess for LA thrombus before PMBC
- Cardiac cath: ∇, calculated MVA; LA tall *a* wave & blunted *y* descent; ↑ PA pressures

Classification of Mitral Stenosis

Stage	Mean ∇ (mmHg)	Pressure 1/2 Time	MVA (cm^2)	PA sys (mmHg)
Normal	0		4–6	<25
Mild-mod	<5	100–149	1.6–2	<30
Severe	5–9	150–219	1.1–1.5	30–50
Very severe	≥10	≥220	≤1	>50

Treatment (*Circ* 2014;129:e521; *Lancet* 2016;387:1324)

- Medical: Na restriction, cautious diuresis, βB, AF control, sx-limited physical stress

- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40
- Anticoag: AF; prior embolism; LA clot; ? LA >55 mm or large LA w/ spont contrast
- Mechanical intervention indicated if heart failure sx w/ MVA ≤1.5; reasonable if asx but very severe (MVA ≤1) and morphology favorable for PMBC; may consider PMBC if MVA >1.5 but hemodyn signif w/ exercise, or if asx but MVA ≤1.5 and new-onset AF
- Percutaneous mitral balloon commissurotomy (PMBC): preferred Rx if RHD; MVA doubles, ∇ ↓ by 50%; ≈ MVR *if* valvuloplasty score <8, ∅ if mod-severe MR or LA clot
- Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5 if PMBC unavailable/failed/contraindicated or valve morphology unsuitable
- Pregnancy: if NYHA class III/IV → PMBC, o/w medical Rx w/ low-dose diuretic & βB

TRICUSPID REGURGITATION (*Circ* 2014;129:2440; *Lancet* 2016;388:2431)

- 1° etiol: rheumatic, CTD, XRT, IE, Ebstein's, carcinoid, tumors, pacemaker leads
- Fxnl etiol (most common): RV and/or PHT (may be 2° to L-sided dis.), RV dilation ± MI
- Holosystolic murmur, 3rd/4th ICS, ↑ w/ insp (Carvallo's sign); S_3; prominent *cv* wave in JVP
- Consider repair or replacement for sx severe TR (eg, ERO ≥0.40 cm^2); emerging transcatheter Rx under study: coaptation, caval implants, orthotopic valve (*JACC* 2018;71:2935)

PROSTHETIC HEART VALVES

Mechanical (60%)

- Bileaflet (eg, St. Jude Medical); tilting disk; caged-ball
- Very durable (20–30 y), but thrombogenic and ∴ require anticoagulation
  consider if age <~50 y or if anticoagulation already indicated (*JACC* 2010;55:2413)

Bioprosthetic (40%)

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >~70 y, lifespan <20 y, or ∅ anticoag
- If 50–69 y, 2× reop but $^1/_2$ bleeding or stroke vs. mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam

- Crisp sounds ± soft murmur during forward flow (normal to have small ∇)

Anticoagulation & antiplatelet therapy for surgical valves (*Circ* 2017;135:e1159)

- *High-risk features:* prior thromboembolism, AF, EF <30–35%, hypercoagulable
- Warfarin (ØNOACs): mech MVR or high-risk mech AVR: INR 3. Low-risk mech AVR or high-risk bio MVR/AVR: INR 2.5. Consider in bio MVR/AVR for 3–6 mo if low bleed risk.
- + ASA (≤100 mg): all prosth. valves unless hx GIB, uncontrolled HTN, erratic INR, or >80 y
- If thrombosis, ↑ intensity (eg, INR 2–3 → 2.5–3.5; 2.5–3.5 → 3.5–4.5; add ASA if not on)
- For TAVR, dual antiplatelet therapy (see TAVR section in "Aortic Stenosis")

Periprocedural "Bridging" of Anticoagulation in Pts with Mechanical Valve(s)	
AVR w/o risk factors	d/c warfarin 2–4 d before surg; restart 12–24 h after surg
MVR or AVR w/ risk factors	Preop: d/c warfarin, start UFH (preferred to LMWH) when INR <2 4–6 h preop: d/c UFH; postop: restart UFH & warfarin ASAP

JACC 2017;70:253. Procedures include noncardiac surgery, invasive procedures, and major dental work.

Correction of overanticoagulation (*Circ* 2014;129:e521)

- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding: if INR 5–10, withhold warfarin; if INR >10 also give vit K 1–2.5 mg PO
- Bleeding: FFP or PCC ± low-dose (1 mg) vit K IV

Endocarditis prophylaxis: for all prosthetic valves (see "Endocarditis")

Complications

- Structural failure (r/o endocarditis); mechanical valves: rare except for Bjork-Shiley; bioprosth: up to 30% rate w/in 10–15 y, mitral > aortic; consider TAVR (*JACC* 2017; 69:2253)
- Paravalvular leak (r/o endocarditis); small *central* jet of regurg is normal in mech. valves
- Obstruction from thrombosis (*JACC* 2013;62:1731) or pannus: ✔ TTE, TEE, CTA, or fluoro
  significantly symptomatic *pannus* ingrowth: remove w/ surgery
  thrombosis: surgery if L-sided valve & either severe sx or large (≥1 cm or 0.8 cm^2); o/w UFH × days; if persists, consider lytic (eg, tPA 10 mg IVB → 90 mg over 2 hrs or 25 mg over 6 hrs repeating prn *JACC CV Imaging* 2013;6:206), success in ~80%, but ~10% risk of death, stroke or major bleed; lytic reasonable for R-sided
- Infective endocarditis ± valvular abscess and conduction system dis. (see "Endocarditis")
- Embolization (r/o endocarditis); risk highest 1st 90 d, ~1%/y w/ warfarin (vs. 2% w/ ASA, or 4% w/o meds); mech MVR 2× risk of embolic events vs. mech AVR (*Circ* 1994;89:635)
- Bleeding (from anticoag), hemolysis (espec w/ caged-ball valves or paravalvular leak)

PERICARDIAL DISEASE

PERICARDITIS AND PERICARDIAL EFFUSION

Anatomy

- Tissue sac surrounding heart & proximal great vessels; 2 layers (parietal & visceral)

Disease states

- Inflammation (w/ or w/o fluid accumulation) → pericarditis
- Fluid accumulation → effusion ± tamponade
- Decrease in compliance (sequela of inflammation) → constrictive pericarditis
- Tamponade and constriction characterized by increased ventricular interdependence

PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Acute Pericarditis (*JAMA* 2015;314:1498; *EHJ* 2015;36:2873)	
Idiopathic (>80%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, echo, adeno, EBV, VZV, CMV, parvo, HIV, flu Bacterial (from endocarditis, pneumonia, or s/p cardiac surgery): *S. pneumo, Neisseria, Coxiella, S. aureus, Borrelia* (Lyme); TB Fungi: *Histo, Coccidio, Candida;* Parasite: *Entamoeba, Echino, Toxo*
Neoplastic (<10%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, RCC) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, ANCA ! (EGPA, GPA) Drug-induced: procainamide, hydralazine, INH, CsA
Uremia	~5–13% of Pts prior to HD; ~20% occurrence in chronic HD Pts
Cardiovascular	STEMI, late post-MI (Dressler's syndrome); ascending AoD; chest trauma; postpericardiotomy; procedural complic. (ie, PCI, PPM)
Radiation	>40 Gy to mediastinum; acute or delayed; may be transudative
Effusion w/o pericarditis	CHF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis. Transudative.

Clinical manifestations (*NEJM* 2014;371:2410)

- Pericarditis: retrosternal CP, pleuritic, positional (often ↓ by sitting forward), → trapezius; may be *absent* in TB, neoplastic, XRT, or uremic; ± fever; ± s/s of systemic etiologies
- Effusion: present in ~2/3 of Pts w/ pericarditis; ranges from asx to tamponade

Physical exam

- Pericarditis: multiphasic friction rub best heard at LLSB w/ diaphragm of stethoscope. Notoriously variable and evanescent leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (*NEJM* 2012;367:e20).
- Effusion: distant heart sounds, dullness over left posterior lung field due to compressive

atelectasis from pericardial effusion (Ewart's sign)

Diagnostic studies (*JAMA* 2015;314:1498; *EHJ* 2015;36:2921)

- Need ≥2 of the following: chest pain (as noted above), friction rub, ECG findings, effusion
- ECG: may show diffuse STE (*concave up*) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, TWI do not occur until STs normalize
  Stages: (I) STE & PR ↓; (II) ST & PR normalize; (III) diffuse TWI; (IV) Tw normalize
  ECG may show evidence of large effusion w/ low-voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis due to swinging heart)
- CXR: if lg effusion (>250 mL) → ↑ cardiac silhouette w/ "water-bottle" heart & epicardial halo
- Echocardiogram: presence, size, & location of *effusion;* presence of *tamponade physiology;* pericarditis itself w/o spec. abnl (∴ echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect LV/RV dysfxn (myocarditis?)
- CT: pericardial effusions (often appear larger by CT than by echo) ± calcifications
- MRI: may reveal pericardial thickening/inflammation, as well as myocardial involvement
- CK-MB or troponin (⊕ in ~30%; *JACC* 2003;42:2144) if myopericarditis. Consider CRP/ESR.

Workup for effusion

- r/o infxn: usually apparent from Hx & CXR; ? value of ✔ acute and convalescent serologies
- r/o noninfectious etiologies: BUN, Cr, ANA, RF, HIV, meds, relevant malignancy evaluation
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent
  ✔ cell counts, TP, LDH, glc, Gram stain & Cx, AFB, cytology
  ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion
  "exudate": TP >3 g/dL, TP_{eff}/TP_{serum} >0.5, LDH_{eff}/LDH_{serum} >0.6 or glc <60 mg/dL; high Se (~90%) but *very low* Sp (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial bx if suspicion for malignancy or TB; perform during every surgical drainage

Treatment of pericarditis (*JAMA* 2015;314:1498; *EHJ* 2015;36:2921)

- High-dose NSAID (eg, ibuprofen 600–800 mg tid) or ASA (eg, 650–1000 mg tid) × 7–14 d then taper over wks; ASA preferred over NSAID in acute MI; consider PPI to ↓ risk of GIB
- Add colchicine 0.6 mg bid (qd if ≤70 kg) × 3 mo; 50% ↓ risk of refractory or recurrent pericarditis (*NEJM* 2013;369:1522). Amio, dilt, verap & atorva ↓ P-gp, ↑ risk of colchicine tox.
- Avoid steroids except for systemic autoimmune disorder, uremic, preg., NSAIDs contraindicated, or refractory idiopathic disease. Appear to ↑ rate of pericarditis recurrence (*Circ* 2008;118:667). If due to TB, steroids ↓ risk of constriction (*NEJM* 2014;371:1121).
- Avoid anticoagulants (although no convincing data that ↑ risk of hemorrhage/tamponade)
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Restrict activity until sx resolve/hsCRP ↓; athletes must also wait ≥3 mos w/ nl TTE/ECG

- Acute idiopathic pericarditis self-limited in 70–90% of cases
- Recurrent pericarditis (*Circ* 2007;115:2739) risk factors: subacute, large effusion/tamponade, T >38°C, no NSAID response after 7 d. Treatment: colchicine 0.6 mg bid × 6 mo (*Annals* 2011;155:409; *Lancet* 2014;383:2232). Nb drug-drug interactions (noted above).
- Recurrent effusions: consider pericardial window (percutaneous vs. surgical)

PERICARDIAL TAMPONADE

Etiology

- Any cause of pericarditis but espec malignancy, infectious, uremia, ascending AoD, myocardial rupture, periprocedural complication, trauma, post-cardiotomy
- Rapidly accumulating effusions most likely to cause tamponade b/c no time for pericardium to stretch (eg, to ↑ compliance) and accommodate ↑ intrapericardial fluid volume

Pathophysiology (*NEJM* 2003;349:684)

- ↑ intrapericardial pressure, compression of heart chambers, ↓ venous return → ↓ CO
- Diastolic pressures ↑ & equalize in all cardiac chambers → minimal flow of blood from RA to RV when TV opens → blunted *y* descent
- ↑ ventricular interdependence → pulsus paradoxus (pathologic exaggeration of nl physio)
  Inspiration → ↓ intrapericardial & RA pressures → ↑ venous return → ↑ RV size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ LV filling → ↓ LV stroke volume & blood pressure & pulse pressure.

Clinical manifestations

- Cardiogenic shock (hypotension, fatigue) without pulmonary edema
- Dyspnea (seen in ~85%) may be due to ↑ respiratory drive to augment venous return

Physical exam (*EHJ* 2014;35:2279)

- Beck's triad (present in minority of cases): distant heart sounds, ↑ JVP, hypotension
- ↑ JVP (76%) w/ blunted *y* descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), cool extremities
- Pulsus paradoxus (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration
  ⊕ LR 3.3 (5.9 if pulsus >12), ⊖ LR 0.03
  Ddx = PE, hypovolemia, severe COPD, auto-PEEP, periconstriction (~$^1/_3$), RV infarct
  ? absent if pre-existing ↑ LVEDP, irregular rhythm, severe AI, ASD, regional tamponade
- Distant heart sounds (28%), ± pericardial friction rub (30%)
- Tachypnea and orthopnea but clear lungs

Diagnostic studies

- ECG: ↑ HR, ↓ voltage (seen in 42%), electrical alternans (20%), ± signs of pericarditis
- CXR: ↑ cardiac silhouette (89%)
- Echocardiogram: ⊕ effusion, IVC plethora, septal shift with inspiration
  diastolic collapse of RA (Se 85%, Sp 80%) and/or RV (Se <80%, Sp 90%)
  respirophasic Δ's in transvalvular velocities (↑ across TV & ↓ across MV w/ inspir.)

postsurgical tamponade may be localized and not easily visible

- Cardiac cath (right heart and pericardial): elevation (15–30 mmHg) and equalization of intrapericardial and diastolic pressures (RA, RV, PCWP), blunted *y* descent in RA
  ↑ in stroke volume postpericardiocentesis = ultimate proof of tamponade
  if RA pressure remains high after drainage, Ddx: effusive-constrictive dis. (visceral pericardium constriction), myocard. dysfxn (eg, concomitant myocarditis)

Treatment (*EHJ* 2014;35:2279)

- Volume (but be careful b/c overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors b/c will ↓ stroke volume & potentially ↓ HR
- Avoid positive pressure ventilation b/c it can further impair cardiac filling (*Circ* 2006;113:1622)
- Pericardiocentesis (except if due to aortic/myocardial rupture, for which emergent surgery treatment of choice; if too unstable, consider small pericardiocentesis to prevent PEA)
- Surgical drainage considered if fluid rapidly reaccumulates, loculated, or hemorrhagic

---

CONSTRICTIVE PERICARDITIS

Etiology (*Circ* 2011;124:1270)

- Any cause of pericarditis (~1–2% incidence overall after acute pericarditis)
- Highest risk w/ TB, bacterial, neoplastic, XRT, connective tissue, postcardiac surgery
- Viral/idiopathic, b/c most common cause of pericarditis, also account for signif proportion

Pathophysiology

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and *prominent x and y descents*
- Kussmaul sign: JVP does not decrease with inspiration (↑ venous return with inspiration, but negative intrathoracic pressure not transmitted to heart because of rigid pericardium)

Clinical manifestations (*NEJM* 2011;364:1350)

- Right-sided > left-sided heart failure (systemic congestion > pulmonary congestion)

Physical exam

- ↑ JVP with prominent *y* descent, ⊕ Kussmaul sign [Ddx: tricuspid stenosis, acute cor pulmonale, RV dysfxn (CMP, RV MI), SVC syndrome]
- Hepatosplenomegaly, ascites, peripheral edema. Consider in Ddx of idiopathic cirrhosis.
- PMI usually not palpable, pericardial knock, usually no pulsus paradoxus

Diagnostic studies

- ECG: nonspecific, AF common (up to 33%) in advanced cases
- CXR: calcification (MTb most common), espec in lateral view (although not specific)
- Echocardiogram: ± thickened pericardium, "septal bounce" = abrupt displacement of

septum during rapid filling in early diastole

- Cardiac catheterization: atria w/ Ms or Ws (prominent *x* and *y* descents)
  ventricles: dip-and-plateau or square-root sign (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
  discordance between LV & RV pressure peaks during respiratory cycle (*Circ* 1996;93:2007)
- CT or MRI: thickened pericardium (>4 mm; Se ~80%) w/ tethering (*Circ* 2011;123:e418)

Treatment

- Diuresis if intravascular volume overload; surgical pericardiectomy if infectious or advanced

Constrictive Pericarditis vs. Restrictive Cardiomyopathy		
Evaluation	Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical exam	⊕ Kussmaul sign Absent PMI ⊕ Pericardial knock	± Kussmaul sign Powerful PMI, ± S_3 and S_4 ± Murmurs of MR, TR
ECG	± Low voltage	Low voltage if infiltrative myopathy ± Conduction abnormalities
Echocardiogram	Respirophasic variation (25–40%): inspir. → ↑ flow across TV and ↓ flow across MV E′ (tissue velocity) nl/↑ (>12 cm/sec) Expir. hepatic vein flow reversal Septal bounce in early diastole Normal wall thickness	<10% respirophasic variation Slower peak filling rate Longer time to peak filling rate E′ ↓ (<8 cm/sec) (Se 95%, Sp 96%; *HF Rev* 2013;18:255) Inspir. hepatic vein flow reversal Biatrial enlargement ± ↑ wall thickness
CT/MRI	Usually w/ thickened pericardium	Normal pericardium
NT-proBNP	Variable	Typically ↑/↑↑ (*JACC* 2005;45:1900)
Cardiac catheterization	Prominent *x* and *y* descents (more so in constriction)	
	Dip-and-plateau sign (more so in constriction)	
	LVEDP = RVEDP RVSP <55 mmHg (Se 90%, Sp 29%) RVEDP >⅓ RVSP (Se 93%, Sp 46%) Discordance of LV & RV pressure peaks during respiratory cycle Systolic area index (ratio of RV to LV pressure–time area in inspir vs. expir) >1.1 (Se 97%, Sp 100%)	LVEDP > RVEDP (esp. w/ vol.) RVSP >55 mmHg RVEDP <⅓ RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (*JACC* 2008;51:315)
Endomyocardial biopsy	Usually normal	± Specific etiology of RCMP (fibrosis, infiltration, hypertrophy)

HYPERTENSION

JNC 8 Classification		
Category	Systolic	Diastolic
Normal	<120	<80
Pre-HTN	120–139	80–89
Stage 1 HTN*	140–159	90–99
Stage 2 HTN	≥160	≥100

2017 AHA/ACC BP Classification		
Category	Systolic	Diastolic
Normal	<120	<80
Elevated BP	120–129	<80
Stage 1HTN	130–139	80–89
Stage 2 HTN	≥140	≥90

BP in mmHg. Average ≥2 measurements >1–2 min apart. Confirm stage 1 w/in 1–4 wk; can Rx stage 2 immediately. (*J Clin HTN* 2014;16:14; *Circ* 2018;138:e426)

Epidemiology (*JAMA* 2014;311:1424; *Circ* 2018;138:e426)

- Prevalence ~30% in U.S. adults, ≥44% in African-Americans; M = F
- Of those with HTN, ~3/4 were treated, ~1/2 achieve target BP, ~1/6 were unaware of dx

Etiologies (*JACC* 2017;71:127)

- Essential (95%): onset 25–55 y; ⊕ FHx. Unclear mechanism but ? additive microvasc renal injury over time w/ contribution of hyperactive sympathetics (*NEJM* 2002;346:913). ↑ Age → ↓ art compliance → HTN. Genetics + environment involved (*Nature* 2011;478:103).
- Secondary: Consider if Pt <30 y or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension			
Diseases		**Suggestive Findings**	**Initial Workup**
RENAL	**Renal parenchymal** (2–3%)	h/o DM, polycystic kidney disease, glomerulonephritis	CrCl, albuminuria See "Renal Failure"
RENAL	**Renovascular** (1–2%) Athero (90%) FMD (10%, young women) PAN, scleroderma	ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (*NEJM* 2009;361:1972)	MRA (>90% Se & Sp, less for FMD), CTA, duplex U/S, angio, plasma renin (low Sp)
ENDO	**Hyperaldo or Cushing's** (1–5%)	Hypokalemia Metabolic alkalosis	See "Adrenal Disorders"
ENDO	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
ENDO	Myxedema (<1%)	See "Thyroid Disorders"	TFTs
ENDO	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv); alcohol		
OTHER	**Medications:** OCP, steroids, licorice; NSAIDs (espec COX-2); Epo; cyclosporine		
OTHER	Aortic coarctation: ↓ LE pulses, systolic murmur, radial-femoral delay; abnl TTE, CXR		
OTHER	Polycythemia vera: ↑ Hct		

Standard workup

- Goals: (1) identify CV risk factors; (2) consider 2° causes (3) assess for target-organ damage
- History: CAD, HF, TIA/CVA, PAD, DM, renal insufficiency, sleep apnea, preeclampsia; ⊕ FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: ✔ BP in both arms; funduscopic exam, BMI, cardiac (LVH, murmurs), vascular (bruits, radial-femoral delay), abdominal (masses or bruits), neuro exam
- Testing: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, peripheral edema), ? renin, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): consider for episodic, masked, resistant, or white coat HTN; stronger predictor of mortality than clinic BP (*NEJM* 2018;378:1509); 24 h target <130/80

Complications of HTN

- Neurologic: TIA/CVA, ruptured aneurysms, vascular dementia
- Retinopathy: stage I = arteriolar narrowing; II = copper-wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: CAD, LVH, HF, AF
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, renal failure

Treatment (*J Clin HTN* 2014;16:14; *Circ* 2018;138:e426; *NEJM* 2018;378:636)

- Every ↓ 10 mmHg → 20% ↓ MACE, 28% ↓ HF, 13% ↓ mort. (*Lancet* 2016;387:957)

- ACC/AHA: initiate BP med if BP ≥130/80 & *either* clinical CVD (ischemic heart disease, HF, stroke) *or* 10-y ASCVD risk ≥10%; otherwise if BP ≥140/90
- JNC8: target <140/90 if <60 y or DM or CKD, <150/90 if ≥60 y w/o DM or CKD
- In high CV risk w/o DM, SBP target of <120 (via unattended automated cuff) ↓ MACE & mortality vs. target of <140, but w/ ↑ HoTN, AKI, syncope, electrolyte abnl (*NEJM* 2015;373:2103). Same pattern in subgp ≥75 y (*JAMA* 2016;315:2673).
- Lifestyle modifications (each may ↓ SBP ~5 mmHg)
  weight loss: goal BMI 18.5–24.9; aerobic exercise: 90–150 min exercise/wk
  diet: rich in fruits & vegetables, low in saturated & total fat (DASH, *NEJM* 2001;344:3)
  limit Na: ideally ≤1.5 g/d or ↓ 1 g/d; enhance K intake (3.5–5 g/d)
  limit alcohol: ≤2 drinks/d in men; ≤1 drink/d in women & lighter-wt Pts; avoid NSAIDs
- Pharmacologic options
  Pre-HTN: ARB prevents onset of HTN, no ↓ in clinical events (*NEJM* 2006;354:1685)
  HTN: *choice of therapy controversial, concomitant disease and stage may help guide Rx*
  Uncomplicated: CCB, ARB/ACEI, or thiazide (chlorthalidone preferred) are 1st line; βB not
  For black, elderly, and ? obese Pts: reasonable to start with CCB or thiazide
  + CAD (*Circ* 2015;131:e435): ACEI or ARB (*NEJM* 2008;358:1547); ACEI+CCB superior to ACEI+thiazide (*NEJM* 2008;359:2417) or βB+diuretic (*Lancet* 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, βB ± ACEI/ARB ± aldo antag (see "ACS")
  + HF: ACEI/ARB/ARNi, βB, diuretics, aldosterone antagonist (see "Heart Failure")
  + prior stroke: ACEI ± thiazide (*Lancet* 2001;358:1033)
  + diabetes mellitus: consider ACEI or ARB; can also consider thiazide or CCB
  + chronic kidney disease: ACEI or ARB (*NEJM* 1993;329:1456 & 2001;345:851 & 861)
- Tailoring therapy: if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo (eg, ACEI + CCB; *NEJM* 2008;359:2417); start at $^1/_2$ max dose; after 1 mo, uptitrate or add drug
- Pregnancy: methyldopa, labetalol, & nifed pref. Hydral OK; avoid diuretics; ∅ ACEI/ARB. Targeting DBP 85 vs. 105 safe and ↓ severe HTN (*NEJM* 2015;372:407).

Resistant HTN (BP > goal on ≥3 drugs incl diuretic; *HTN* 2018;72:e53)

- Exclude: 2° causes (see table) and *pseudoresistance:* inaccurate measure (cuff size), diet noncomp (↑ Na), poor Rx compliance/dosing, white coat HTN (✔ ABPM)
- Ensure effective diuresis (chlorthalidone or indapamide > HCTZ; loop > thiazide if eGFR <30)
- Can add aldosterone antagonist (*Lancet* 2015;386:2059), β-blocker (particularly vasodilators such as labetalol, carvedilol, or nebivolol), α-blocker, or direct vasodilator

HYPERTENSIVE CRISES

- Hypertensive emergency: SBP >180 or DBP >120 w/ target-organ damage
  Neurologic damage: encephalopathy, hemorrhagic or ischemic stroke, papilledema
  Cardiac damage: ACS, HF/pulmonary edema, aortic dissection
  Renal damage: proteinuria, hematuria, acute renal failure; scleroderma renal crisis
  Microangiopathic hemolytic anemia; preeclampsia-eclampsia
- Hypertensive urgency: SBP >180 or DBP >120 w/o target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (espec clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine

Treatment – tailor to clinical condition (*Circ* 2018;138:e426)

- AoD, eclampsia/severe preeclampsia, pheo: target SBP <140 (<120 for AoD) in 1 hour
- Emerg w/o above: ↓ BP by ~25% in 1 h; to 160/100–110 over next 2–6 h, then nl over 1–2 d
- Acute ischemic stroke (w/in 72 hr from sx onset): <185/110 before lysis initiated, o/w target <220/120 (same SBP goal for ICH)
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

IV Drugs for Hypertensive Emergency (*Circ* 2018;138:e426; *Stroke* 2018;49:46)

Drug	Dose	Preferred for
Labetalol	20–80 mg IVB q10min or 0.4–2 mg/min	AoD, ACS, Stroke, Eclampsia
Esmolol	0.5–1 mg/kg load → 50–200 µg/kg/min	AoD, ACS
Nitroprusside*	0.25–10 µg/kg/min	Pulm edema
Nitroglycerin	5–500 µg/min	Pulm edema, ACS
Nicardipine	5–15 mg/h (can ↑ 2.5 mg/h q 5 min)	Stroke, AKI, Eclampsia, Pheo
Clevidipine	1–32 mg/h (can titrate q 5–10 min)	Stroke, Pulm edema, AKI, Pheo
Fenoldopam	0.1–1.6 µg/kg/min	AKI
Hydralazine	10–20 mg q20–30min prn	Eclampsia
Phentolamine	5–15 mg bolus q5–15min	Pheo
Enalaprilat	1.25–5 mg q6h	

*Metabolized to cyanide →Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 µg/kg/min) to <10 min.

- HTN urgency: goal to return to normal BP over hrs to days. Reinstitute/intensify anti-HTN Rx. Additional PO options: labetalol 200–800 mg q8h, captopril 12.5–100 mg q8h, hydralazine 10–75 mg q6h, clonidine 0.2 mg load → 0.1 mg q1h.

AORTIC ANEURYSMS

Definitions

- True aneurysm (≥50% dilation of all 3 layers of aorta) vs. false (rupture within adventitia)
- Location: root (annuloaortic ectasia), thoracic aortic aneurysm (TAA), thoracoabdominal aortic aneurysm (TAAA), abdominal aortic aneurysm (AAA)
- Type: fusiform (circumferential dilation) vs. saccular (localized dilation of aortic wall)

Epidemiology (*Circ* 2010;121:e266, 2011;124:2020; *Nat Rev Cardiol* 2011;8:92)

- TAA: ♂:♀ 2:1; ~60% root/ascending; 40% desc.
- AAA: ~4–8% prev in those >60 y; 5× more common in ♂; mostly infrarenal

Pathophysiology & risk factors (*NEJM* 2009;361:1114; *Nat Med* 2009;15:649)

- Medial degen and/or ↑ wall stress; wall stress ∝ [(ΔP × r) / (wall thickness)] (Laplace's law)
- TAA: medial degeneration (muscle apoptosis, elastin fiber weakening); a/w CTD, aortitis
- AAA: long-standing HTN + athero/inflammation → medial weakening
- Classic clinical risk factors: HTN, atherosclerosis, smoking, age, ♂
- CTD (Marfan, Ehlers-Danlos type IV, Loeys-Dietz); congenital (bicuspid AoV, Turner's) aortitis (Takayasu's GCA, spondyloarthritis, IgG4, syphilis); trauma

Screening (*Circ* 2010;121:e266 & 2011;124:2020; *Annals* 2014;161:281; *JAMA* 2015;313:1156)

- TAA: if bicuspid AoV or 1° relative w/: (a) TAA or bicuspid AoV, (b) CTD as above
- AAA: ✔ for pulsatile abd mass; U/S ♂ >60 y w/ FHx of AAA & ♂ 65–75 y w/ prior tobacco

Diagnostic studies (*Circ* 2010;121:e266 & 2011;124:2020)

- Contrast CT: quick, noninvasive, high Se & Sp for all aortic aneurysms
- TTE/TEE: TTE most useful for root and proximal Ao; TEE can visualize other sites of TAA
- MRI: favored over CT for AoRoot imaging; useful in AAA but time consuming; noncontrast "black blood" MR to assess aortic wall
- Abdominal U/S: screening/surveillance test of choice for infrarenal AAA

Treatment (*Circ* 2008;117:1883 & 2010;121:e266 & 2016;133:680; *NEJM* 2014;371:2101)

- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- Risk factor modification: smoking cessation; LDL-C <70–100 mg/dl
- BP control: **β**B (↓ dP/dt) ↓ aneurysm growth (*NEJM* 1994;330:1335); ACEI a/w ↓ rupture risk (*Lancet* 2006;368:659); ARB may ↓ rate of aortic root growth in Marfan (*NEJM* 2008;358:2787)
- Mod CV exercise OK, no burst activity requiring Valsalva maneuvers (eg, heavy lifting)
- Indications for surgery (individualized based on FHx, body size, gender, anatomy)
  TAA: sxs; ascending Ao ≥5.5 cm (4–5 cm if Marfan, L-D, EDS, bicuspid AoV); descending Ao >6 cm; ≥4.5 cm and planned AoV surgery; ↑ >0.5 cm/y

AAA: sx; infrarenal >5.5 cm; consider ≥5.0 cm in ♀; ↑ >0.5 cm/y; inflam/infxn

Endovascular repair (EVAR) (*NEJM* 2008;358:494; *Circ* 2011;124:2020 & 2015;131:1291)

- Requires favorable aortic anatomy
- TEVAR (thoracic EVAR) for descending TAA ≥5.5 cm may ↓ periop morbidity and possibly mortality (*Circ* 2010;121:2780; *JACC* 2010;55:986; *J Thorac CV Surg* 2010;140:1001 & 2012;144:604)
- AAA: guidelines support open repair or EVAR for infrarenal AAA in good surg candidates

  ↓ short-term mort., bleeding, LOS; but long-term graft complic. (3–4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no difference in mortality long term (*Lancet* 2016;388:2366; *NEJM* 2019;380:2126)

  In Pts unfit for surgery or high periop risks: ↓ aneurysm-related mortality but no Δ in overall mortality over med Rx (*NEJM* 2010;362:1872). EVAR noninferior (? superior) to open repair in ruptured AAA w/ favorable anatomy (*Ann Surg* 2009;250:818).

Complications (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92)

- Pain: gnawing chest, back, or abdominal pain; new or worse pain may signal rupture
- Rupture: risk ↑ w/ diameter, ♀, current smoking, HTN

  TAA: ~2.5%/y if <6 cm vs. 7%/y if >6 cm

  AAA: ~1%/y if <5 cm vs. 6.5%/y if 5–5.9 cm; ~80% mortality at 24 h
- Aortic insufficiency (TAA), CHF, acute aortic syndromes (qv)
- Thromboembolic ischemic events (eg, to CNS, viscera, extremities)
- Compression of adjacent structures (eg, SVC, trachea, esophagus, laryngeal nerve)

Follow-up (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92; *JAMA* 2013;309:806)

- Expansion rate ~0.1 cm/y for TAA, ~0.3–0.4 cm/y for AAA
- AAA: <4 cm q2–3y; 4–5.4 cm q6–12mo; more often if rate of expansion >0.5 cm in 6 mo
- TAA: 6 mo after dx to ensure stable, and if stable, then annually (*Circ* 2005;111:816)
- Screen for CAD, PAD, and aneurysms elsewhere, espec popliteal. About 25% of Pts w/ TAA will also have AAA, and 25% of AAA Pts will have a TAA: consider pan-Ao imaging.

ACUTE AORTIC SYNDROMES

Definitions (*Circ* 2010;121:e266; *Eur Heart J* 2012;33:26)

- Aortic dissection: intimal tear → blood extravasates into Ao media (creates false lumen)
- Intramural hematoma (IMH): vasa vasorum rupture → medial hemorrhage that does not communicate with aortic lumen; 6% of aortic syndromes; clinically managed as AoD
- Penetrating ulcer: atherosclerotic plaque penetrates elastic lamina → medial hemorrhage

Classification (proximal twice as common as distal)

- Proximal: involves ascending Ao, regardless of origin (= Stanford A, DeBakey I & II)
- Distal: involves descending Ao only, distal to L subclavian art. (= Stanford B, DeBakey III)

Risk factors (*Lancet* 2015;385:800)

- Classic (in older Pts): HTN (h/o HTN in >70% of dissections); age (60s–70s), sex (~65% ♂); smoking; ↑ lipids. Acute ↑ BP: cocaine, Valsalva (eg, weightlifting).
- Genetic or acquired predisposition: *CTD* (Marfan, Loeys-Dietz, Ehlers-Danlos type IV); *congenital anomaly* (bicuspid AoV, coarct [eg, Tuner's syndrome], PCKD); *aortitis* (Takayasu's, GCA, Behçet's, syphilis); *preg.* (typically 3rd trim.); fluoroquinolone exposure
- Trauma: blunt, decel. injury (eg, MVA); IABP, cardiac/aortic surgery, Impella, cardiac cath

Clinical Manifestations and Physical Exam* (*JAMA* 2000;283:897)		
Feature	Proximal	Distal
"Aortic" pain (abrupt, severe, tearing or ripping quality, *maximal at onset* [vs. crescendo for ACS])	94% (chest, back)	98% (back, chest, abd)
Syncope (often due to tamponade)	13%	4%
HF (usually due to acute AI)	9%	3%
CVA	6%	2%
HTN	36%	70%
HoTN or shock (tamponade, AI, MI, rupture)	25%	4%
Pulse deficit (if involves carotid, subclavian, fem)	19%	9%
AI murmur	44%	12%

*S/S correlate w/ affected branch vessels & distal organs; may Δ as dissection progresses

Initial evaluation & diagnostic studies (*Circ* 2010;121:e266; *JACC CV Img* 2014;7:406)

- H&P, incl. bilat BP & radial pulses for symmetry; ECG w/ STE if propagates to cor
- CXR: abnl in 60–90% [↑ mediast. (absence ⊖ LR 0.3), L pl effusion] but *cannot* r/o AoD
- CT: quick and available, Se ≥93%, Sp 98%; facilitates "triple rule-out" ACS vs. PE vs. AoD
- MRI: Se & Sp >98%, but time-consuming test & not readily available

- TEE: Se >95% prox, 80% for distal; can assess cors/peric/AI; "blind spot" behind trachea
- ⊖ Initial imaging but high clinical suspicion → further studies ($^2/_3$ w/ AoD have ≥2 studies)
- D-dimer <500 ng/mL has Se/NPV ~97%, Sp ~50%, *but not if high risk* and not for IMH
- ? risk score (0–3 points): high-risk (eg, genetics, recent Ao manip); aortic pain; e/o perfusion deficit, AI or shock. Score >1 → imaging; ≤1 & DD <500 has NPV >99% (*Circ* 2018;137:250)

Treatment (*Circ* 2010;121:1544; *JACC* 2013;61:1661; *Lancet* 2015;385:800)

- ↓ dP/dt targeting HR <60 & central BP <120 (or lowest that preserves perfusion; r/o pseudohypotension, eg, arm BP ↓ due to subclavian dissection; use highest BP reading)
- *First* IV **β**B (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy in response to vasodilators; verap/dilt if **β**B contraindic; *then* ↓ *SBP w/* IV vasodilators (eg, nitroprusside)
- If HoTN: urgent surgical consult, IVF to achieve euvolemia, pressors to keep (MAP 70 mmHg); r/o complication (eg, tamponade, contained rupture, severe AI)
- Proximal: surgery considered in all acute and in chronic if c/b progression, AI or aneurysm
- Distal: med Rx unless complication (see below), however pre-emptive endovascular intervention may ↓ late complications, mort (*JACC* 2013;61:1661; *Circ Cardiovasc Int* 2013;6:407)

Complications (occur in ~20%; *Circ* 2010;121:e266; *Lancet* 2015;385:800)

- *Freq assess (sx, BP, UOP), pulses, labs (Cr, Hb, lactic acid), imaging (~7 d or sooner if Δs)*
- *Uncontrolled BP or persistent pain may indicate complication/extension*
- Progression: propagation of dissection, ↑ aneurysm size, ↑ false lumen size
- Rupture: pericardial sac → tamponade (avoid pericardiocentesis unless PEA); blood in pleural space, mediast., retroperitoneum; ↑ in hematoma on imaging portends rupture
- Malperfusion (partial or complete obstruction of branch artery) *coronary* → MI (usually RCA → IMI b/c dissection follows outer Ao curvature); *innominate/carotid* → CVA, Horner; *intercostal/lumbar* → spinal cord ischemia/paraplegia; *innominate/subclavian* → upper ext ischemia; *iliac* → lower ext ischemia; *celiac/mesenteric* → bowel ischemia; *renal* → AKI or slow ↑ Cr, refractory HTN
- AI: due to annular dilatation or disruption or displacement of leaflet by false lumen
- Mortality: ~1%/h × 48 h for acute prox AoD w/ 10–35% at 30 d; ↑ mort. if HTN or HoTN
- Long-term serial imaging (CT or MRI; ↓ rad w/ MRI) at 1, 3, and 6 mo, and then annually

ARRHYTHMIAS

BRADYCARDIAS, AV BLOCK, AND AV DISSOCIATION

Sinus bradycardia (SB) (*NEJM* 2000;342:703)

- Etiologies: meds (incl βB, CCB, amio, Li, dig), ↑ vagal tone (incl. athletes, sleep, IMI), metabolic (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no sx, none; atropine, β_1 agonists (short-term) or pacing if symptomatic
- Most common cause of sinus pause is *blocked premature atrial beat*

Sick sinus syndrome (SSS)

- Features may include: periods of unprovoked SB, SA arrest, paroxysms of SB and atrial tachyarrhythmias ("tachy-brady" syndrome), chronotropic incompetence w/ ETT
- Treatment: meds alone usually fail (adeq. control tachy → unacceptable brady); usually need combination of meds (βB, CCB, dig) for tachy & PPM for brady

AV Block	
Type	Features
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1).
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (→ "grouped beating"). Due to AV node abnl: ischemia (IMI), inflammation (myocarditis, endocarditis, MV surgery), high vagal tone (athletes), drug induced. Classically (~50%), absolute ↑ in PR *decreases* over time (→ ↓ RR intervals, duration of pause <2× preceding RR interval); nl QRS. AVB usually worsens w/ carotid sinus massage, improves w/ atropine. Often paroxysmal/nocturnal/asx, no Rx required.
2° Mobitz II	Blocked impulses w/ consistent PR interval, often prolonged QRS Due to His-Purkinje abnl: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/AoV surgery/TAVR. AVB may improve w/ carotid sinus massage, may worsen w/ atropine. May progress to 3° AVB. Pacing pads; transven. pacing often required.
3° (complete)	No AV conduction. Escape, if present, narrow (jxnal) or wide (vent.)

Nb, if 2:1 block, cannot distinguish type I vs. II 2° AVB (no chance to observe PR prolongation); usually categorize based on other ECG & clinical data. High-grade AVB usually refers to block of ≥2 successive impulses.

AV dissociation

- *Default:* slowing of SA node allows subsidiary pacemaker (eg, AV junction) to take over
- *Usurpation:* acceleration of subsidiary pacemaker (eg, AV junctional tach, VT)
- *3° AV block:* atrial pacemaker unable to capture ventricles, subsidiary pacemaker emerges distinguish from *isorhythmic dissociation* (A ≈ V rate, some P waves nonconducting)

Temporary pacing wires

- Consider w/ bradycardia with hemodyn instability or unstable escape rhythm when perm pacer not readily available. Risks: infxn, RV perf, VT, PTX, CHB if existing LBBB.

- Consider instead of PPM for sx brady from reversible cause (βB/CCB O/D, Lyme, SBE, myocarditis, s/p cardiac surgery/trauma/TAVR), TdP, acute MI (sx brady/high-grade AVB)

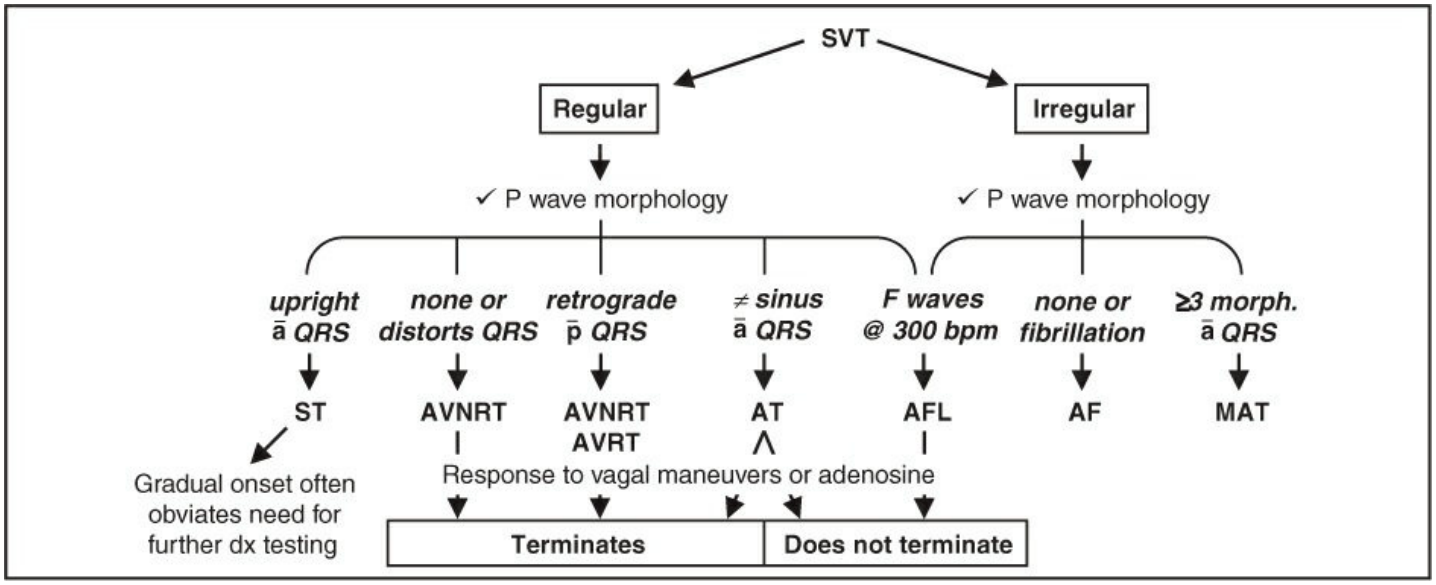
SUPRAVENTRICULAR TACHYCARDIAS (SVTS)

Arise above the ventricles, ∴ narrow QRS unless aberrant conduction or pre-excitation.

Common Etiologies of SVT (*NEJM* 2012;367:1438)		
	Type	Features
Atrial	Sinus tachycardia (ST)	Caused by pain, fever, hypovolemia, hypoxia, PE, anemia, anxiety, withdrawal, β-agonists, etc.
	Atrial tachycardia (AT)	Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.
	Multifocal atrial tachycardia (MAT)	↑ automaticity at multiple sites in the atria; seen with underlying pulmonary disease
	Atrial flutter (AFL)	Clockwise or counterclockwise macroreentry, usually w/in right atrium
	Atrial fibrillation (AF)	Chaotic atrial activation with rapid, irregular AVN bombardment; often from pulmonary veins
AV Jxn	AV nodal reentrant tach (AVNRT)	Reentrant circuit using dual pathways w/in AVN
	Atrioventricular reciprocating tachycardia (AVRT)	Reentry using AVN & access. path. May show pre-excitation (WPW) or not (concealed access. path.). Can be ortho or antidromic (see below).
	Nonparoxysmal junctional tachycardia (NPJT)	↑ jxnal automaticity. May see retro. P, AV dissoc. A/w myo/endocarditis, cardiac surg, IMI, dig.

Diagnosis of SVT Type (*NEJM* 2012;367:1438)	
Onset	Abrupt on/off argues against sinus tachycardia
Rate	Not dx b/c most can range from 140–250 bpm, *but:* ST usually <150; AFL often conducts 2:1 → vent. rate 150; AVNRT & AVRT usually >150
Rhythm	Irregular → AF, AFL w/ variable block, or MAT
P wave morphology	Before QRS (ie, long RP) → ST, AT (P ≠ sinus), MAT (≥3 morphologies) After QRS (ie, short RP) & inverted in inf. leads → *retrograde* atrial activ. AVNRT: buried in or distort terminal portion of QRS (pseudo RSR′ in V_1) AVRT: slightly after QRS (RP interval >100 ms favors AVRT vs. AVNRT) NPJT: either no P wave or retrograde P wave similar to AVNRT *Fibrillation or no P waves* → AF *Saw-toothed "F" waves* (best seen in inferior leads & V_1) → AFL
Response to vagal stim. or adenosine	Slowing of HR often seen with ST, AF, AFL, AT, whereas reentrant rhythms (AVNRT, AVRT) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ AT may terminate. In AFL & AF, ↑ AV block may unmask "F" waves or fibrillation

Figure 1-4 Approach to SVT (adapted from *NEJM* 2012;367:1438)



Treatment of SVT (*Circ* 2016;133:e506)		
Rhythm	Acute Treatment	Long-term Treatment
Unstable	Cardioversion per ACLS	n/a
ST	Treat underlying stressor(s)	n/a
AT	βB, CCB or adenosine; ? amiodarone	radiofrequency ablation (RFA); βB or CCB, ± class IC/III AAD
AVNRT or AVRT	Vagal maneuvers Adenosine (caution in AVRT*) CCB or βB, DCCV if other Rx fail	*For AVNRT* (*see next section for AVRT*): RFA. CCB, βB, or dig (chronic or prn) ± Class IC/III AAD (if nl heart)
NPJT	CCB, βB, amiodarone	Rx underlying dis. (eg, dig tox, ischemia)
AF	βB, CCB, digoxin, AAD	See "Atrial Fibrillation"
AFL	βB, CCB, AAD	RFA; βB or CCB ± class III AAD
MAT	CCB or βB if tolerated	Treat underlying disease. CCB or βB. AVN ablation + PPM if refractory to meds

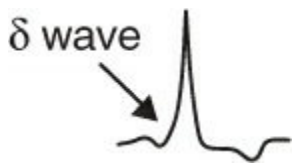
*Avoid adenosine & nodal agents if accessory pathway + pre-excited tachycardia, see below (*JACC* 2003;42:1493)

- *Catheter ablation:* high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~70%)
  complications: stroke, MI, bleeding, perforation, conduction block (*JAMA* 2007;290:2768)

ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)

Definitions

- Accessory pathway (bypass tract) of conducting myocardium connecting atria & ventricles, allowing impulses to bypass normal AVN delay



- Pre-excitation (WPW) pattern: ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, *can be subtle*). ST & Tw abnl (can mimic old IMI).
  Only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde, then ECG will be normal during SR; "concealed" bypass tract).
- PAC can exaggerate pre-excitation if AV node conduction slowed
- WPW syndrome: WPW accessory pathway + paroxysmal tachycardia

Classic tachycardias of WPW accessory pathways

- Orthodromic AVRT: *narrow-complex* SVT (typically), conducting ↓ AVN & ↑ accessory pathway; requires retrograde conduction and ∴ can occur w/ concealed bypass tracts
- Antidromic AVRT (rare): *wide-complex* SVT, conducting ↓ accessory pathway & ↑ AVN;
  requires antegrade conduction and ∴ should see pre-excitation pattern during SR
- AF w/ rapid conduction down accessory pathway; ∴ wide-complex irregular SVT; requires antegrade conduction; ∴ should see pre-excitation in SR. Rarely can degenerate into VF.

Treatment (*Heart Rhythm* 2012;9:1006; *Circ* 2016;133:e506)

- AVRT (orthodromic): vagal, βB, CCB; care w/ adenosine (can precip AF); *have defib ready*
- AF/AFL w/ conduction down accessory pathway: need to Rx arrhythmia *and* ↑ pathway refractoriness. Use procainamide, ibutilide, or DCCV; *avoid* CCB, βB, amio, dig, & adenosine, b/c can ↓ refractoriness of pathway → ↑ vent. rate → VF (*Circ* 2016;133:e506).
- Long term: RFA if sx; if not candidate for RFA, then AAD (IA, III) or CCB/βB.
  Consider RFA if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) or if rapid conduction possible (✔ w/ EPS if pre-excitation persists during exercise testing)
  Risk of SCD related to how short RR interval is in AF (eg, ≤250 ms) and if SVT inducible

---

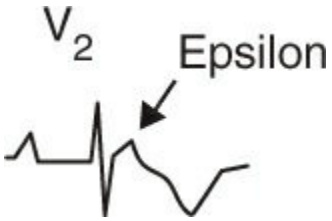
WIDE-COMPLEX TACHYCARDIAS (WCTS)

Etiologies (*Lancet* 2012;380:1520)

- Ventricular tachycardia (VT): accounts for 80% of WCT in unselected population
- SVT conducted with aberrancy: either fixed BBB, rate-dependent BBB (usually RBBB), conduction via an accessory pathway or atrially triggered ventricular pacing

Monomorphic ventricular tachycardia (MMVT)

- All beats look similar; predominantly upward in V_1 = RBBB-type vs. downward = LBBB-type
- In structurally *abnormal* heart: prior MI (scar); CMP; myocarditis



arrhythmogenic RV CMP (ARVC): incomplete RBBB,
ε wave (terminal notch in QRS) & TWI in V_1–V_3 on resting ECG
LBBB-type VT, dx w/ MRI (*Lancet* 2009;373:1289)

- In structurally *normal* heart (w/ normal resting ECG):
  RVOT VT: LBBB-type VT or PVCs w/ inferior axis; typically ablate
  Idiopathic LV VT: RBBB-type VT or PVCs w/ superior axis; responds to verapamil

Polymorphic ventricular tachycardia (PMVT)

- QRS morphology changes from beat to beat
- Etiologies: ischemia; CMP; catecholaminergic;
  torsades de pointes (TdP = "twisting of the points," PMVT + ↑ QT): ↑ QT *acquired* (meds, lytes, stroke, see "ECG") w/ risk ↑ w/ ↓ HR, freq PVCs (pause dependent) *or congenital* (K/Na channelopathies) w/ resting Tw abnl & TdP triggered by sympathetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750)
  Brugada syndrome (Na channelopathy; *JACC* 2018;72:1046): ♂ > ♀; pseudo-RBBB w/ STE in V_1–V_3 (provoked w/class IA or IC) on resting ECG



Diagnostic clues that favor VT (assume until proven o/w)

- Prior MI, CHF, or LV dysfunction *best predictors* that WCT is VT (*Am J Med* 1998;84:53)
- Hemodynamics and rate do *not* reliably distinguish VT from SVT
- MMVT is regular, but initially it may be slightly irregular, mimicking AF w/ aberrancy; *grossly* irregularly irregular rhythm suggests AF w/ aberrancy or pre-excitation
- ECG features that favor VT (*Circ* 2016;133:e506)
  AV dissociation (independent P waves, capture or fusion beats) proves VT
  Very wide QRS (>140 ms in RBBB-type or >160 in LBBB-type); *extreme axis deviation*
  QRS morphology atypical for BBB
    RBBB-type: absence of tall R′ (or presence of monophasic R) in V_1, r/S ratio <1 in V_6
    LBBB-type: onset to nadir >60–100 ms in V_1, q wave in V_6
  Initial R wave in aVR; concordance (QRS in all precordial leads w/ same pattern/direction)

Long-term management (*EHJ* 2015;36:2793; *Circ* 2016;133:1715; *NEJM* 2019;380:1555)

- Workup: echo to ✔ LV fxn, cath or stress test to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? EP study to assess inducibility
- ICD: 2° prevention after documented VT/VF arrest (unless due to reversible cause). 1° prev. if high risk, eg, EF <30–35%, ? ARVC, ? Brugada, certain LQTS, severe HCMP. See "Cardiac Rhythm Mgmt Devices." Wearable vest if reversible or waiting for ICD? (*NEJM* 2018;379:1205). Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock.
- Meds: βB, verapamil if idiopathic LV VT, or AAD (eg, amio, mexiletine) to suppress VT
- If med a/w TdP → QT >500 ± VPBs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- RFA if isolated VT focus or if recurrent VT triggering ICD firing (↓ VT storm by 34%; *NEJM* 2016;375:111); ablation before ICD implantation ↓ discharge rate by 40% (*Lancet* 2010;375:31). Non-invasive radioablation (15-min ablation time) under investigation (*Circ* 2019;139:313).

ATRIAL FIBRILLATION

Classification (*Circ* 2014;130:e199)

- Paroxysmal (self-terminating, usually <48 h, often triggered in pulm veins) vs. persistent (>7 d) vs. long-standing persistent (>1 y) vs. permanent (no plan for SR)
- Nonvalvular (AF absent rheumatic MS, prosthetic valve, or mitral valve repair) vs. valvular

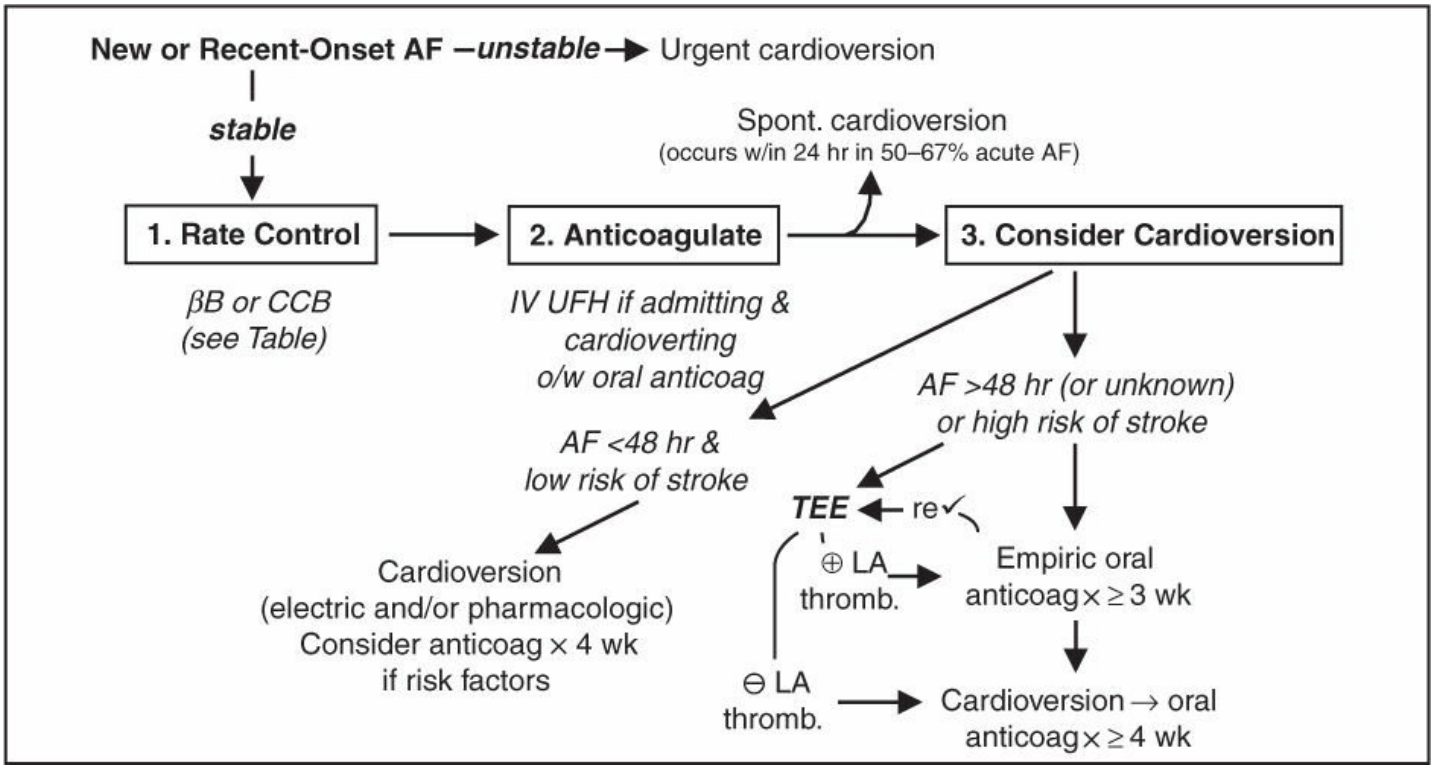
Epidemiology and etiologies (*Circ* 2011;124:1982; *Nat Rev* 2016;2:1)

- 1–2% of pop. has AF (10% of those age ≥80); M > F; lifetime risk ~25%
- Acute (up to 50% w/o identifiable cause)
  - Cardiac: HF, new CMP, myo/pericarditis, ischemia/MI, HTN crisis, valve dis., cardiac surg
  - Pulmonary: acute pulmonary disease or hypoxemia (eg, COPD flare, PNA), PE, OSA
  - Metabolic: high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis
  - Drugs: alcohol, cocaine, amphetamines, theophylline, caffeine, smoking, ibrutinib
  - Neurogenic: subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), K, Mg, Cr, FOBT before anticoag, TFTs; r/o MI not necessary unless other ischemic sx
- In acute AF <48º, ~70% spont. convert to SR w/in 48 hrs (*NEJM* 2019;380:1499)

Figure 1-5 Approach to acute AF (Adapted from *Circ* 2014;130:e199)



Rate Control (if sx, goal HR <80; if asx & EF >40%, goal HR <110; *Circ* 2014;130:e199)				
	Agent	**Acute (IV)**	**Maint. (PO)**	**Comments**
CCB	**Verapamil**	5–10 mg over 2′ may repeat in 30′	120–360 mg/d in divided doses	↓ BP (Rx w/ Ca gluc) Can worsen HF Preferred if severe COPD Can ↑ dig levels
CCB	**Diltiazem**	0.25 mg/kg over 2′ may repeat after 15′ 5–15 mg/h infusion	120–360 mg/d in divided doses	
βB	**Metoprolol**	2.5–5 mg over 2′ may repeat q5′ × 3	25–100 mg bid or tid	↓ BP (Rx w/ glucagon) Preferred if CAD Risks: HF & bronchospasm.
Digoxin* (onset >30 min)		0.25 mg q2h up to 1.5 mg/24 h	0.125–0.375 mg qd (adj for CrCl)	Consider in HF or low BP Poor exertional HR ctrl
Amiodarone		300 mg over 1 h → then 10–50 mg/h × 24 h		

Lancet 2016;388:818. IV βB, CCB & dig *contraindic.* if evidence (ie, pre-excitation or WCT) of WPW (qv).
*Many meds incl. amio, verapamil, quinidine, propafenone, macrolides & azole antifungals ↑ digoxin levels.

Cardioversion

- Consider if: 1st AF, sx, tachycardia-mediated CMP, or difficult to rate control
  If AF >48 h 2–5% risk stroke w/ cardioversion (*pharmacologic or electric*) ∴ either TEE to r/o thrombus or ensure therapeutic anticoagulation ≥3 wk prior
  If needs to cardiovert urgently, often anticoagulate acutely (eg, IV UFH)
- Likelihood of success ∝ AF duration & atrial size; control precipitants (eg, vol status, thyroid)
- Before electrical cardiovert, consider pre-Rx w/ AAD (eg, ibutilide), esp. if 1st cardiovert failed

- For pharmacologic cardioversion, class III and IC drugs have best proven efficacy
- If SR returns (spont. or w/ Rx), atria may be *mech. stunned;* also, high risk of recurrent AF over next 3 mo. ∴ Anticoag postcardioversion ≥4 wk (? unless AF <48 h and low risk).

Rhythm control (*Lancet* 2016;388:829)

- No ↓ mortality or stroke vs rate control (*NEJM* 2002;347:1825 & 2008;358:2667 & 2016;374:1911)
- Consider if *sx* w/ rate control (eg, HF), difficult to control rate, or tachycardia-mediated CMP

Antiarrhythmic Drugs (AAD) for AF (*EHJ* 2012;33:2719; *Circ* 2014;130:e199)

Agent		Conversion	Maintenance	Comments
III	Amiodarone	5–7 mg/kg IV over 30–60′→ 1 mg/min, 10-g load	200–400 mg qd (most effective AAD for SR)	↑ QT, TdP rare. Often delay to convert. Poss. pulm, liver, thyroid tox. ↑ INR w/ warfarin.
	Dronedarone	n/a	400 mg bid	↓ side effects & effic. vs. amio
	Ibutilide	1 mg IV over 10′ may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT (3–8% risk of TdP): give w/ IV Mg
	Dofetilide	500 mcg PO bid	500 mcg bid	↑ QT, ↑ risk of TdP; renal adj
	Sotalol	n/a	80–160 mg bid	✓ for ↓ HR, ↑ QT; renal adj
IC	Flecainide	300 mg PO × 1	100–150 mg bid	PreRx w/ AVN blocker. ∅ *if structural/ischemic heart dis.*
	Propafenone	600 mg PO × 1	150–300 mg tid	
IA	Procainamide	10–15 mg/kg IV	n/a	↓ BP; ↑ QT; ± AVN blocker

Underlying disease & maintenance AAD of choice:
None or minimal (incl HTN w/o LVH): class IC ("pill in pocket"), sotalol, dronedarone;
HTN w/ LVH: amio; ***CAD:*** sotalol, dofetilide, amio, dronedarone; ***HF:*** amio, dofetilide

Ablation

- Pulm vein isolation (radiofreq or cryo; *NEJM* 2016;374:2235): ~70% success; no need to interrupt anticoag; superior to AAD (*JAMA* 2014;311:692) & ↑ QoL (*JAMA* 2019;321:1059)
- If NYHA II-IV + EF <35%, ablation ↓ D/HF hosp vs. rate/rhythm meds (*NEJM* 2018;378:417)
- AV node ablation + PPM if other Rx inadequate (*NEJM* 2001;344:1043 & 2002;346:2062)

Oral anticoagulation (*Circ* 2014;130:e199 & 2019;139:epub; *EHJ* 2018;39:1330)

- *All valvular AF* (ie, rheum MS, valve prosthesis or repair), because stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ~4.5%/y
- CHA_2DS_2-VASc to guide Rx: CHF (1 point); HTN (1); Age ≥75 y (2); DM (1), Stroke/TIA (2); Vascular disease (eg, MI, PAD, Ao plaque) (1); Age 65–74 (1); ♀ Sex category (1)
  Annual risk of stroke (*Lancet* 2012;379:648): at low end, ~1% per point: 0 → ~0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑↑ (5 → 6.7%, ≥6 → ≥10%)
  Score ≥2 → anticoagulate; score 1 → consider anticoag. or ASA (? latter reasonable

if risk factor 65–74 y, vasc dz or ♀) or no Rx; score 0 → reasonable to not Rx

- Rx options: DOAC (NVAF only) prefered over warfarin (INR 2–3); if Pt refuses anticoag, ASA + clopi or, even less effective, ASA alone (*NEJM* 2009;360:2066)
- AF + CAD/ PCI: consider DOAC (some data for reduced dose but unclear if ischemic stroke prevention adequate), clopi (not ticag or prasugrel), and consider stopping ASA (? after ~1 wk) (*Lancet* 2013;381:1107; *NEJM* 2016;375:2423 & 2017;377:1513 & 2019;380:1509).
- If concern for procedural bleed, interrupt OAC (1–2 d DOAC, 4–5 d VKA). If CHA_2DS_2-VASc ≥7 (or ≥5 w/ h/o CVA/TIA), consider bridge w/ UFH/LMWH, else no (*JACC* 2017;69:735).

Direct Oral Anticoagulants (DOACs) for NVAF (*Lancet* 2014;383:955)		
Anticoag	Dosing	Efficacy & Safety vs. Warfarin
Dabigatran (Direct thromb inhib)	150 mg bid (110 not avail in U.S.) (75 mg bid if CrCl 15–30)	150 mg: ↓ ischemic stroke & ICH, but ↑ GIB 110 mg: ≈ ischemic stroke & ↓ major bleed/ICH Risks: GI side effects, ↑ MI c/w warfarin
Rivaroxaban (FXa inhib)	20 mg qd (15 mg qd if CrCl 15–50) w/ pm meal	≈ ischemic stroke & major bleeds, but ↓ fatal bleed incl ICH
Apixaban (FXa inhib)	5 mg bid (2.5 mg bid if ≥2 of: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL)	≈ ischemic stroke & ↓ major bleed incl ICH, 11% ↓ death. In Pts felt not cand for warfarin, apixa 55% ↓ stroke w/o ↑ bleed vs ASA alone.
Edoxaban (Fxa inhib)	60 mg qd if CrCl 51–95 (30 mg if CrCl 15–50)	≈ ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death. ↑ ischemic CVA if CrCl >95.
Onset w/in hrs. Reversal: idarucizumab for dabi; andexanet for FXa; 4F-PCC.		

Nonpharmacologic stroke prevent (*JACC* 2015;66:1497)

- If contraindic. to long-term OAC, consider perc. left atrial appendage (LAA) occlusion (*JACC* 2017;70:2964). Nb, ideally warfarin + ASA × 45 d → DAPT out to 6 mo → ASA.
- Consider perc. epicardial LAA ligation or surgical resection if undergoing other card surg

Atrial flutter

- Macroreentrant atrial loop. Typical involves cavotricuspid isthmus (if counterclockwise, flutter waves ⊖ in inf leads, if clockwise, ⊕). Atypical: other pathways related to prior scar.
- Risk of stroke similar to that of AF, ∴ anticoagulate same as would for AF
- Ablation of typical (cavotricuspid isthmus) AFL has 95% success rate

SYNCOPE

Definition

- Symptom of sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then SCD and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without LOC

Etiologies (*JACC* 2017;70:e39; *EHJ* 2018;39:1883)

- Neurocardiogenic (a.k.a. vasovagal, ~25%): ↑ sympathetic tone → vigorous contraction of LV → LV mechanoreceptors trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhib.) and/or ↓ BP (vasodepressor). Cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants. Carotid sinus hypersensitivity (exag vagal resp to carotid massage) is related disorder.
- Orthostatic hypotension (~10%)
  - hypovolemia/diuretics, deconditioning; vasodilat. (esp. if combined w/ ⊖ chronotropes)
  - autonomic neuropathy [1° = Parkinson's, MSA/Shy-Drager, Lewy body dementia, POTS (dysautonomia in the young); 2° = DM, EtOH, amyloidosis, CKD] (*NEJM* 2008;358:615)
- Cardiovascular (~20%, more likely in men than women)
  - *Arrhythmia* (~15%): challenging to dx because often transient
    - Bradyarrhythmias: SB, SSS, high-grade AV block, ⊖ chronotropes, PPM malfunction
    - Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)
  - *Mechanical* (5%)
    - Endocardial/Valvular: critical AS, MS, PS, prosthetic valve thrombosis, myxoma
    - Myocardial: outflow obstruction from HCMP (or VT); Pericardial: tamponade
    - Vascular: PE (in ~25% w/o alt dx; *NEJM* 2016;375:1524), PHT, AoD, ruptured AAA
- Neurologic (~10%): vertebrobasil insuff, cerebrovasc dissection, SAH, TIA/CVA, migraine
- Misc. causes of LOC (but not syncope): seizure, ↓ glc, hypoxia, narcolepsy, psychogenic

Workup (etiology cannot be determined in ~40% of cases) (*jama* 2019;321:2448)

- *H&P incl. orthostatic VS have highest yield and most cost effective* (*Archives* 2009;169:1299)
- *R/o life-threatening dx including: cardiac syncope, severe blood loss, PE, SAH*
- History (from Pt and *witnesses* if available)
  - activity and posture before the incident
  - precipitating factors: exertion (AS, HCMP, PHT), positional Δ (orthostatic HoTN), stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/deglutition/micturition/defecation (neurocardiogenic), head turning or shaving (carotid sinus hypersens.); arm exercise

(subclavian steal)
sudden onset → cardiac; prodrome (eg, diaphoresis, nausea, blurry vision) → vasovagal
associated sx: chest pain, palp., neurologic, postictal, bowel/bladder incontinence, (convulsive activity for <10 sec may occur w/ transient cerebral HoTN & mimic seizure)

- PMH: prior syncope, previous cardiac or neurologic dis.; no CV disease at baseline → 5% cardiac, 25% vasovagal; CV disease → 20% cardiac, 10% vasovagal (*NEJM* 2002;347:878)
- Medications that may act as precipitants
  vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep.
  diuretics; ⊖ chronotropes (eg, βB and CCB)
  proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics (see "ECG")
  psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- Family history: CMP, SCD, syncope (vasovagal may have genetic component)
- Physical exam
  VS incl. *orthostatics* (⊕ if supine → standing results in ≥20 mmHg ↓ SBP or ≥10 ↓ DBP or SBP <90 mmHg w/in 3 min; POTS if ≥30 bpm ↑ HR w/in 10 min), BP in both arms
  Cardiac: HF (↑ JVP, displ. PMI, S_3), murmurs, LVH (S_4, LV heave), PHT (RV heave, ↑ P_2)
  Vascular: ✔ for *asymmetric pulses*, carotid/vert/subclavian *bruits; carotid sinus massage* to ✔ for carotid hypersens (if no bruits): ⊕ if asystole >3 sec or ↓ SBP >50 mmHg
  Neurologic exam: focal findings, evidence of tongue biting; FOBT
- ECG (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)
  Conduction: SB, sinus pauses/sinus arrhythmia, AVB, BBB/IVCD
  Arrhythmia: ectopy, ↑ or ↓ QT, preexcitation (WPW), Brugada, ε wave (ARVC), SVT/VT
  Ischemic changes (new or old): atrial or ventricular hypertrophy
- Lab: glc, Hb, HCG (pre-menop ♀), ? D-dimer, ? troponin/NT-proBNP (↓ yield w/o other s/s)

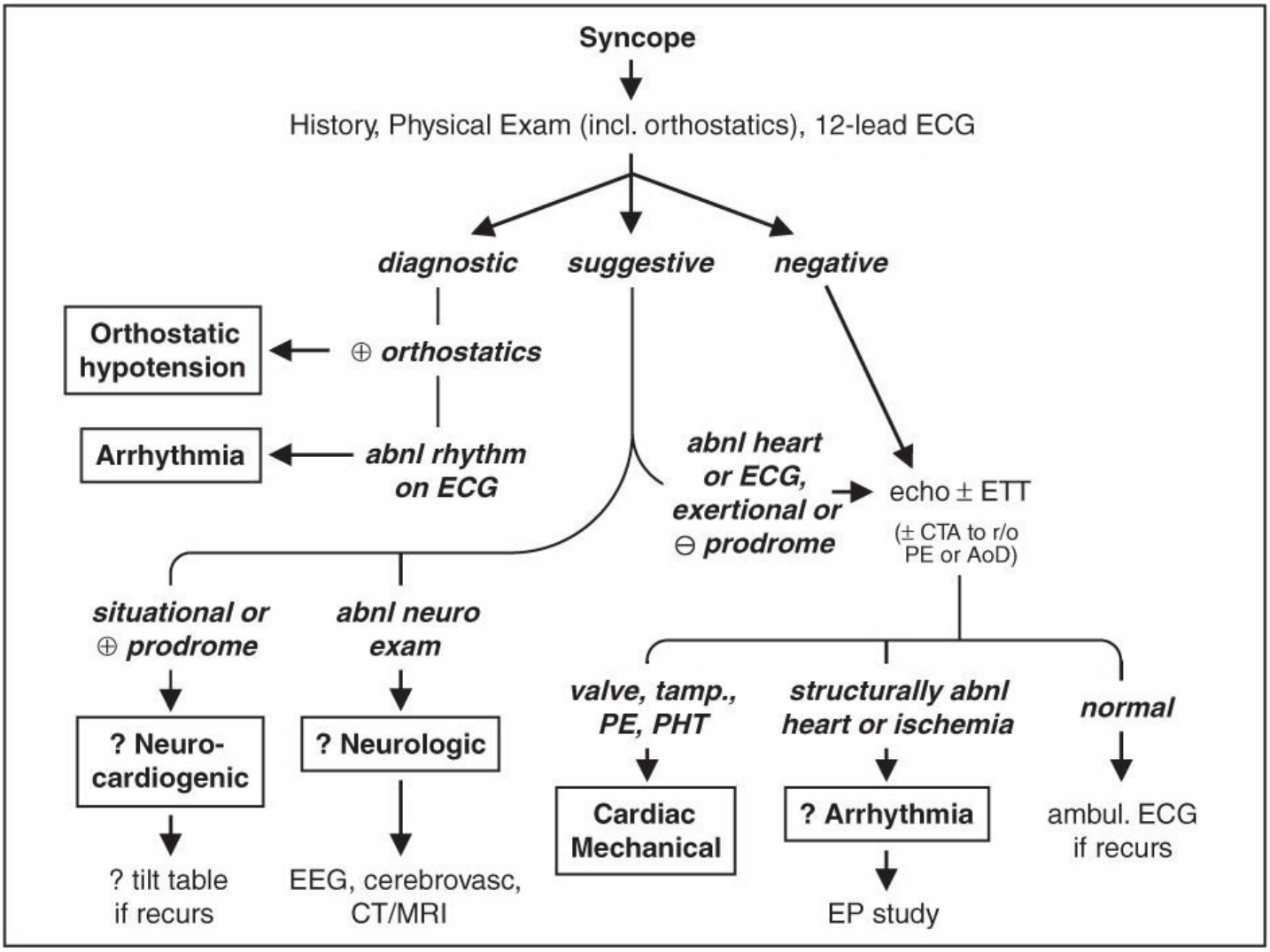
Other diagnostic studies (consider based on results of H&P and ECG)

- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope
  Holter monitoring (continuous ECG 24–72 h): useful if *frequent* events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)
  Event recorder (activated by Pt to record rhythm strip): limited role in syncope because only useful if established prodrome (because must be Pt activated)
  External loop recorders (continuously saves rhythm, ∴ can be activated *after* an event): useful for episodes (including w/o prodrome) likely to occur w/in 1 mo; can be coupled w/ mobile cardiac telemetry than can be auto-triggered for specific rhythms
  Implantable loop recorders (SC; can record 2–3 y; can be triggered): useful if episodes

<1/mo; dx in 55% of cases; rec for recurrent syncope w/o prodrome

- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ARVC], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT/CCTA/Cath: esp. w/ exertional syncope; r/o ischemia or catechol-induced arrhythmia
- Electrophysiologic studies (EPS): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected (eg, prior MI), but cannot be confirmed; avoid if ECG/Echo normal.
  50% abnl (inducible VT, conduction abnormalities) if heart disease, but ? significance
  3–20% abnl if abnl ECG; <1% abnl if normal heart and normal ECG
- Tilt table: debated utility due to poor Se/Sp/reproducibility; consider if suspected neurocardiogenic, orthostatic HoTN, POTS, or psychogenic, and initial eval unrevealing
- Cardiac MRI: helpful to dx sarcoid or ARVC if suggestive ECG, echo (RV dysfxn) or ⊕ FHx
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield

Figure 1-6 Approach to syncope



(*Adapted from JACC* 2017;70:e39)

High-risk features (admit w/ tele; *JACC* 2017;70:620; *EHJ* 2018;39:1883)

- Age >60 y, h/o CAD, HF/CMP, valvular or congenital heart dis., arrhythmias, FHx SCD
- Syncope c/w cardiac cause (lack of prodrome, exertional, resultant trauma) or recurrent
- Complaint of chest pain or dyspnea; abnl VS, cardiac, pulm, or neuro exam; low Hct
- ECG suggesting conduction abnormality, arrhythmia, or ischemia; Pt w/ PPM/ICD
- Canadian Syncope Risk Score (*CMAJ* 2016;188:e289) stratifies from <1% to >20% risk of serious arrhythmias. If low-risk & no arrhythmia in ED × 2 h, 0.2% risk over 30 d.

Treatment (*EHJ* 2018;39:1883)

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder, ? ICD if Brugada pattern, sarcoid, ARVC, early repol + syncope
- Neurocardiogenic: consider fludrocortisone or midodrine (*JACC* 2016;68:1; *Neuro* 2014;83:1170); ? βB or SSRI (*Circ A&E* 2012; 5:920)
  consider dual-chamber PPM if rec episodes + prolonged pauses (*Circ* 2012;125:2566)
- Orthostatic: 2–3 L fluid & 10 g Na per day; rise from supine to standing *slowly*, compression stockings; consider midodrine or fludrocortisone; ? atomoxetine (*HTN* 2014;64:1235)

Prognosis (*Ann Emerg Med* 1997;29:459; *NEJM* 2002;347:878)

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope has poor prognosis (20–40% 1-y SCD rate); vasovagal good prognosis
- Unexplained syncope w/ 1.3-fold ↑ in mort., but noncardiac or unexplained syncope w/ nl ECG, no h/o VT, no HF, age <45 → low recurrence rate and <5% 1-y SCD rate
- ✔ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

CARDIAC RHYTHM MANAGEMENT DEVICES

Pacemaker Code				
A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	1st letter	2nd letter	3rd letter	4th letter
	Chamber paced	Chamber sensed	Response to sensed beat	Program features

Common Pacing Modes	
VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & *triggers V pacing* → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF.
Mode Switch	In atrial tachyarrhythmia (eg, AF), PPM Δs from DDD to nontracking mode (eg, VVI). Prevents PPM from pacing at max V rate in response to rapid atrial rate.
Magnet over generator	PPM: fixed rate pacing (VOO/DOO). ICD: no shock, pacing preserved. Indic: ✔ capture; surgery; inapprop PPM inhib/ICD shock, PM-mediated tachy
Leadless intracardiac PPM approved for single chamber RV pacing (*Circ* 2017;135:1458); His bundle pacing ↓ death/HF/CRT upgrade vs RV pacing alone (*JACC* 2018;71:2319).	

Indications for Permanent Pacing (*Circ* 2008;117:350 & 2012;126:1784)	
AV block	3° or type II 2° AVB a/w sx or w/ either HR <40 or asystole ≥3 sec (≥5 if in AF) while awake; ? asx 3° or type II 2° AVB; bifasc or alter. L & R BBB
Sinus node	SB, pauses (SSS), chronotrop incompet a/w sx or ? if sx w/o clear assoc
Tachy-arrhythmia	AF w/ SSS; sx recurrent SVT term. by pacing after failing drugs/ablation; Sustained pause-dependent VT; ? high-risk congenital long QT
Syncope	Carotid sinus hypersensitivity with asystole >3 sec ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi- or trifascicular block and not likely 2° to other causes

Pacemaker Complications		
Issue	Manifestation	Description & etiologies
Perforation	Effusion/tamp/pain	Typically acute, consider if HoTN
Failure to pace	Bradycardia	↓ Battery, lead fx/dislodgment, ↑ pacing threshold due to tissue rxn/injury; oversense → inapprop. inhib
Failure to sense	Inapprop. pacing	Lead dislodgment or sensing threshold too high
PM-mediated tachycardia	WCT at device upper rate	Seen w/ DDD. V → A retrograde conduction; sensed by A lead → triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI, due to loss of AV synchrony

Cardiac resynch therapy (CRT)/Biventricular (BiV) pacing (*JACC* 2013;61:e6)

- 3-lead pacemaker (RA, RV, coronary sinus to LV); R > S in V_1 suggests approp LV capture
- Synch LV fxn (↑ CO/EF, ↓ adv remodeling); ↓ HF sx & hosp, ↑ survival (*NEJM* 2010;363:2385)

- Indications: LVEF ≤35% + NYHA II–IV despite med Rx + SR + LBBB ≥150 ms (also reasonable if LBBB ≥120 ms, any non-LBBB ≥150 ms, or >40% V-pacing); mort. benefit w/ CRT-D only if LBBB (& QRS ≥130ms) (*NEJM* 2014;370:1694)
  ? benefit in NYHA I–III, EF ≤50% w/ PPM indication for AVB (*NEJM* 2013;368:1585)

Implantable cardiac defibrillator (ICD) (*JACC* 2013;61:e6; *Circ* 2015;132:1613)

- RV lead: defib & pacing (± antitachycardia pacing [ATP] = burst pacing > VT rate to stop VT); ± RA lead for dual-chamber PPM. Subcut-ICD (consider if young), but ∅ pace/ATP.
- Pt selection (*JACC* 2008;51:e1; *Circ* 2012;126:1784)
  2° prev: survivors of VT/VF arrest w/o revers cause; asx sustained VT + struct. heart dis.
  1° prevention: LVEF ≤30% & post-MI *or* LVEF ≤35% & NYHA II–III (wait: ≥40 d if post-MI, ≥90 d for niCMP) *or* LVEF ≤40% & inducible VT/VF; *life expectancy must be >1 y;*
  More recently, for niCMP ICD ↓ SCD but not overall mortality (*NEJM* 2016;375:1221);
  Consider if unexplained syncope + DCM, or if HCM, ARVC, Brugada, sarcoid, LQTS, Chagas, or congenital heart disease if risk for SCD;
  Pts w/ recent MI: wearable vest ? ↓ death (*NEJM* 2018;379:1205)
- Risks: inapprop shock in ~15–20% at 3 y (commonly d/t misclassified SVT); infxn; lead fx
- ICD discharge: ✔ device to see if approp; r/o ischemia; 6-mo driving ban (✔ state law)
- MRI: older systems may be OK (*NEJM* 2017;377:2555); may need to reprogram prior to MRI

Device infection (*JAMA* 2012;307:1727; *NEJM* 2012;367:842 & 2019;380:1895)

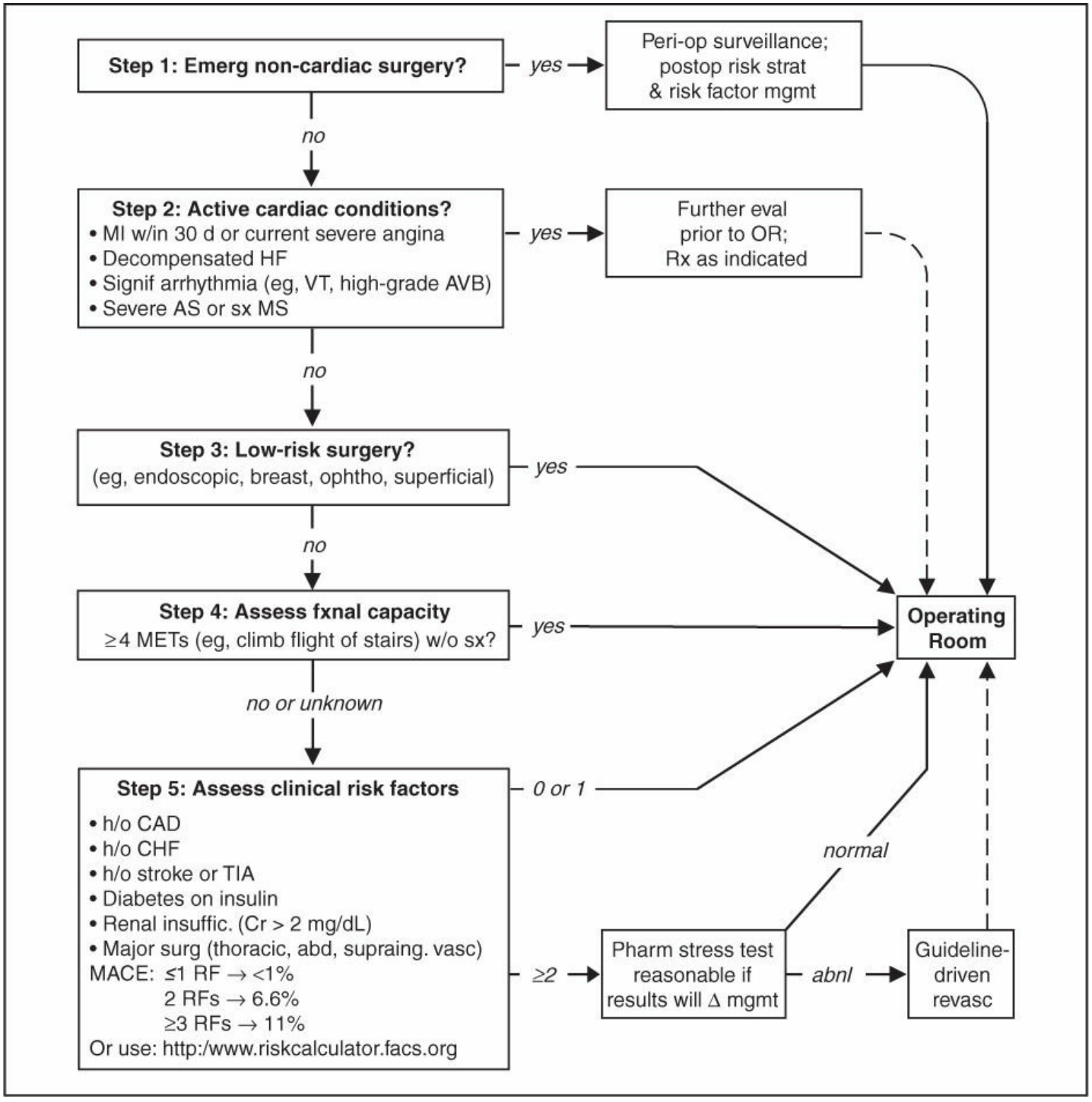
- Presents as *pocket infection* (warmth, erythema, tenderness) and/or *sepsis w/ bacteremia*
- ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%; antibacterial envelope ↓ risk
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Rx: abx; system removal if pocket infxn or GPC bacteremia; ∅ routine abx prior to inv. proc.

CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Goal: characterize risk of Pt & procedure → appropriate testing (ie, results will Δ management) and interventions (ie, reasonable probability of ↓ risk of MACE)

Preoperative evaluation (*NEJM* 2015;373:2258)

Figure 1-7 Approach to preop CV eval for non-CV surgery (modified from *Circ* 2014;130:e278)



Noninvasive Testing Result		
High Risk	Intermediate Risk	Low Risk
Ischemia at <4 METs manifested by ≥1 *of:* • Horiz/down ST ↓ ≥1 mm or STE • ≥5 abnl leads or ischemic ECG Δs lasting >3 min after exertion • SBP ↓ 10 mmHg or typical angina	*Ischemia at* 4–6 *METs manifested by* ≥1 *of:* • Horiz/down ST ↓ ≥1 mm • 3–4 abnl leads • 1–3 min after exertion	*No ischemia or at* >7 METs w/ • ST ↓ ≥1 mm or • 1–2 abnl leads

Additional preoperative testing (*Circ* 2014;130:e278)

- ECG if known cardiac disease and possibly reasonable in all, except if low-risk surgery
- TTE if any of following & prior TTE >12 mo ago or prior to Δ in sx: dyspnea of unknown origin; hx of HF w/ ↑ dyspnea; suspect (eg, murmur) or known ≥ moderate valvular dis.

Coronary artery disease

- If possible, wait ~60 d after MI in the absence of revascularization before elective surgery
- Coronary revasc guided by standard indications. Has not been shown to Δ risk of death or postop MI when done prior to elective vasc. surgery (*NEJM* 2004;351:2795).

Heart failure (*JACC* 2014;64:e77)

- Decompensated HF should be optimally Rx'd prior to elective surgery
- 30-d CV event rate: symptomatic HF > asx HFrEF > asx HFpEF > no HF

Valvular heart disease

- If meet criteria for valve intervention, do so before elective surgery (postpone if necessary)
- If severe valve disease and surgery urgent, intra- & postoperative hemodynamic monitoring reasonable (espec for AS, because at ↑ risk even if sx not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)

Cardiac implantable electronic devices

- Discuss w/ surgical team need for device (eg, complete heart block) & consequences if interference w/ fxn, and likelihood of electromagnetic interference
- Consider reprogramming, magnet use, etc. as needed

Pre- & perioperative pharmacologic management

- ASA: continue in Pts w/ existing indication. Initiation prior to surgery does not ↓ 30-d ischemic events and ↑ bleeding (*NEJM* 2014;370:1494), but Pts w/ recent stents excluded.
- Dual antiplatelet therapy: delay elective surg 14 d after balloon angioplasty, 30 d after BMS and ideally 6 mo (min 3 mo) after DES (*JACC* 2016; 68:1082) unless risk of bleeding > risk of stent thrombosis or ACS. If must discontinue $P2Y_{12}$ inh, continue ASA and restart $P2Y_{12}$ inh ASAP; can consider IV cangrelor if high-risk (*JAMA* 2012;307:265).
- **β**-blockers (*JAMA* 2015;313:2486)

  Continue βB in Pts on them chronically. Do not stop βB abruptly postop (may cause reflex sympathetic activation). Use IV if Pt unable to take PO.

  Reasonable to initiate if intermed- or high-risk ⊕ stress test, or RCRI ≥3, espec if vasc surgery. Initiate ≥1 wk prior to surgery (*not day of*), use low-dose, short-acting βB, and titrate to achieve HR and BP goal (? HR ~55–65). Avoid bradycardia and

HoTN.

- Statins: ↓ ischemia & CV events in Pts undergoing vascular surg (*NEJM* 2009;361:980). Consider if risk factors & non–low-risk surgery and in all Pts undergoing vascular surgery.
- ACEI/ARB: holding 24 h preop to ↓ intraop HoTN (*Anes* 2017;126:16). Restart ASAP.
- Amiodarone: ↓ incidence of postop AF if started prior to surgery (*NEJM* 1997;337:1785)

Postoperative monitoring

- ECG if known CAD or high-risk surgery. Consider if >1 risk factor for CAD.
- Routine troponin prognostic (*JAMA* 2017;317:1642) but ✔ only if sx/ECG Δs suggestive of ACS

PERIPHERAL ARTERY DISEASE (PAD)

Clinical features (*NEJM* 2016;374:861)

- Prev. ↑ w/ age: <1% if <40 y, ~15% if ≥70 y; risk factors incl. smoking, DM, HTN, chol
- Claudication (ache/cramp, often in calves) precip by walking and relieved by stopping (vs. spinal stenosis, qv); Leriche synd = claudic., ↓ or ∅ fem pulses, & erectile dysfxn
- Critical limb ischemia (CLI): rest pain (↑ w/ elevation b/c ↓ perfusion), ulcer (typically at pressure foci, often dry; in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition) or gangrene, due to PAD, and >2-wk duration (implies chronicity vs. acute limb ischemia; see below)

Diagnosis (*Circ* 2016;135:e686)

- ↓ peripheral pulses, bruits; signs of chronic PAD: hair loss, skin atrophy, nail hypertrophy
- Ankle:brachial index (ABI): nl 1–1.4; borderline 0.91–0.99; abnl ≤0.90; if >1.4, non-dx possibly due to calcified noncompressible vessel → ✔ PVR, TBI (toe-brachial index). If ABI abnl → segmental ABI w/ PVR to localize disease. If ⊕ sx but nl ABI, ✔ for ↓ lower extrem BP after exercise (≥20% ↓ in ABI w/ exercise or ≥30 mmHg ↓ in ankle pressure).
- Duplex arterial U/S; CTA w/ distal run-off; MRA or angio if dx in ? or possible intervention

Treatment (*JACC* 2013;61:1555; *JAMA* 2013;309:453 & 2015;314:1936)

- Risk factor modif. Screen for CAD/AAA. Structured exercise program (*JAMA* 2013;310:57).
- If sx or if asx with ABI ≤0.90, ASA, clopi, or ticag to ↓ D/MI/stroke (*NEJM* 2017; 376:32) More intensive antiplt Rx ↓ both MACE & limb ischemic events (*JACC* 2016;67:2719) Adding riva 2.5 mg bid to ASA ↓ MACE & death but ↑ bleeding (*NEJM* 2017;377:1319)
- Statins & PCSK9i ↓ MACE & limb ischemic events (*Circ* 2018;137:338). Cilostazol (if no HF).
- Endovascular (angioplasty vs. stent) or surgical revasc if limiting/refractory sx or CLI

Acute limb ischemia (ALI) (*Circ* 2016;135:e686)

- Sudden decrement in limb perfusion (ie, acutely cold & painful) that threatens viability
- Etiologies: embolism > acute thrombosis (eg, athero, APS, HITT), trauma to artery
- Clinical manifestations (6 Ps): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: pulse & neuro exam; arterial & venous Doppler; angiography, CTA or MRA
- Urgent consultation w/ vascular medicine and/or vascular surgery

Categorization & Treatment of ALI						
Audible Doppler		Motor		Cap.		
Art.	Ven.	fxn Loss	Sen. Loss	Refill	Status	Treatment
Y	Y	None	None	OK	Viable	A/C + urgent revasc
N	Y	Some	Some	Slow	Threatened	A/C + *emerg* revasc
N	N	Total	Complete	Absent	Irreversible	Amputation

NOTES

DYSPNEA

Pathophysiology	Etiologies
Airway obstruction (↑ resistance to airflow)	Asthma, COPD, bronchiectasis, cystic fibrosis, tumor, foreign body, vocal cord dysfunction, anaphylaxis
Alveolar / Parenchymal disease	Pulmonary edema: *cardiogenic* or *noncardiogenic* ILD; pneumonia; atelectasis
Vascular (V/Q mismatch)	Large vessel: PE, tumor emboli Small vessel: PHT, vasculitis, ILD, emphysema, PNA
Chest wall (↑ resistance to expansion; weakness of respir. muscles)	Pleural disease: large effusion, fibrosis, pneumothorax Chest wall/diaphragm: kyphoscoliosis, ↑ abd girth Neuromuscular disorders (ALS, GBS, MG) Hyperinflation (COPD, asthma)
Stimulation of receptors	Chemoreceptors: hypoxemia, metabolic acidosis Mechanoreceptors: ILD, pulmonary edema, PHT, PE
↓ O_2 carrying cap. (but nl P_aO_2)	Anemia, methemoglobinemia, CO poisoning
Psychological	Anxiety, panic attack, depression, somatization

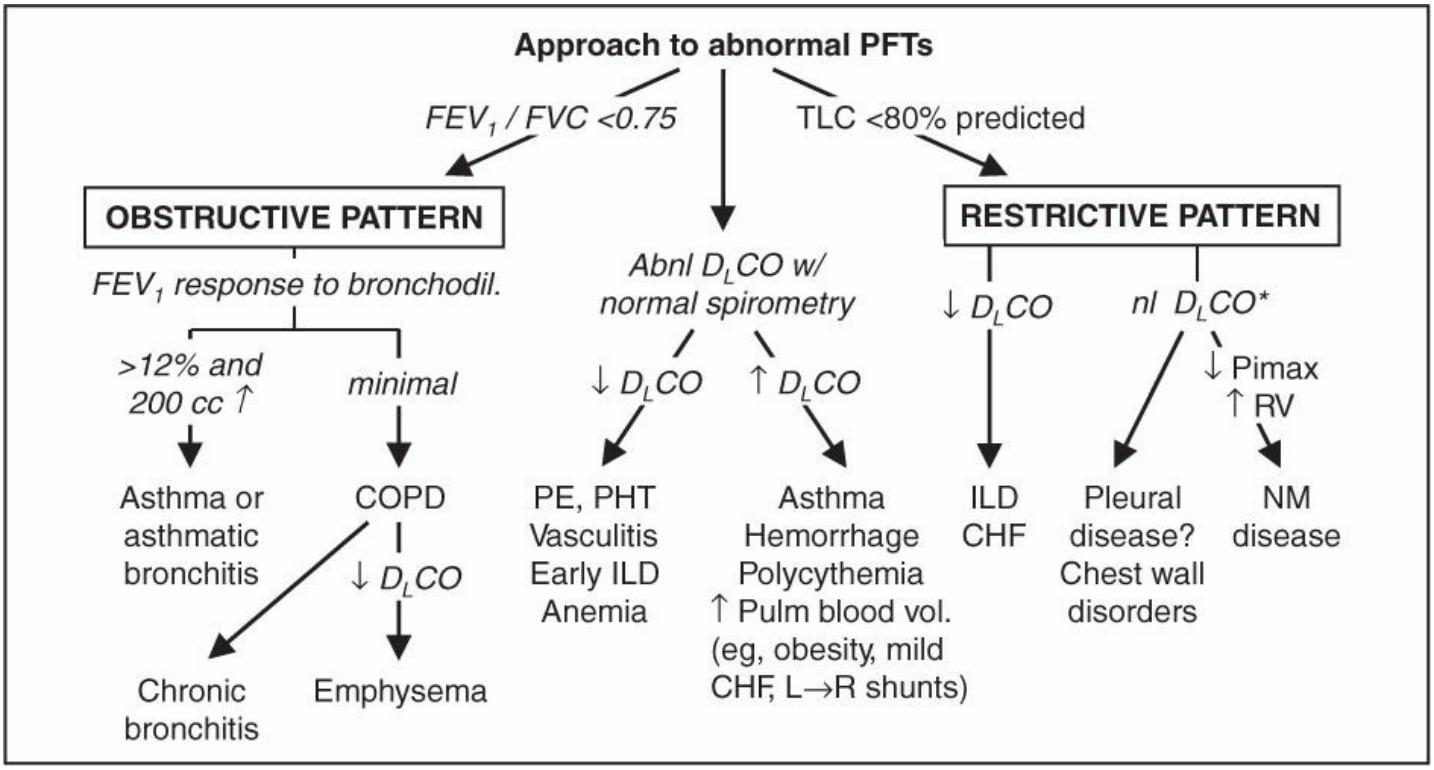
Evaluation

- History: quality of sensation, tempo, positional dependence, exac./allev. factors, exertion
- Cardiopulmonary exam, S_aO_2, CXR (see Appendix & Radiology inserts), ECG, ABG, U/S
  predictors of CHF: h/o CHF, PND, S_3, CXR w/ venous congestion, AF (*JAMA* 2005;294:1944) dyspnea w/ nl CXR: CAD, asthma, PE, PHT, early ILD, anemia, acidosis, NM disease
- Based on results of initial evaluation: PFT, chest CT, TTE, cardiopulmonary testing
- BNP & NT-proBNP ↑ in CHF (also ↑ in AF, RV strain from PE, COPD flare, PHT, ARDS)
  BNP <100 pg/mL to r/o CHF (90% Se), >400 to r/i (*NEJM* 2002;347:161)
  NT-proBNP <300 pg/mL to r/o CHF (99% Se); age-related cut points to r/i: >450 pg/mL (<50 y), >900 (50–75 y), >1800 (>75 y) (*EHJ* 2006;27:330)
  In chronic heart failure, ∴ need to compare to known "dry BNP"

PULMONARY FUNCTION TESTS (PFTs)

- Spirometry: evaluate for obstructive disease
  Flow-volume loops: diagnose and/or localize obstruction
  Bronchodilator: indicated if obstruction at baseline or asthma clinically suspected
  Methacholine challenge: helps dx asthma if spirometry nl, > 20% ↓ FEV_1 → asthma
- Lung volumes: evaluate for hyperinflation or restrictive disease including NM causes
- D_LCO: evaluates functional surface area for gas exchange; helps differentiate causes of obstructive and restrictive diseases and screens for vascular disease & early ILD

Figure 2-1 Approach to abnormal PFTs



FEV_1/FVC LLN typically 0.75. D_LCO can be diminished due to secondary atelectasis.

ASTHMA

Definition and epidemiology (*Lancet* 2018;391:783)

- Chronic inflam disorder w/ airway hyperresponsiveness + variable airflow obstruction
- Affects 5–10% population; ~85% of cases by age 40 y

Clinical manifestations (*NEJM* 2013;369:549)

- Classic triad = wheezing, cough, dyspnea; others include chest tightness, sputum; symptoms typically *chronic* with *episodic exacerbation*
- Precipitants (triggers)
  - *respiratory irritants* (smoke, perfume, etc.) & *allergens* (pets, dust mites, pollen, etc.)
  - *infections* (URI, bronchitis, sinusitis)
  - *drugs* (eg, ASA & NSAIDs via leukotrienes, βB via bronchospasm, MSO_4 via histamine)
  - emotional stress, cold air, exercise (increase in ventilation dries out airways)

Physical examination

- Wheezing and prolonged expiratory phase
- Presence of nasal polyps, rhinitis, rash → *allergic component*
- Exacerbation → ↑ RR, ↑ HR, accessory muscle use, diaphoresis, pulsus paradoxus

Diagnostic studies (*JAMA* 2017;318:279)

- Spirometry: ↓ FEV_1, ↓ FEV_1/FVC, coved flow-volume loop; lung volumes: ± ↑ RV & TLC
  - ⊕ bronchodilator response (↑ FEV_1 ≥12% & ≥200 mL) strongly suggestive of asthma
  - methacholine challenge (↓ FEV_1 ≥20%) if PFTs nl: Se >90%
- Allergy suspected → consider checking serum IgE, eos, skin testing/RAST

Ddx ("all that wheezes is not asthma…")

- Hyperventilation & panic attacks
- Upper airway obstruction or inh foreign body; laryngeal/vocal cord dysfxn (eg, 2° to GERD)
- CHF ("cardiac asthma"); COPD; bronchiectasis; ILD (including sarcoidosis); vasculitis; PE

"Asthma plus" syndromes

- Atopy = asthma + allergic rhinitis + atopic dermatitis
- Aspirin-exacerbated respiratory disease (Samter's syndrome) = asthma + ASA sensitivity + nasal polyps (*J Allergy Clin Immunol* 2015;135:676)
- ABPA = asthma + pulmonary infiltrates + allergic rxn to *Aspergillus* (*Chest* 2009;135:805)
  - Dx: ↑ IgE to *Asperg.* & total (>1000), ↑ *Asperg.* IgG levels, ↑ eos, central bronchiectasis

Rx: steroids ± itra-/voriconazole for refractory cases (*NEJM* 2000;342:756)

- Eosinophilic granulomatosis w/ polyangiitis (EGPA, previously Churg-Strauss) = asthma + eosinophilia + granulomatous vasculitis

---

CHRONIC MANAGEMENT

"Reliever" medications (used prn to quickly relieve sx)

- *Short-acting* inh β_2-agonists (SABA): albuterol Rx of choice
- *Short-acting* inh anticholinergics (ipratropium) ↑ β_2-agonist delivery → ↑ bronchodilation

"Controller" meds (taken daily to keep control) (*JAMA* 2017;318:279)

- Inh corticosteroids (ICS) Rx of choice. Superior to LAMA if sputum w/ ≥2% eos (*NEJM* 2019;380:2009). PO steroids may be needed for severely uncontrolled asthma; avoid if possible b/c of systemic side effects.
- *Long-acting* inh β_2-agonists (LABA; eg, salmeterol) safe & ↓ exacerbations when added to ICS (*NEJM* 2018;378:2497)
- *Long-acting* inh antimuscarinics (LAMA; eg, tiotropium, umeclidinium): may consider if sx despite ICS+LABA (*JAMA* 2018;319:1473)
- Leukotriene receptor antagonists (LTRA): some Pts very responsive, esp. ASA-sens (*AJRCCM* 2002;165:9) and exercise-induced (*Annals* 2000;132:97). May be noninferior to ICS initial Rx and LABA add-on Rx (*NEJM* 2011;364:1695).
- Nedocromil/cromolyn: limited use in adults. Useful in young Pts, exercise-induced bronchospasm; ineffective unless used before trigger or exercise exposure.

Immunotherapies (*NEJM* 2017;377:965)

- Allergen ImmunoRx ("allergy shots") may help if sig. allerg. component (*JAMA* 2016;315:1715)
- Anti-IgE (omalizumab) for uncontrolled mod-to-severe allergic asthma (w/ IgE >30) on ICS ± LABA (*JAMA* 2017; 318:279)
- Anti-IL5 (mepolizumab, reslizumab) ↓ exacerb in severe asthma (*NEJM* 2014;371:1189 & 1198)
- Anti-IL5Rα (benralizumab) ↓ steroid use, ↓ exac. in sev asthma w/ eos (*NEJM* 2017;376:2448)
- Anti-IL4Rα (dupilumab) blocks IL-4 & IL-13; ↓ exacerb in severe asthma, ↓ steroid use, ↑ FEV_1 (*NEJM* 2018;378:2475 & 2486)

Principles of treatment

- Education and avoidance of environmental triggers (*Lancet* 2015;386:1075); yearly flu shot
- Use quick-relief rescue medication as needed for all Pts
- Goal to achieve complete control = daily sx ≤2/wk, ∅ nocturnal sx or limitation of activity, reliever med ≤2/wk, nl peak expiratory flow rate or FEV_1; partly controlled = 1–2 of the above present in a wk; uncontrolled = ≥3 of the above present in a wk
- Step up treatment as needed to gain control, step down as tolerated
- Can abort exacerb by quadrupling ICS if deteriorating control (*NEJM* 2018;378:902)

Asthma Stepwise Therapy (Adapted from Global Initiative for Asthma [GINA] 2018 update)					
For all patients, rapid-acting β_2-agonists prn					
Controller options	Step 1	Step 2	Step 3	Step 4	Step 5
	Consider	*Select one*	*Select one*	*Do one or more*	*Add one or both*
	Low-dose ICS	**Low-dose ICS** LTRA	**Low-dose ICS + LABA**	↑ **ICS dose (w/ LABA)**	**Refer for biologics**
			Medium-dose ICS	Add LAMA	Oral steroids (lowest dose)
			Low-dose ICS + LTRA	Add LTRA	
			Low-dose ICS + theoph	Add theoph	

EXACERBATION

Evaluation

- History: baseline PEF, steroid requirement, ED visits, hospital admissions, prior intubation
  Current exacerbation: duration, severity, potential precipitants, meds used
  Risk factors for life-threatening: prior intubation, h/o near-fatal asthma, ED visit/hosp for asthma w/in 1 y, current/recent PO steroids, not using ICS, overdependent on SABA, Ψ, h/o noncompliance
- Physical exam: VS, pulm, accessory muscle use, pulsus paradoxus, abdominal paradox
  Assess for barotrauma: asymmetric breath sounds, tracheal deviation, subcutaneous air → pneumothorax, precordial (Hamman's) crunch → pneumomediastinum
- Diagnostic studies: peak expiratory flow (know personal best; <80% personal best c/w poor control, <50% c/w severe exacerbation); S_aO_2; CXR to r/o PNA or PTX; ABG if severe (low P_aCO_2 initially; nl or high P_aCO_2 *may* signify tiring)

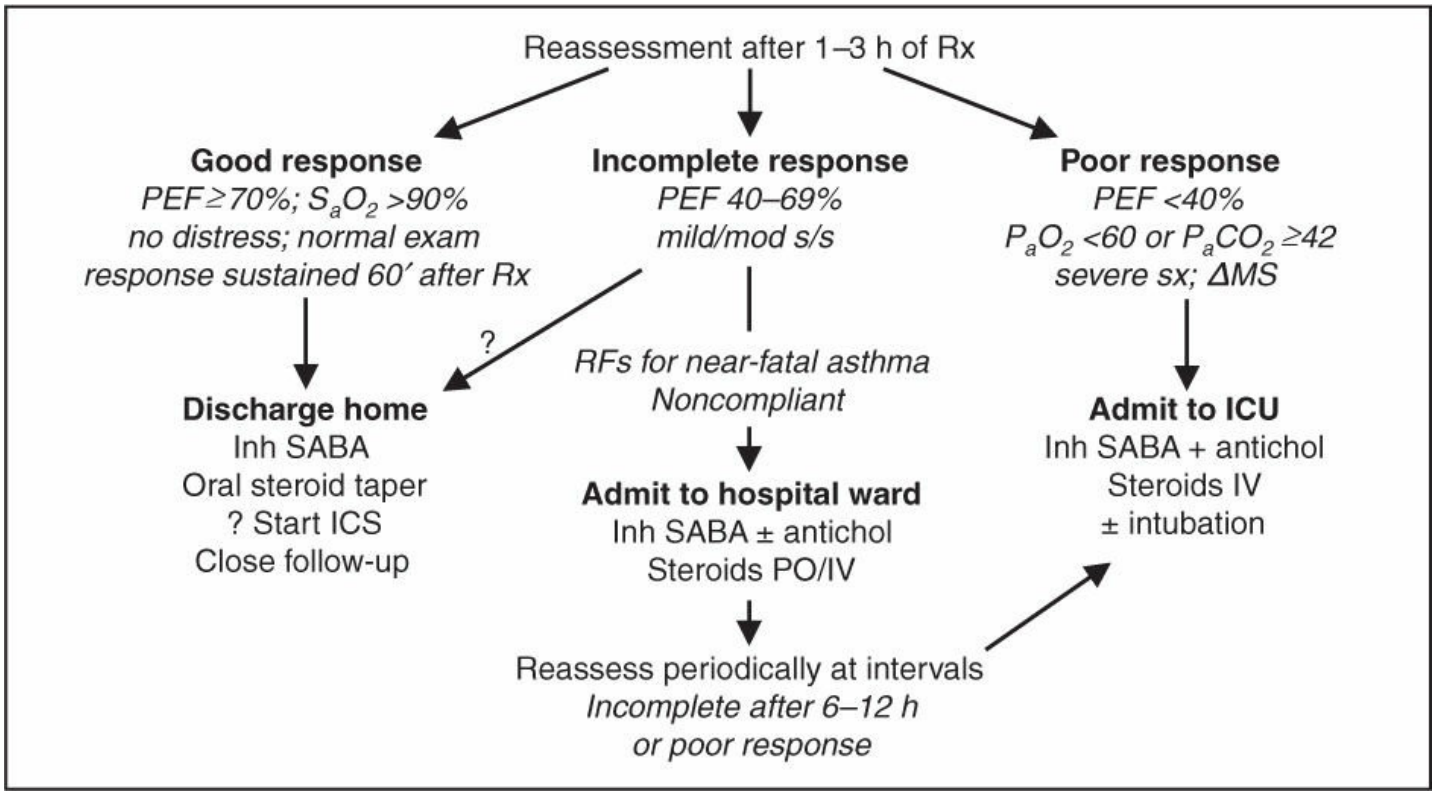
Severity of Asthma Exacerbation			
Feature	**Mild**	**Moderate**	**Severe**
Breathless w/. . .	Walking	Talking	At rest
Talking in . . .	Sentences	Phrases	Words
RR	↑	↑	>30
Accessory muscles	∅	⊕	⊕
Wheeze	Moderate, end-expir	Loud	Usually loud
HR	<100	100–120	>120
Pulsus paradoxus	Normal (<10)	10–25	>25
PEF	>80%	60–80%	<60%
S_aO_2	>95%	91–95%	<90%
P_aO_2	Normal	>60	<60
P_aCO_2	<45	<45	>45

Resp arrest imminent: drowsy, abdominal paradox, wheezes inaudible (b/c ∅ air movement), bradycardia, loss of abdominal paradox (respiratory muscle fatigue). Presence of several parameters (not necessarily all) indicates classification (adapted from GINA 2019 update).

Initial treatment (*NEJM* 2010;363:755)

- Oxygen to keep S_aO_2 ≥90%
- Inhaled SABA (eg, albuterol) by MDI (4–8 puffs) or nebulizer (2.5–5 mg) q20min
- Corticosteroids: prednisone 40-60 mg PO if outPt; methylpred IV if ED or inPt
- Ipratropium MDI (4–6 puffs) or nebulizer (0.5 mg) q20min if severe (*Chest* 2002;121:1977)
- *Reassess after 60–90 min of Rx*
  - Mild-mod exacerbation: cont SABA q1h
  - Sev exacerbation: SABA & ipratropium q1h or cont.; if refractory, consider Mg ± heliox
- *Decide disposition within 4 h of presentation and after 1–3 h of Rx*

Figure 2-2 Disposition of patients after initial treatment of asthma exacerbation



ICU-level care

- High-dose steroids: methylpred 125 mg IV q6h (*NEJM* 1999;340:1941)
- Invasive ventilation:
  Large ET tube, P_{plat} <30 cm H_2O (predicts barotrauma better than PIP), max exp time
  PEEP individualized to patient physiology
  Paralysis, inhalational anesthetics, bronchoalveolar lavage w/ mucolytic, heliox (60–80% helium) and ECMO have been used with success
- NPPV likely improves obstruction (*Chest* 2003;123:1018), but controversial and rarely used

ANAPHYLAXIS

Definition and pathophysiology (*Ann Emerg Med* 2006;47:373)

- Severe, rapid onset (mins to hrs), potentially life-threatening systemic allergic response
- IgE-mediated mast cell degranulation with release of histamine, tryptase, and TNF
- Precipitates systemic reactions (bronchospasm, tissue swelling, fluid shifts, vasodilation)
- Common triggers: penicillins, cephalosporins, shellfish, nuts, insect stings, IV contrast (not truly an IgE-mediated mechanism, but clinically similar)

Diagnosis: any of the three following criteria

1) Acute illness with skin ± mucosal involvement (rash, flushing, hives), AND at least one of:
   Respiratory compromise (wheeze, stridor, dyspnea, hypoxemia)
   Hypotension or hypoperfusion (syncope, incontinence)
2) Two or more of the following after exposure to a likely allergen: skin/mucosal involvement, respiratory compromise, ↓ BP or hypoperfusion, GI symptoms
3) Hypotension after exposure to known allergen for that Pt

Treatment

- Epi: IM 0.3–0.5 mL of 1:1000 dilution q5–20min; gtt at 0.1 mcg/kg/min if HoTN; avoid IVB
- Airway: suppl O_2 ± intubation or cricothyroidotomy (if laryngeal edema); β_2-agonists
- Fluid resuscitation w/ ≥1–2 L crystalloid (may extravasate up to 35% of intravasc volume)
- Antihistamines relieve hives & itching, *no effect on airway or hemodynamics*; H1RA (diphenhydramine 50 mg IV/IM) ± H2RA (ranitidine 50 mg IV)
- Steroids w/o immediate effect but may help prevent relapse: methylpred 125 mg IV q6h
- Avoid unopposed α-adrenergic vasopressors

Disposition

- Mild rxn limited to urticaria or mild bronchospasm can be observed for ≥6 h; admit all others
- Watch for biphasic reaction; occurs in 23%, typically w/in 8–10 h but up to 72 h

Angioedema (*J Allergy Clin Immunol* 2013;131:1491)

- Localized swelling of skin/mucosa; involves face, lips, tongue, uvula, larynx, and bowels
- Etiologies: mast cell-mediated (eg, NSAIDs); bradykinin-mediated (eg, ACEi, ARNi, hereditary angioedema, acquired C1 inhibitor deficiency); idiopathic
- Diagnosis: C4 and C1 inhibitor level, tryptase (if suspect anaphylaxis), ESR/CRP
- Rx: intubation if risk of airway compromise. Allergic angioedema: H1/H2 antihist., steroids.
  If 2° ACEi: d/c ACEi, antihist., icatibant (bradykinin-receptor antag; *NEJM* 2015;372:418).

Hereditary angioedema: plasma-derived C1 inhibitor (*NEJM* 2010;363:513), ecallantide (kallikrein inhibitor; *NEJM* 2010;363:523).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition and epidemiology (*Lancet* 2017;389:1931)

- Progressive airflow limitation caused by airway and parenchymal inflammation

Emphysema vs. Chronic Bronchitis		
	Emphysema	Chronic Bronchitis
Definition	Dilation/destruction of parenchyma (path definition)	Productive cough >3 mo/y × ≥2 y (clinical definition)
Pathophysiology	Tissue destruction V/Q: ↑ dead space fraction → hypercarbia, but only mild hypoxemia	Small airways affected V/Q: ↑ shunt fraction → severe hypoxemia, hypercapnia PHT, cor pulmonale
Clinical manifestations	Severe, constant dyspnea Mild cough	Intermittent dyspnea Copious sputum production
Physical exam	"Pink puffer" Tachypneic, noncyanotic, thin Diminished breath sounds	"Blue bloater" Cyanotic, obese, edematous Rhonchi & wheezes

Pathogenesis (*Lancet* 2017;389:1931)

- Cigarette smoke (centrilobular emphysema, affects 15–20% of smokers)
- Recurrent airway infections
- α_1-antitrypsin deficiency: early-onset panacinar emphysema, 1–3% of COPD cases. Suspect if age <45, lower lungs affected, extrathoracic manifestations (liver disease [not if MZ subtype], FMD, pancreatitis). ✔ serum AAT level (nb, acute phase reactant).
- Low FEV_1 in early adulthood associated w/ COPD (*NEJM* 2015;373:111)

Clinical manifestations

- Chronic cough, sputum production, dyspnea; later stages → freq exacerb, AM HA, wt loss
- Exacerbation triggers: infxn, other cardiopulmonary disease, including PE
  Infxn: overt tracheobronchitis/pneumonia from viruses, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* or triggered by changes in strain of colonizers (*NEJM* 2008;359:2355)
- Physical exam: ↑ AP diameter of chest ("barrel chest"), hyperresonance, ↓ diaphragmatic excursion, ↓ breath sounds, ↑ expiratory phase, rhonchi, wheezes
  during exacerbation: tachypnea, accessory muscle use, pulsus paradoxus, cyanosis
- *Asthma-COPD overlap syndrome* (ACOS; *NEJM* 2015;373:1241): features of both present. For example: reversibility of airway obstruction w/ bronchodilator in COPD; neutrophilic inflammation in asthma (more classic in COPD); eos in COPD

Diagnostic studies (*JAMA* 2019;321:786)

- CXR (see Radiology inserts): hyperinflation, flat diaphragms, ± interstitial markings & bullae
- PFTs: obstruction: ↓↓ FEV_1, ↓ FVC, FEV_1/FVC <0.7 (no sig Δ post bronchodilator),

expiratory scooping of flow-volume loop; hyperinflation: ↑↑ RV, ↑ TLC, ↑ RV/TLC; abnormal gas exchange: ↓ D_LCO (in emphysema)

- ABG: ↓ P_aO_2, ± ↑ P_aCO_2 (in chronic bronchitis, usually only if FEV_1 <1.5 L) and ↓ pH
- Screen *symptomatic* Pts w/ spirometry; don't screen if asx; screen for α1-AT deficiency

Chronic treatment (*JAMA* 2019;321:786)

- Bronchodilators (*1st-line*): long-acting muscarinic antag (LAMA), β_2-agonists (LABA)
  - LAMA (eg, tiotropium): ↓ exacerb, slows ↓ FEV_1, ↓ admit, ↓ resp failure; better than ipratropium or LABA (*NEJM* 2008;359:1543; 2011;364:1093; 2017;377:923)
  - LABA: ~11% ↓ in exacerbations, no ↑ in CV events (*Lancet* 2016;387:1817)
  - LAMA + LABA: ↑ FEV_1, ↓ sx vs. either alone (*Chest* 2014;145:981) and superior to LABA + inh steroid (*NEJM* 2016;374:2222)
- Corticosteroids (inhaled, ICS): ~11% ↓ in exacerbations & slows ↓ FEV_1; no Δ in risk of PNA or in mortality (*Lancet* 2016;387:1817)
- "Triple Therapy" (ICS-LAMA-LABA) ↓ exac, ↓ hosp, ↑ PNA (*Lancet* 2016;388:963 & 2018;391:1076; *NEJM* 2018; 378:1671)
- Roflumilast (PDE-4 inhib) + bronchodil: ↑ FEV_1, ↓ exacerb (*Lancet* 2015;385:857)
- Anti-IL5 (eg, mepolizumab, benralizumab): mixed data on ↓ exacerb in Pts w/ eos (*NEJM* 2017;377:1613 & 2019;DOI:10.1056/NEJMoa1905248)
- Antibiotics: daily azithro ↓ exacerbations, but not routine (*JAMA* 2014;311:2225)
- Oxygen: if P_aO_2 ≤55 mmHg or S_aO_2 ≤89% (during rest, exercise, or sleep) to prevent cor pulmonale; only Rx proven to ↓ mortality (*Annals* 1980;93:391; *Lancet* 1981;i:681); no benefit in Pts w/ moderate hypoxemia (S_aO_2 89–93%) (*NEJM* 2016;375:1617)
- NPPV if recent exacerb & P_aCO_2 >53 ↓ risk of readmit or death (*JAMA* 2017;317:2177)
- Prevention: Flu/Pneumovax; smoking cessation → 50% ↓ in lung function decline (*AJRCCM* 2002;166:675) and ↓ long-term mortality (*Annals* 2005;142:223)
- Rehabilitation: ↓ dyspnea and fatigue, ↑ exercise tolerance, ↓ QoL (*NEJM* 2009;360:1329)
- Surgery & bronchoscopic interventions
  - Lung volume reduction surgery: ↑ exercise capacity, ↓ mortality *if* FEV_1 >20%, upper lobe, low exercise capacity (*NEJM* 2003;348:2059)
  - Bronchoscopic lung reduction w/ endobronchial valves or coils: ↑ lung fxn but significant complications (PTX, PNA) (*NEJM* 2015;373:2325; *Lancet* 2015;386:1066; *JAMA* 2016;315175)
- Lung transplant: ↑ QoL and ↓ sx (*Lancet* 1998;351:24), ? survival benefit (*Am J Transplant* 2009;9:1640)

Staging and prognosis

- Assess breathlessness, cough, sputum, exercise capacity & energy (tools such as CAT and mMRC may be used as part of assessment)
- Ratio of diam PA/aorta >1 associated with ~3× ↑ risk of exacerbations (*NEJM* 2012;367:913)

COPD Staging and Recommended Therapies by GOLD Criteria			
GOLD FEV_1 Stage	**Exacerbation per Year**	**Mild Symptoms**	**Mod/Severe Symptoms**
I: ≥80%	<2	**A** Short-acting inh dilator prn	**B** LAMA
II: 50–79%			
III: 30–49%	≥2	**C** LAMA+LABA	**D** LAMA+LABA+ICS
IV: <30%		Consider adding PDE-4 inhib to bronchodilator	

Smoking cessation & vaccinations in all. Pulm rehab in groups B–D. O_2 as indicated per S_aO_2. (Adapted from GOLD Executive Summary [*AJRCCM* 2017;195:557])

EXACERBATION

COPD Exacerbation Treatment		
Agent	Dose	Comments
Ipratropium	MDI 4–8 puffs q1–2h *or* Nebulizer 0.5 mg q1–2h	First-line therapy (*NEJM* 2011;364:1093)
Albuterol	MDI 4–8 puffs q1–2h *or* Nebulizer 2.5–5 mg q1–2h	Benefit if component of reversible bronchoconstriction
Corticosteroids	Prednisone 40 mg/d × 5d (*JAMA* 2013;309:2223); some Pts will benefit from higher dose/longer course if severe Methylprednisolone 125 mg IV q6h × 72 h for more severe exacerbations	↓ treatment failure, ↓ hosp. stay ↑ FEV_1 but no mortality benefit, ↑ complications (*Cochrane* 2009:CD001288) OutPt Rx after ED visit ↓ relapse (*NEJM* 2003;348:2618)
Antibiotics	Amox, TMP-SMX, doxy, clarithro, antipneumococcal FQ all reasonable (no single abx proven superior). Consider local flora and avoid repeat courses of same abx. ≤5d course likely enough for mild-mod exacerbation (*JAMA* 2010;303:2035).	*H. flu*, *M. catarrhalis*, *S. pneumo* ↑ PEF, ↓ Rx failure, ? ↓ short-term mort, ↓ subseq exacerb (*Chest* 2008;133:756 & 2013;143:82) Consider if ↑ sputum purulence or CRP >40 (*Chest* 2013;144:1571)
Oxygenation	↑ F_iO_2 to achieve P_aO_2 ≥55–60 *or* S_aO_2 90–93%	Watch for CO_2 retention (due to ↑ V/Q mismatch, loss of hypoxemic resp drive, Haldane effect) *but must maintain oxygenation!*
Noninvasive positive-pressure ventilation	Initiate *early* if moderate/severe dyspnea, ↓ pH / ↑ P_aCO_2, RR >25 Results in 58% ↓ intubation, ↓ LOS by 3.2 d, 59% ↓ mortality Contraindications: Δ MS, inability to cooperate or clear secretions, hemodynamic instability, UGIB (*NEJM* 1995;333:817; *Annals* 2003;138:861; *Cochrane* 2004;CD004104; *ERJ* 2005;25:348)	
Endotracheal intubation	Consider if P_aO_2 <55–60, ↑'ing P_aCO_2, ↓'ing pH, ↑ RR, respiratory fatigue, Δ MS or hemodynamic instability	
Other measures	Mucolytics overall not supported by data (*Chest* 2001;119:1190) Monitor for cardiac arrhythmias	
Post-exacerb care	Follow up w/in 1 mo; smoking cessation if current smoker; vaccinations (influenza, pneumococcal), referral to pulm rehab (*AJRCCM* 2007;176:532)	

SOLITARY PULMONARY NODULE

Principles

- Definition: single, well-defined, <3 cm, surrounded by nl lung, no LAN or pleural effusion
- Often "incidentalomas," esp with ↑ CT use, but may still be early, curable malignancy

Etiologies	
Benign (70%)	Malignant (30%)
Granuloma (80%): TB, histo, coccidio Hamartoma (10%) Bronchogenic cyst, AVM, pulm infarct Echinococcosis, ascariasis, aspergilloma GPA, rheumatoid nodule, sarcoidosis Lipoma, fibroma, amyloidoma	Bronchogenic carcinoma (75%) periph: adeno (most common) & large cell central: squamous & small cell Metastatic (20%): sarcoma, melanoma, breast, head & neck, colon, testicular, renal Carcinoid, primary sarcoma

Initial evaluation

- History: h/o cancer, smoking, age (<30 y = 2% malignant, +15% each decade >30)
- CT: size/shape, Ca^{2+}, LAN, effusions, bony destruction, compare w/ old studies
  ∅ Ca → ↑ likelihood malignant; laminated → granuloma; "popcorn" → hamartoma
- High-risk features for malig: size (eg, ≥2.3 cm diameter), spiculated, upper lobe, ♀, >60 yo, >1 ppd current smoker, no prior smoking cessation (*NEJM* 2003;348:2535 & 2013;369:910)

Diagnostic studies

- PET: detects metabolic activity of tumors, 97% Se & 78% Sp for malig (esp if >8 mm)
  useful for surgical staging b/c may detect unsuspected mets (*JAMA* 2001;285:914)
  useful in deciding which lesions to bx vs. follow w/ serial CT (*J Thor Oncol* 2006;1:71)
- Transthoracic needle biopsy (TTNB): if tech feasible, 97% will obtain definitive tissue dx (*AJR* 2005;185:1294); if noninformative or malignant → resect
- Video-assisted thoracoscopic surgery (VATS): for percutaneously inaccessible lesions; highly sensitive and allows resection; has replaced thoracotomy
- Transbronchial bx (TBB): most lesions too small to reliably sample w/o endobronchial U/S (*Chest* 2003;123:604); bronch w/ brushings low-yield unless invading bronchus; navigational bronchoscopy w/ 70% yield, ↑ sens w/ larger nodules (*Chest* 2012;142:385)
- PPD, fungal serologies, ANCA

Management (if >8 mm; if ≤8 mm, serial CT q6-12mo) (*Chest* 2013;143:840)

- Low risk (<5%, see ref): serial CT (freq depending on risk); shared decision w/ Pt re: bx
- Intermediate risk (5–60%): PET; if → → follow low-risk protocol, if ⊕ → → high-risk protocol
- High risk (and surgical candidate): TBB, TTNB, or VATS → lobectomy if malignant
- Ground-glass nodules: longer f/u (b/c if malignant can be slow-growing) & PET

HEMOPTYSIS

Definition and pathophysiology

- Expectoration of blood or blood-streaked sputum
- Massive hemoptysis: >100 mL/h or >500 mL in 24 h; massive hemoptysis usually from tortuous or invaded bronchial arteries

Etiologies (*Crit Care Med* 2000;28:1642)	
Infection/ Inflammation	Bronchitis (most common cause of trivial hemoptysis) Bronchiectasis incl CF (common cause of massive hemoptysis) TB or aspergilloma (can be massive); pneumonia or lung abscess
Neoplasm	Usually primary lung cancer, sometimes metastasis (can be massive)
Cardiovasc	PE (can be massive), pulmonary artery rupture (2° to instrumentation), CHF, mitral stenosis, trauma/foreign body, bronchovascular fistula
Other	Vasculitis (GPA, Goodpasture's, Behçet's), AVM, anticoag (w/ underlying lung dis), coagulopathy, cocaine, pulm hemosiderosis

Diagnostic workup

- Localize bleeding site (r/o *GI or ENT source* by H&P ± endo); determine whether unilateral or bilateral, localized or diffuse, parenchymal or airway by CXR/chest CT ± bronch
- PT, PTT, CBC to rule out coagulopathy
- Sputum culture/stain for bacteria, fungi and AFB; cytology to r/o malignancy
- ANCA, anti-GBM, urinalysis to ✔ for vasculitis or pulmonary-renal syndrome

Treatment

- Death is from asphyxiation not exsanguination; maintain gas exchange, reverse coagulopathy and Rx underlying condition; cough suppressant may ↑ risk of asphyxiation
- Inhaled tranexamic acid promising (*Chest* 2018;154:1379)
- Massive hemoptysis: put bleeding side dependent; selectively intubate nl lung if needed
  - *Angiography:* Dx & Rx (vascular occlusion balloons or selective embol of bronchial art)
  - *Rigid bronch:* allows more options (electrocautery, laser) than flexible bronch
  - *Surgical resection*

BRONCHIECTASIS

Definition and epidemiology (*NEJM* 2002;346:1383)

- Obstructive airways disease of bronchi and bronchioles, chronic transmural inflammation w/ airway dilatation and thickening, collapsibility, mucus plugging w/ impaired clearance

Initial workup

- H&P: cough, dyspnea, copious sputum production, ±hemoptysis, inspiratory "squeaks"
- CXR: scattered or focal; rings of bronchial cuffing; "tram track" of dilated, thick airways
- PFTs: obstructive; chest CT: airway dilation & thickening ± cystic Δs, infiltrates, adenopathy

Etiology	Other Features	Diagnostic Testing
Chronic infxns (eg, MTb, ABPA)	Chronic cough, freq/persist infiltrate, refract asthma (ABPA)	Sputum cx (incl mycobact, fungal), ± bronch/BAL, IgE & eos (ABPA)
1° ciliary dyskin	Sinusitis, infertility, otitis	Dynein mutations
Immunodefic	Recurrent infxns often as child	IgA, IgG, IgM, IgG subclasses
RA, SLE	Resp sx may precede joint sx	RF, ANA
IBD	Not relieved by bowel resection	Colonoscopy, biopsy
α_1-AT deficiency	Lower lobe emphysema	α_1-AT level
Anatomic	R middle lobe synd. from sharp takeoff, foreign body aspiration	Bronchoscopy

Treatment

- Acute exacerbations: antibiotics directed against prior pathogens; if no prior Cx data → FLQ
- Chronic mgmt: treat underlying condition, chest PT, inhaled hypertonic saline, bronchodil.; prophylactic azithro shown to ↓ exacerb in non-CF bronchiectasis (*JAMA* 2013:1251)

Non-tuberculous mycobacterium (NTM; ubiquitous hydrophilic bacteria)

- Chronic cough, ↓ wt; Lady Windermere syndrome: R middle lobe bronchiectasis in elderly ♀ who suppress expectoration
- Dx: CT scan (tree-in-bud, nodules, cavities, bronchiect.), sputum ×3 or BAL, AFB stain + Cx
- Treatment: [azithro or clarithro] + rifamycin & ethambutol for ≥12 mo (*Chest* 2004;126:566)

CYSTIC FIBROSIS

Definition and pathophysiology (*NEJM* 2015;372:351)

- Autosomal recessive genetic disorder due to mutations in chloride channel (CFTR gene)
- ↑ mucus thickness, ↓ mucociliary clearance, ↑ infections → bronchiectasis

Clinical features

- Recurrent PNA, sinus infections
- Distal intestinal obstruction syndrome (DIOS), pancreatic insufficiency (steatorrhea, malabsorption, failure to thrive, weight loss), CF-related diabetes, infertility

Treatment (*Lancet* 2016;388:2519)

- Acute exacerbations: may be assoc w/ persistent drop in FEV_1 (*AJRCCM* 2010;182:627); continue aggressive airway clearance, target abx based on sputum cx (incl double coverage for PsA); common pathogens include PsA, *S. aureus*, non-typeable *H flu*, *Stenotrophomonas*, *Burkholderia*, NTM
- Chronic mgmt: airway clearance with chest PT, inhaled hypertonic saline, inhaled DNAse (dornase alfa), SABA; oral azithromycin if chronic respiratory symptoms, inhaled tobramycin or aztreonam if persistent PsA infection
- CFTR potentiator (ivacaftor) or corrector (lumacaftor, tezacaftor) depending on mutation; combination approved for patients homozygous for ΔF508 (most common mutation) (*NEJM* 2011;365:1663; 2015;373:220; 2017;377:2013 & 2024)
- Lung transplantation; refer to lung transplant center when FEV_1 <30% predicted, rapidly declining FEV_1, 6MWT <400 m, evidence of PHT, significant clinical decline

INTERSTITIAL LUNG DISEASE

WORKUP OF ILD (*Thorax* 2008;63:v1)

May present as incidental finding, subacute dyspnea, or rapidly progressive hypox. resp fail.

Broad categories

- (1) Sarcoid; (2) Exposure-related (eg, drugs, XRT, organic & inorganic dusts); (3) Collagen vascular dis. (eg, scleroderma, GPA, RA); (4) Idiopathic PNAs (eg, IPF)

Rule out mimickers of ILD

- Congestive heart failure (✔ BNP, trial of diuresis); infection: viral, atypical bacterial; malignancy: lymphangitic carcinomatosis, bronchoalveolar, leukemia, lymphoma

History and physical exam

- Occupational, exposures (eg, birds), tobacco, meds, XRT, FHx, precipitating event
- Tempo (acute → infxn, CHF, hypersens pneumonitis, eos PNA, AIP, COP, drug-induced)
- Extrapulm signs/sx (skin Δs, arthralgias, arthritis, myalgias, muscle weakness, clubbing)

Diagnostic studies (see Appendix & Radiology inserts)

- CXR and high-resolution chest CT
  - Upper lobe predom: hypersensitivty pneumonitis, coal, silica, smoking-related ILD
  - Lower lobe predom: IPF, NSIP, asbestosis
  - Adenopathy: malignancy, sarcoidosis, berylliosis, silicosis
  - Pleural disease: collagen-vascular diseases, asbestosis, infections, XRT
- PFTs: ↓ D_LCO (*early sign*), restrictive pattern (↓ volumes), ↓ P_aO_2 (esp. w/ exercise); If restrictive + obstructive, consider sarcoid If combined pulmonary fibrosis and emphysema (CFPE) → near-nl lung vol on PFTs
- Serologies: ✔ ACE, ANA, RF, ANCA, CCP, SSA/SSB, Scl 70, CK, aldolase, myositis panel
- If diffuse alveolar hemorrhage (DAH), Hb typically ↓ 1-2 g/dL
- Bronchoalveolar lavage: dx infxn, hemorrhage, eosinophilic syndromes
- Bx (transbronch, CT-guided, VATS depending on location of findings) if unclear etiology

SPECIFIC ETIOLOGIES OF ILD

Sarcoidosis (*Lancet* 2014;383:1155)

- Prevalence: African Americans, northern Europeans, and females; onset in 3rd-5th decade
- Pathophysiology: depression of cellular immune system peripherally, activation centrally

Clinical Manifestations of Sarcoidosis	
Organ System	Manifestations

Pulmonary	Hilar LAN; fibrosis; pulm hypertension. Stages: I = bilat hilar LAN; II = LAN + ILD; III = ILD only; IV = diffuse fibrosis.
Cutaneous (~15%)	Waxy skin plaques; lupus pernio (violaceous facial lesions) Erythema nodosum (red tender nodules due to panniculitis, typically on shins). Ddx: idiopathic (34%), infxn (33%, strep, TB), sarcoid (22%), drugs (OCP, PCNs), vasculitis (Behçet's), IBD, lymphoma.
Ocular (10–30%)	Anterior > posterior uveitis; ↑ lacrimal gland
Endo & renal (10%)	Nephrolithiasis, hypercalcemia (10%), hypercalciuria (40%) Due to vitamin D hydroxylation by macrophages
Neuro (10% clin, 25% path)	CN VII palsy, periph neuropathies, CNS lesions, seizures
Cardiac (5% clin, 25% path)	Conduction block, VT, CMP
Liver, spleen, BM	Granulomatous hepatitis (25%), splenic & BM gran. (50%)
Constitutional	Fever, night sweats, anorexia & wt loss (a/w hepatic path)
Musculoskeletal	Arthralgias, periarticular swelling, bone cysts

- *Löfgren's syndrome:* erythema nodosum + hilar adenopathy + arthritis (good prognosis)
- Diagnostic studies: LN bx → noncaseating granulomas + multinucleated giant cells
  Endobronchial ultrasonography superior to conventional bronch (*JAMA* 2013;309:2457)
  ^{18}FDG PET can be used to identify extent and potentially targets for dx bx
  ↑ ACE (Se 60%, 90% w/ active dis., Sp 80%, false ⊕ in granulomatous diseases)
- To assess extent: CXR, PFTs, full ophtho exam, ECG, CBC (lymphopenia, ↑ eos), Ca, 24-h urine for Ca, LFTs; ± Holter, echo, cardiac MRI, brain MRI, etc., based on s/s
- Rx: steroids if sx or extrathoracic organ dysfxn (eg, prednisone 20–40 mg/d), improves sx, but doesn't Δ long-term course; hydroxychloroquine for extensive skin disease; MTX, AZA, mycophenolate, or anti-TNF for chronic/refractory disease
- Prognosis: ~2/3 spontaneously remit w/in 10 y (60–80% of stage I, 50–60% stage II, 30% stage III), w/ relapses uncommon; ~1/3 have progressive disease

Exposure

- Drugs/Iatrogenic
  Amiodarone: interstitial pneumonitis ↔ org. PNA ↔ ARDS; Rx: d/c amio; steroids
  Other drugs: nitrofurantoin, sulfonamides, INH, hydralazine
  Chemo: bleomycin, busulfan, cyclophosphamide, MTX, immunotherapy, XRT
- Pneumoconioses (inorganic dusts) (*NEJM* 2000;342:406; *Clin Chest Med* 2004;25:467)
  Coal worker's: upper lobe coal macules; may progress to massive fibrosis
  Silicosis: upper lobe opacities ± eggshell calcification of lymph nodes; ↑ risk of TB
  Asbestosis: lower lobe fibrosis, calcified pleural plaques, DOE, dry cough, rales on exam. Asbestos exposure → pleural plaques, benign pleural effusion, diffuse pleural thickening, rounded atelectasis, mesothelioma, lung Ca (esp. in smokers).
  Berylliosis: multisystemic granulomatous disease that mimics sarcoidosis
- Hypersensitivity pneumonitides (organic dusts): loose, noncaseating *granulomas*
  Antigens: farmer's lung (spores of thermophilic actinomyces); pigeon fancier's lung (proteins from feathers and excreta of birds); humidifier lung (thermophilic bacteria)

Collagen vascular diseases (*Chest* 2013;143:814)

- Rheumatologic disease

Scleroderma: fibrosis in ~50%; PHT seen in ~10% of CREST Pts
PM-DM: ILD & skin/muscle findings; MCTD: PHT & fibrosis
SLE & RA: pleuritis and pleural effusions more often than ILD; SLE can cause DAH

- Vasculitis (can p/w *DAH*)
  Granulomatosis w/ polyangiitis (GPA): ⊕ c-ANCA w/ necrotizing granulomas
  Eosinophilic GPA (EGPA): ⊕ c- or p-ANCA w/ eosinophilia & necrotizing granulomas
  Microscopic polyangiitis: ⊕ p-ANCA w/o granulomas
- Goodpasture's syndrome = DAH + RPGN; typically in smokers; ⊕ anti-GBM in 90%
- Lymphangioleiomyomatosis (LAM): cystic, ↑ in ♀, Rx w/ sirolimus (*NEJM* 2011;364:1595)

Idiopathic interstitial pneumonias (IIPs) (*AJRCCM* 2013;188:733)

- Definition: ILD of unknown cause; dx by radiographic, histologic, and clinical features

IIPs		
Type	Imaging/Histology	Clinical
IPF	UIP pattern: reticular opacities, honeycombing, traction bronchiectasis; peripheral, subpleural, & basal	Sx >12 mo 5-y mort ~80%
NSIP	Homogenous ground-glass opacities or consolid., reticular irreg lines; symmetric, peripheral, basal, subpleural. Cellular & fibrotic subtypes, latter similar to UIP.	Sx mos–y 5-y mort 10%
COP	Patchy, migratory consolidations; subpleural & peribronchial. Excessive proliferation of granulation tissue in small airways and alveolar ducts.	Post-infxn, XRT, rxn to drug. 5-y mort <5%
AIP	Diffuse ground-glass opacities, consolidations w/ lobular sparing. Path similar to DAD.	Sx <3 wk 6-mo mort 60%
DIP	Diffuse ground-glass opacities, reticular lines; lower zones. Peripheral Mφ in alveoli.	30–50 yo *smokers* Sx wks–mos Death rare
RB-ILD	Bronchial thickening, centrilobular nodules, patchy ground-glass opacities; upper lobe predom. Mφ in alveoli.	

UIP, usual interstitial PNA (IP); IPF, idiopathic pulm fibrosis (*Lancet* 2017;389:1941 & *NEJM* 2018;378:1811); NSIP, non-specific IP; COP, cryptogenic organizing PNA; AIP, acute IP (Hamman-Rich syndrome); DIP, desquamative IP; RB-ILD, resp bronchiolitis-assoc ILD.

- Rx for IPF: suppl O_2, pulm rehab, Rx for GERD, PHT screening, lung tx referral;
  pirfenidone (antifibrotic) or nintedanib (tyrosine kinase inhib mediating fibrogenic growth factors) ↓ rate of FVC decline (*NEJM* 2014;370:2071 & 2083; *AJRCCM* 2015;192:3)
  high-dose steroids may be used for acute exacerbations, but no RCT data
- Steroids for other IIPs: NSIP (esp. cellular type) and COP (*AJRCCM* 2000;162:571); ? benefit for AIP and DIP/RB-ILD (for which Pts should stop smoking)

Pulmonary infiltrates w/ eosinophilia (PIE) = eos on BAL ± peripheral blood

- Allergic bronchopulmonary aspergillosis (ABPA)
- Löffler's syndrome: parasites/drugs → transient pulm infilt + cough, fever, dyspnea, eos
- Acute eosinophilic PNA (AEP): acute hypox febrile illness; Rx: steroids, tobacco cessation
- Chronic eosinophilic pneumonia (CEP): "photonegative" of CHF, typically in women

Miscellaneous

- Pulm alveolar proteinosis (PAP): accumulation of surfactant-like phospholipids; white & gummy sputum; BAL milky fluid (*NEJM* 2003;349:2527); Rx w/ lung lavage & GMCSF
- Langerhans cell granulomatosis (LCG): young ♂ smokers; apical cysts; PTX (25%)

PLEURAL EFFUSION

Pathophysiology

- Systemic factors (eg, ↑ PCWP, ↓ oncotic pressure) → *transudative* effusion
- Local factors (ie, Δ pleural surface permeability) → *exudative* effusion

Transudates

- Congestive heart failure (40%): 80% bilateral, ± cardiomegaly on CXR occasionally exudative (especially after aggressive diuresis or if chronic)
- Constrictive pericarditis (knock on exam, calcification or thickening on imaging)
- Cirrhosis ("hepatic hydrothorax"): diaphragmatic pores allow passage of ascitic fluid often right-sided ($^2/_3$) & massive (even w/o marked ascites)
- Nephrotic syndrome: usually small, bilateral, asymptomatic (r/o PE b/c hypercoag)
- Other: PE (usually exudate), malignancy (lymphatic obstruction), myxedema, CAPD

Exudates

- Lung parenchymal infection (25%)
  - Bacterial (parapneumonic): can evolve along spectrum of *exudative* (but sterile) → *fibropurulent* (infected fluid) → *organization* (fibrosis & formation of rigid pleural peel). Common causes: *Strep pneumo, Staph aureus, Strep milleri, Klebsiella, Pseudomonas, Haemophilus, Bacteroides, Peptostreptococcus*, mixed flora in aspiration pneumonia.
  - Mycobacterial: >50% lymphs 80% of the time, ADA >40, pleural bx ~70% Se
  - Fungal, viral (usually small), parasitic (eg, amebiasis, echinococcosis, paragonimiasis)
- Malignancy (15%): primary lung cancer most common, metastases (esp. breast, lymphoma, etc.), mesothelioma (✔ serum osteopontin levels; *NEJM* 2005;353:15)
- Pulmonary embolism (10%): effusions in ~40% of PEs; exudate (75%) > transudate (25%); hemorrhagic—*must have high suspicion b/c presentation highly variable*
- Collagen vascular disease: RA (large), SLE (small), GPA, EGPA
- Abdominal diseases: pancreatitis, cholecystitis, esophageal rupture, abdominal abscess
- Hemothorax (Hct_{eff}/Hct_{blood} >50%): trauma, PE, malignancy, coagulopathy, leaking aortic aneurysm, aortic dissection, pulmonary vascular malformation
- Chylothorax (triglycerides >110): thoracic duct damage due to trauma, malignancy, LAM
- Other:
  - Post-CABG: left-sided; initially bloody, clears after several wks
  - Dressler's syndrome (pericarditis & pleuritis post-MI), uremia, post-radiation therapy
  - Asbestos exposure: benign; ⊕ eosinophils
  - Drug-induced (eg, nitrofurantoin, methysergide, bromocriptine, amiodarone): ⊕ eos
  - Uremia; post-XRT; sarcoidosis
  - Meigs' syndrome: benign ovarian tumor → ascites & pleural effusion
  - Yellow-nail syndrome: yellow nails, lymphedema, pleural effusion, bronchiectasis

Diagnostic studies (*NEJM* 2018;378:740)

- Thoracentesis (ideally U/S guided) (*NEJM* 2006;355:e16)
  Indications: all effusions >1 cm in decubitus view
  if suspect due to CHF, can diurese and see if effusions resolve (75% do so in 48 h); *asymmetry, fever, chest pain or failure to resolve* → thoracentesis
  parapneumonic effusions should be tapped ASAP (*cannot* exclude infxn clinically)
  Diagnostic studies: ✔ total protein, LDH, glucose, cell count w/ differential, Gram stain & culture, pH; remaining fluid for additional studies as dictated by clinical scenario
  Complications: PTX (5–10%), hemothorax (~1%), re-expansion pulm edema (if >1.5 L removed), spleen/liver lac.; post-tap CXR not routinely needed (*Annals* 1996;124:816)
  ↓ PTX w/ U/S and experienced supervisor; even with INR ~1.9, risk of bleed low w/ U/S & experienced operator (*Chest* 2009;135:1315 & 2013;144:456; *Archives* 2010;170:332)
- Transudate vs. exudate (*JAMA* 2014;311:2422)
  Light's criteria: exudate = TP_{eff}/TP_{serum} >0.5 *or* LDH_{eff}/LDH_{serum} >0.6 *or* LDH_{eff} $>^2/_3$ ULN of LDH_{serum}; 97% Se, 85% Sp; best Se of all methods; however, will misidentify 25% of transudates as exudates; ∴ if clinically suspect transudate but meets criterion for exudate, confirm w/ test w/ higher Sp
  Exudative criteria w/ better Sp: $chol_{eff}$ >55 mg/dL (95–99% Sp); $chol_{eff}$ >45 mg/dL *and* LDH_{eff} >200 (98% Sp); $chol_{eff}/chol_{serum}$ >0.3 (94% Sp); serum-effusion alb gradient ≤1.2 (92% Sp); serum-effusion TP gradient ≤3.1 (91% Sp)
  CHF effusions: *TP may ↑ with diuresis or chronicity* → "pseudoexudate"; alb gradient ≤1.2, $chol_{eff}$ >60 mg/dL (Se 54%, Sp 92%) or clin judgment to distinguish (*Chest* 2002;122:1524)
- Complicated vs. uncomplicated parapneumonic (*Chest* 1995;108:299)
  complicated = ⊕ Gram stain or culture *or* pH <7.2 *or* glucose <60
  complicated parapneumonic effusions usually require tube thoracostomy for resolution
  empyema = frank pus, also needs tube thoracostomy (*J Thorac CV Surg* 2017;153:e129)
- Additional pleural fluid studies (*NEJM* 2002;346:1971)
  NT-proBNP ≥1500 pg/mL has 91% Se & 93% Sp for CHF (*Am J Med* 2004;116:417)
  WBC & diff.: exudates tend to have ↑ WBC vs. transudates but nonspecific neutrophils → parapneumonic, PE, pancreatitis lymphocytes (>50%) → cancer, TB, rheumatologic eos (>10%) → blood, air, drug rxn, asbestos, paragonimiasis, Churg-Strauss, PE
  RBC: Hct_{eff} 1–20% → cancer, PE, trauma; Hct_{eff}/Hct_{blood} >50% → hemothorax
  AFB: yield in TB 0–10% w/ stain, 11–50% w/ culture, ~70% w/ pleural bx
  adenosine deaminase (ADA): seen w/ granulomas, >70 suggests TB, <40 excludes TB
  cytology: ideally ≥150 mL and at least 60 mL should be obtained (*Chest* 2010;137:68)
  glucose: <60 mg/dL → malignancy, infection, RA
  amylase: seen in pancreatic disease and esophageal rupture (salivary amylase)
  rheumatoid factor, C_H50, ANA: *limited utility* in dx collagen vascular disease
  triglycerides: >110 → chylothorax, 50–110 → ✔ lipoprotein analysis for chylomicrons
  cholesterol: >60; seen in chronic effusions (eg, CHF, RA, old TB)

creatinine: effusion/serum ratio >1 → urinothorax
fibulin-3: ↑ plasma and/or effusion levels → mesothelioma (*NEJM* 2012;367:1417)

- Chest CT; pleural biopsy; VATS
- Undiagnosed persistent pleural effusions (*Clin Chest Med* 2006;27:309)
  Transudative: most commonly CHF or hepatic hydrothorax. ✔ s/s CHF or cirrhosis, NT-proBNP$_{eff}$; consider intraperitoneal injection of technetium-99m sulfur colloid
  Exudative (ensure using Sp test listed above): most commonly malig, empyema, TB, PE. ✔ s/s malig, chest CT (I^+), ADA or IFN-γ release assay; consider thoracoscopy.

Characteristics of Pleural Fluid (not diagnostic criteria)

Etiology	Appear	WBC Diff	RBC	pH	Glc	Comments
CHF	clear, straw	<1000 *lymphs*	<5000	normal	≈ serum	bilateral, cardiomegaly
Cirrhosis	clear, straw	<1000	<5000	normal	≈ serum	right-sided
Uncomplicated parapneumonic	turbid	5–40,000 *polys*	<5000	normal to ↓	≈ serum (>40)	
Complicated parapneumonic	turbid to purulent	5–40,000 *polys*	<5000	↓↓	↓↓ (<40)	need drainage
Empyema	purulent	25–100,000 *polys*	<5000	↓↓↓	↓↓	need drainage
Tuberculosis	serosang.	5–10,000 *lymphs*	<10,000	normal to ↓	normal to ↓	⊕ AFB ⊕ ADA
Malignancy	turbid to bloody	1–100,000 *lymphs*	<100,000	normal to ↓	normal to ↓	⊕ cytology
Pulmonary embolism	*sometimes* bloody	1–50,000 *polys*	<100,000	normal	≈ serum	no infarct → transudate
Rheumatoid arthritis/SLE	turbid	1–20,000 *variable*	<1000	↓	RA ↓↓↓ SLE nl	↑ RF, ↓ C_H50 ↑ imm. complex
Pancreatitis	Serosang. to turbid	1–50,000 *polys*	<10,000	normal	≈ serum	left-sided, ↑ amylase
Esophageal rupture	turbid to purulent	<5000 >50,000	<10,000	↓↓↓	↓↓	left-sided, ↑ amylase

Treatment

- Symptomatic effusion: therapeutic thoracentesis, treat underlying disease process
- Parapneumonic effusion (*Chest* 2000;118:1158)
  uncomplicated → antibiotics for pneumonia
  >½ hemithorax *or* complicated *or* empyema → tube thoracostomy (otherwise risk of organization and subsequent need for surgical decortication)
  loculated→ tube thoracostomy or VATS; intrapleural t-PA + DNase ↓ need for surgical referral (*NEJM* 2011;365:518)
- Malignant effusion: serial thoracenteses vs. tube thoracostomy + pleurodesis (success rate ~80–90%) vs. indwelling pleural catheter, which ↓ hosp days but ↑ adverse events

(*JAMA* 2017;318:1903); systemic steroids & pH <7.2 a/w ↑ pleurodesis failure rate

- TB effusions: effusion will often resolve spontaneously; however, treat Pt for active TB
- Hepatic hydrothorax

  Rx: Δ pressure gradient (ie, ↓ ascitic fluid volume, NIPPV)

  avoid chest tubes; prn thoracenteses, pleurodesis, TIPS or VATS closure of diaphragmatic defects if medical Rx fails; NIPPV for acute short-term management

  spontaneous bacterial empyema (SBEM) can occur (even w/o SBP being present), ∴ thoracentesis if suspect infection

  transplant is definitive treatment and workup should begin immediately

VENOUS THROMBOEMBOLISM (VTE)

Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT): *Proximal* = thrombosis of iliac, femoral, or popliteal veins (nb, "superficial" femoral vein part of deep venous system). *Distal* = calf veins below knee; lower risk of PE/death than proximal (*Thromb Haem* 2009;102:493).
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

Risk factors

- Virchow's triad for thrombogenesis
  stasis: bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h (*NEJM* 2001:779)
  injury to endothelium: trauma, surgery, prior DVT, inflam, central catheter
  thrombophilia: genetic disorders (qv), HIT, OCP, HRT, tamoxifen, raloxifene
- Malignancy (12% of "idiopathic" DVT/PE; *Circ* 2013;128:2614)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

Thromboprophylaxis (*Chest* 2012;141:e195S, 227S, 278S)	
Patient & Situation	Prophylaxis
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation
Minor surgery in mobile Pt	Mechanical Ppx
High-risk medical (immobile, h/o VTE, thrombophilia or cancer) & most surgery Pts	UFH 5000 U SC bid/tid, or LMWH, or fonda (if HIT ⊕), or mech Ppx (esp. if high bleed risk); ? extended Ppx w/ DOAC (*NEJM* 2016;375:534). DOAC in ambul. cancer Pts (*NEJM* 2019;380:711 & 720).*
High-risk surg. (trauma, stroke, spinal cord injury, h/o VTE/thrombophilia)	[LMWH or UFH SC] + mech Ppx
Orthopedic surgery	LMWH [or fonda or warfarin (INR 2–3)] + mech Ppx; DOACs appear favorable vs LMWH After 5 d of DOAC, ASA≈DOAC (*NEJM* 2018;378:699)

For enox, 30 mg bid for highest risk or 40 mg qd for mod. risk or spinal/epidural anesth. *If Khorana score ≥2.

Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord, ⊕ Homan's sign (calf pain on dorsiflexion, seen in <5%)
- *Phlegmasia cerulea dolens:* massive prox DVT w/ edema, *cyanosis*, pain, compart. synd.
- 50% of Pts with sx DVT have asx PE
- Popliteal (Baker's) cyst: may lead to DVT due to compression of popliteal vein

"Simplified Wells" Pretest Probability Scoring of DVT (*JAMA* 2006;295:199)
+1 point each for: active cancer (Rx ongoing or w/in 6 mo or palliative); paralysis, paresis, or recent immobilization of

lower extremities; recently bedridden for ≥3 d or major surgery w/in 12 wk; localized tenderness along distribution of deep venous system; entire leg swelling; calf ≥3 cm larger than asx calf (at 10 cm below tibial tuberosity); pitting edema confined to sx leg; collateral superficial veins (nonvaricose); previous DVT –2 points if alternative dx at least as likely as DVT

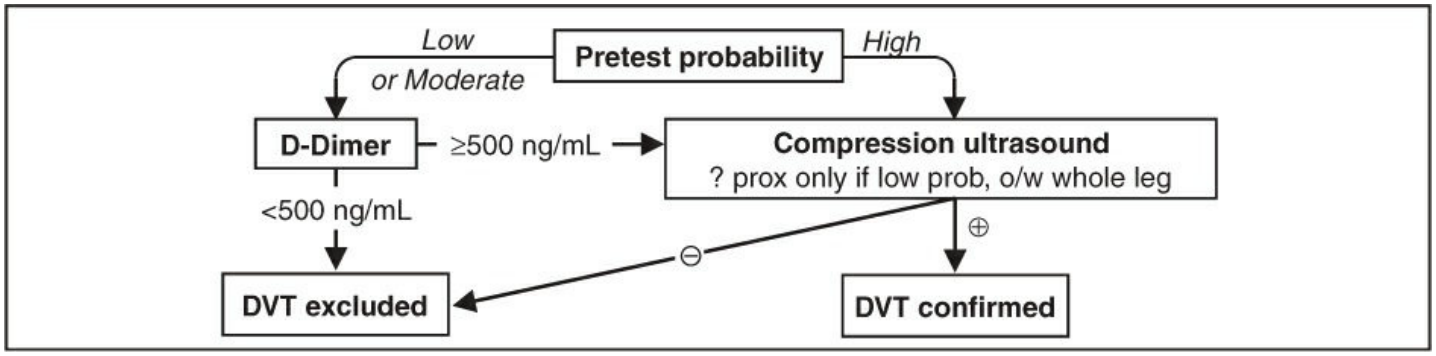
Pretest Probability Assessment (useful if outPt, less so if inPt; *JAMA IM* 2015;175:1112)		
Score ≤0	Score 1 or 2	Score ≥3
Low probability (5%)	Moderate probability (17%)	High probability (53%)

- For UE DVT, +1 point each for venous cath, local pain, & unilateral edema, –1 if alternative dx. ≤1 = unlikely; ≥2 = likely. U/S if likely or if unlikely but abnl D-dimer (*Annals* 2014;160:451)

Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (*Annals* 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower if asx); survey whole leg if ≥ mod prob

Figure 2-3 Approach to suspected DVT



Clinical manifestations—PE

- Dyspnea (~50%), pleuritic chest pain (~40%), cough (~23%), hemoptysis (~8%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P_2
- *Massive:* syncope, HoTN, PEA; ↑ JVP, R-sided S_3, Graham Steell (PR) murmur

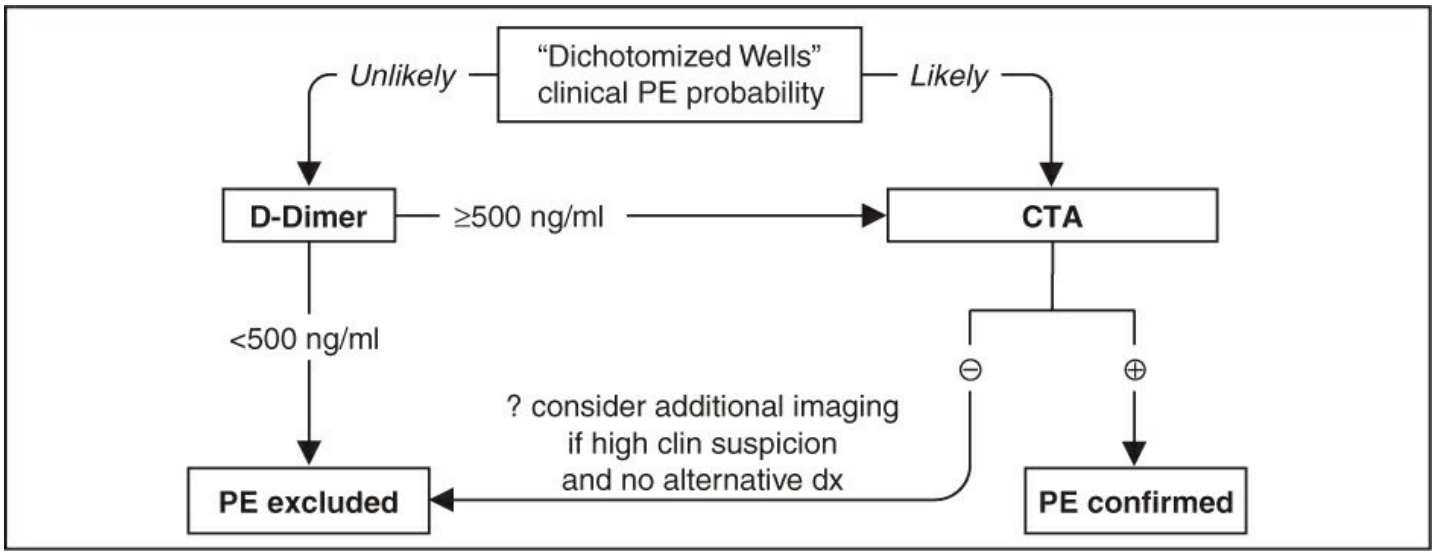
Simplified Wells Pretest Probability Scoring for PE (*Annals* 2011;154:709)	
• Prior PE or DVT • Active cancer • Immobilization (bed rest ≥3 d) or surgery w/in 4 wk • Alternative dx less likely than PE	• Clinical signs of DVT • HR >100 bpm • Hemoptysis
Dichotomized Wells Probability Assessment	
≤1 Variable = "Unlikely" (13% probability)	≥2 Variables = "Likely" (39% probability)

Diagnostic studies—PE (*EHJ* 2014;35:3033)

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, $S_IQ_{III}T_{III}$ & TWI V_1–V_4 (McGinn-White pattern; *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78) 18% w/ room air P_aO_2 85–105 mmHg, 6% w/ nl A-a gradient (*Chest* 1991;100:598)

- D-dimer: high Se, poor Sp (~25%); ELISA has >99% NPV ∴ use to r/o PE if "unlikely" pretest prob (*JAMA* 2006;295:172); cut-off 500 if <50 y, 10× age if ≥ 50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high-prob VQ. Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low-prob VQ, but 4% false (*JAMA* 1990;263:2753).
- CT angiography (CTA; see Radiology inserts; *JAMA* 2015;314:74): Se ~90% & Sp ~95%; PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant (∴ need to consider both); ~1/4 of single & subseg may be false ⊕; CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA

Figure 2-4 Approach to suspected PE



Workup for idiopathic VTE (*NEJM* 2015;373:697)

- Thrombophilia workup: ✔ if ⊕ FH, may be helpful but consider timing as thrombus, heparin and warfarin Δ results. Not helpful for Pt if will not Δ management (eg, plan for long-term anticoagulation regardless), although could be of use to relatives.
- Malignancy workup: 12% Pts w/ "idiopathic" DVT/PE will have malignancy; age-appropriate screening adequate; avoid extensive w/u

Risk stratification for Pts with PE

- High risk ("massive"): sustained hypotension (SBP <90), bradycardia, or cardiac arrest
- Intermediate risk ("submassive"): evidence of right heart strain w/o hypotension
  - echocardiogram: RV dysfxn (even if normal troponin) (*Chest* 2013;144:1539)
  - biomarkers: ↑ troponin, ↑ BNP (*Chest* 2015;147:685)
  - CTA: RV/LV dimension ratio >0.9 (*Circ* 2004;110:3276)
  - clinical assessment (persistent tachycardia, low BP or hypoxemia) may prompt consideration of advanced Rx (see below)
- Low risk: no right heart strain or hypotension

Whom to treat (*Lancet* 2016;388;3060; *Chest* 2016;149:315; *JAMA* 2018;320:1583)

- Superficial venous thrombosis: elevate extremity, warm compresses, compression stockings, NSAIDs for sx. *Anticoag* if high risk for DVT (eg, ≥5 cm, proximity to deep vein ≤5 cm, other risk factors) for 4 wk as ~10% have VTE w/in 3 mo (*Annals* 2010;152:218)
- LE DVT: proximal → anticoag; distal → anticoag if severe sx, o/w consider serial imaging over 2 wk and anticoag if extends (although if bleeding risk low, many would anticoag).
- UE DVT: anticoagulate (same guidelines as LE; *NEJM* 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- PE: anticoagulate

Anticoagulation options (*Chest* 2016;149:315)

- *Initiate parenteral Rx immediately if high or intermed suspicion while dx testing underway*
- Direct oral anticoag (DOAC; *NEJM* 2010;363:2499; 2012;366:1287; 2013;369:799 & 1406)
  preferred b/c as good/better than warfarin in preventing recurrent VTE w/ less bleeding
  can give as sole anticoag w/ initial loading dose (riva or apixa) or initiate after ≥*5 d of parenteral anticoag* (edox or dabi; 1st dose when d/c IV UFH or w/in 2 h before when next LMWH dose would have been due)
- LMWH (eg, enoxaparin 1 mg/kg SC bid *or* dalteparin 200 IU/kg SC qd)
  preferred over UFH (especially in *cancer*) except: renal failure (CrCl <25), extreme obesity, hemodynamic instability or bleed risk (*Cochrane* 2004;CD001100)
  can use as outPt bridge to long-term oral anticoagulation
- If cancer, LMWH ↓ recurrence and mortality c/w UFH & warfarin (*Lancet Oncol* 2008;9:577); ✔ head CT for brain mets if melanoma, renal cell, thyroid, chorioCA; edoxaban may be as effective, but ↑ major bleeding, espec in GI malig (*NEJM* 2018;378:615)
- Fondaparinux: 5–10 mg SC qd (*NEJM* 2003;349:1695); use if HIT ⊕; avoid if renal failure
- IV UFH: 80 U/kg bolus → 18 U/kg/h → titrate to PTT 1.5–2.3 × cntl (eg, 60–85 sec); preferred option when contemplating thrombolysis or catheter-based Rx (qv)
- IV direct thrombin inhibitors (eg, argatroban, bivalirudin) used in HIT ⊕ Pts
- Warfarin (goal INR 2–3): start w/ parenteral anticoag unless instability and ? need for lytic, catheter-based Rx or surg; overlap ≥5 d w/ parenteral anticoag & until INR ≥2 × ≥24 h

Systemic thrombolysis (*Chest* 2012;141:e419S & 2016;149:315)

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus; risk of ICH ~1.5%, ↑ w/ age
- Consider if low bleed risk w/ acute PE + HoTN or cardiopulm deterioration after anticoag
- High-risk PE: ↓ death & recurrent PE each by ~50% (*JAMA* 2014;311:2414; *EHJ* 2015;36:605) & lower PVR long term (*JACC* 1990;15:65)
- Intermediate-risk PE: ↓ hemodyn decompensation, ↑ ICH & other major bleeding, ↓ mortality in short term, but no long-term benefit on mortality, PHT or RV fxn; ? consider if <75 y and/or low bleed risk (*NEJM* 2014;370:1402; *JAMA* 2014;311:2414; *JACC* 2017;69:1536)
- *Half-dose lytic* (50 mg or 0.5 mg/kg if <50 kg; 10-mg bolus → remainder over 2 h) in ~intermed. PE: ↓ pulm HTN & ? PE or death w/ ≈ bleeding vs. heparin alone (*AJC* 2013;111:273)

- DVT: consider if (a) acute (<14 d) & extensive (eg, iliofemoral), (b) severe sx swelling or ischemia, and (c) low bleed risk

Mechanical intervention

- Catheter-directed (fibrinolytic & thrombus fragmentation/aspiration; *Circ* 2012;126:1917)
  - Consider if PE w/ hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy (*Circ* 2011;124:2139). Preferred to systemic lytic by some centers.
  - U/S-assisted improves hemodynamics & RV fxn vs. anticoag alone (*EHJ* 2015;36:597)
  - No benefit in extensive DVT (*NEJM* 2017;377:2240)
- Thrombectomy: if large, proximal PE + hemodynamic compromise + contraindic. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn (*J Thorac CV Surg* 2005;129:1018)
- IVC filter: use if anticoag contraindic.; no benefit to adding to anticoag (*JAMA* 2015;313:1627)
  - Complications: migration, acute DVT, ↑ risk of recurrent DVT & IVC obstruction (5–18%)

Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 wk
- 1st prox DVT *or* PE 2° reversible/time-limited risk factor *or* distal DVT: 3–6 mo
- 1st *unprovoked* prox DVT/PE: ≥3 mo, then reassess; benefit to prolonged Rx Consider clot, bleed risk, Pt preference, and intensity of Rx when crafting strategy
- 2nd VTE event or cancer: indefinite (or until cancer cured) (*NEJM* 2003;348:1425)

Extended antithrombotic strategies

- After ≥6 mo of anticoag, following regimens compared w/ no extended Rx (or ASA):
- Full-dose DOAC: 80–90% ↓ recurrent VTE, 2–5× bleeding, but no signif excess in major bleeding (*NEJM* 2010;363:2499; 2013;368:699 & 709)
- ½ dose apixa or riva: ≥75% ↓ recur. VTE, w/o ↑ bleeding (*NEJM* 2013;368:699 & 2017;376:1211)
- Warfarin, either regular (*JAMA* 2015;314:31) or low-intensity (*NEJM* 2003;348:1425)
- Aspirin: 32% ↓ recurrent VTE (*NEJM* 2012;366:1959 & 367:1979)

Complications & prognosis

- Postthrombotic syndrome (23–60%): pain, edema, venous ulcers
- Recurrent VTE: 1%/y (after 1st VTE) to 5%/y (after recurrent VTE)
- Chronic thromboembolic PHT after acute PE ~2–3%, consider thromboendarterectomy
- Mortality: ~10% for DVT and ~10–15% for PE at 3–6 mo (*Circ* 2008;117:1711)

PULMONARY HYPERTENSION (PHT)

PHT defined as PA mean pressure ≥25 mmHg at rest (in future ? ≥20 mmHg based on emerging data *[* Lancet Respir Med *2018;6:168]*)

PA mean = CO × PVR + PA wedge pressure. Trans pulm gradient = PA mean – PA wedge.

Etiologies (Revised WHO Classification) (*JACC* 2013;62:D34)	
Primary pulmonary arterial HTN (PAH) (group 1) Precapillary PHT PCWP ≤15 mmHg ↑ transpulm grad ↑ PVR	• Idiopathic (IPAH): yearly incidence 1–2 per million; mean age of onset 36 y (♂ older than ♀); ♂:♀ = ~2:1, usually mild ↑ in PAP • Familial (FPAH) • Associated conditions (APAH) • Connective tissue dis.: CREST, SLE, MCTD, RA, PM, Sjögren • Congenital L→R shunts: ASD, VSD, PDA • Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) • HIV; drugs & toxins: anorexic agents, SSRIs, L-tryptophan • Pulmonary veno-occlusive disease: ? 2° chemo, BMT; orthopnea, pl eff, CHF, nl PCWP; art vasodil. *worsen* CHF (*AJRCCM* 2000;162:1964) • Pulmonary capillary hemangiomatosis
Left heart disease (group 2). ↑ PCWP	• Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR)
Lung diseases and/ or chronic hypoxemia (group 3)	• COPD • Alveolar hypoventilation (eg, NM disease) • ILD • Chronic hypoxemia (eg, high altitude) • Sleep apnea • Developmental abnormalities
Chronic thrombo-embolic dis (group 4)	• Prox or distal PEs; ~1/2 w/o clinical h/o PE (*NEJM* 2011;364:351) • Nonthrombotic emboli (tumor, foreign body, parasites)
Miscellaneous/ Multifactorial (group 5)	• Sarcoidosis, histiocytosis X, LAM, schistosomiasis, ESRD • Compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT) • Other: thyroid dis., glycogen storage dis., Gaucher dis, HHT, sickle cell etc, chronic myeloprolif d/o, splenectomy

Clinical manifestations

- Dyspnea, exertional syncope (hypoxia, ↓ CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II= sx w/ ord. activ; III = sx w/ min activ.; IV = sx at rest

Physical exam

- PHT: prominent P_2, R-sided S_4, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (*JACC* 2013;62:D40; *Circ* 2014;130:1820)

- High-res chest CT: dilat. & pruning of pulm arteries, ↑ RA & RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE (“P pulmonale”), RVH (Se 55%, Sp 70%)

- PFTs: disproportionate ↓ $D_L$co, mild restrictive pattern; r/o obstructive & restrictive lung dis.
- ABG & polysomnography: ↓ P_aO_2 and S_aO_2 (espec w/ exertion), ↓ P_aCO_2, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but estimate over/under by ≥10 mmHg in ½ of PHT Pts; *Chest* 2011;139:988) ↑ RA, RV, & PA; ↑ pressure → interventricular septum systolic flattening ("D" shape) ↓ RV systolic fxn (TAPSE <1.6 cm); TR, PR; r/o LV dysfxn, MV, AoV, congenital disease
- RHC: ↑ RA, RV, & PA pressures; ✔ L-sided pressures and for shunt
  if PAH: nl PCWP, ↑ transpulmonary gradient (mean PAP-PCWP >12–15), ↑ diastolic pulmonary gradient (PA diastolic – PCWP >7), ↑ PVR, ± ↓ CO
  if 2° to L-heart disease: PCWP (or LVEDP) >15; if PVR nl → "passive PHT"; PVR >240 suggests mixed picture: if ↓ PCWP → ↓ PVR, then "reactive" PHT; if no Δ, then "fixed"
- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH), ± pulm angio if ↑ concern
- Labs: ANA (~40% ⊕ in PAH), RF, anti-Scl-70, anticentromere, ESR; LFTs; HIV
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Treatment (*JACC* 2013;62:25S & 2015;65:1976; *EHJ* 2016;37:67)

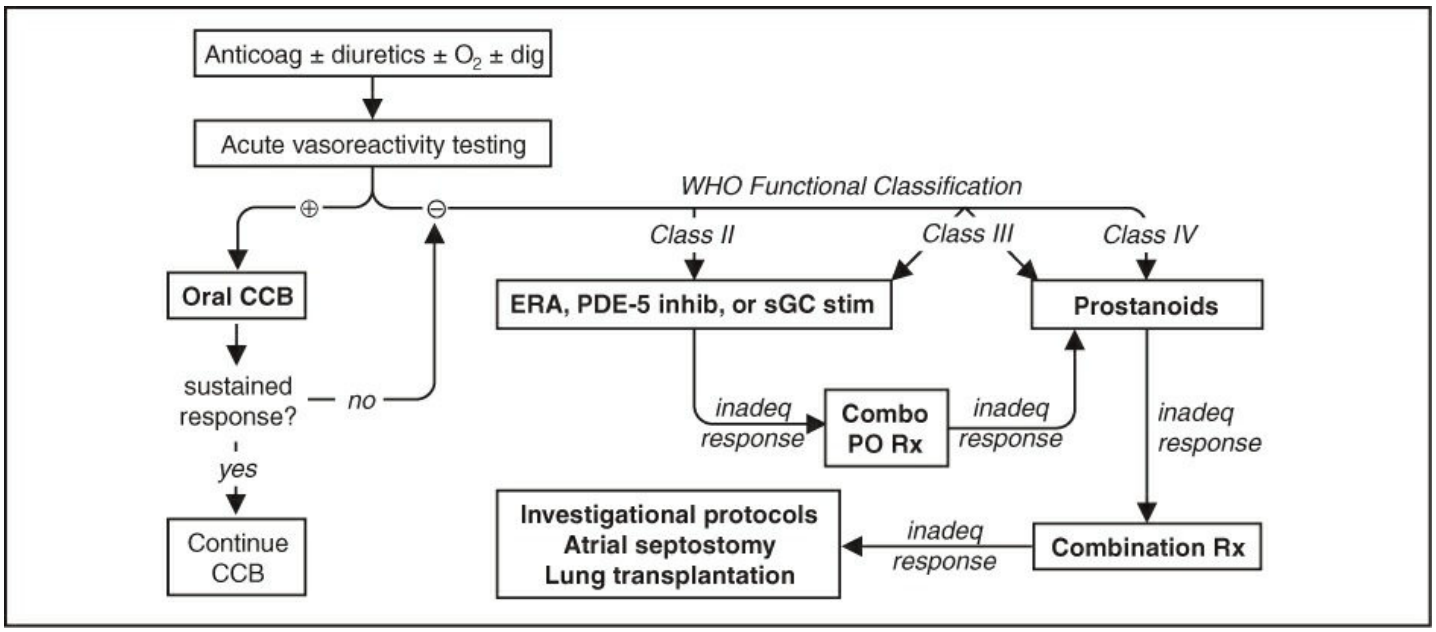
- Principles: 1) prevent & reverse vasoactive substance imbalance and vascular remodeling
  2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq systemic DBP
- Supportive
  Oxygen: maintain S_aO_2 >90–92% (reduces vasoconstriction)
  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent
  Digoxin: control AF, ? counteract neg inotropic effects CCB
  Anticoag: not routinely used; ↓ VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mortality benefit even if in NSR, no RCTs (*Chest* 2006;130:545)
  Supervised exercise training; aggressive apnea/hypoventilatory Rx w/ CPAP/BiPAP
- Vasodilators (ideally right heart catheterization prior to initiation; *NEJM* 2004;351:1425)
  acute vasoreactivity test: use inh NO, adenosine or prostacyclin to identify Pts likely to have long-term response to CCB (⊕ response = ↓ PAP ≥10 mmHg to <40 mmHg w/ ↑ or stable CO); ~10% Pts acute responders; no response → still candidate for other vasodilators

Vasoactive Agents	Comments (data primarily in Group 1; little evidence in 2° PHT)
PDE-5 inhibitor sildenafil, tadalafil, vardenafil	↑ cGMP → vasodilation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT, no data on clinical outcomes. Often first-line b/c minimal side-effect profile: HA, vision Δ's, sinus congestion (*NEJM* 2009;361:1864).
Endothelin receptor antagonists (ERAs) bosentan, ambrisentan, macitentan	↓ Smooth muscle remodeling, vasodilation, ↓ fibrosis, ↓ sx, ↑ 6MWT, ↓ worsening PAH or need for prostanoids w/ trend for ↓ PAH mort (w/ macitentan). Side effects: ↑ LFTs, HA, anemia, edema, teratogen (*NEJM* 2002;346:896; *Circ* 2008;117:3010; *NEJM* 2013;369:809).
IV Prostacyclin epoprostenol (Flolan)	Vasodilation, ↓ plt agg, ↓ smooth muscle proliferation; benefits ↑ w/ time (? vascular remodeling). ↑ 6MWT, ↑ QoL, ↓ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn (*NEJM* 1996;334:296 & 1998;338:273; Annals

	2000;132:425).
Prostacyclin analogues [iloprost (inh) treprostinil (IV, inh, SC)] & receptor agonist selexipag (PO)	Same mechanism as prostacyclin IV but easier to take, ↓ side effects, and w/o risk of catheter infxn, ↓ sx, ↑ 6MWT; trend to ↓ clinical events w/ iloprost but not treprostinil. Inh Rx with improved V/Q matching. Selexipag ↓ disease prog & hosp by ~40% (*NEJM* 2015;373:2522).
Soluble guanylate cyclase (sGC) stim riociguat	NO-independent ↑ cGMP → vasodilation, ↓ smooth muscle proliferation, ↓ sx, ↑ 6MWT in PAH; ↓ sx, ↓ PVR, ↑ 6MWT in CTEPH (*NEJM* 2013;369:319 & 330)
Oral CCB nifedipine, diltiazem	Consider if ⊕ acute vasoreactive response; not 1st line b/c side effects: HoTN, lower limb edema

- Upfront combination Rx (tadalafil + ambrisentan vs. monotherapy): ↓ sx, ↓ NT-BNP, ↑ 6MWT, ↓ hospitalizations (*NEJM* 2015;373:834)
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence
- CTEPH: Rx as above. Pulm endarterectomy potentially curative (*AJRCCM* 2011;183:1605).
- Refractory PHT: balloon atrial septostomy: R→L shunt causes ↑ CO, ↓ S_aO_2, net ↑ tissue O_2 delivery; lung txp (single or bilateral; heart-lung needed if Eisenmenger physiology)

Figure 2-5 Treatment of PAH (modified from *JACC* 2013;62:D60 & *EHJ* 2016;37:67)



Management of ICU patient

- Avoid tachyarrhythmias & overly aggressive volume resuscitation
- Caution w/ vasodilators if any L-sided dysfxn. *Intubation can cause hemodynamic collapse.*
- Dobutamine and inhaled NO or prostacyclin
- Consider R-sided mechanical support (*Circ* 2015;132:536)
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

Prognosis

- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78–S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO

(modified NYHA) class IV, 6MWT <300 m, peak VO_2 <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)

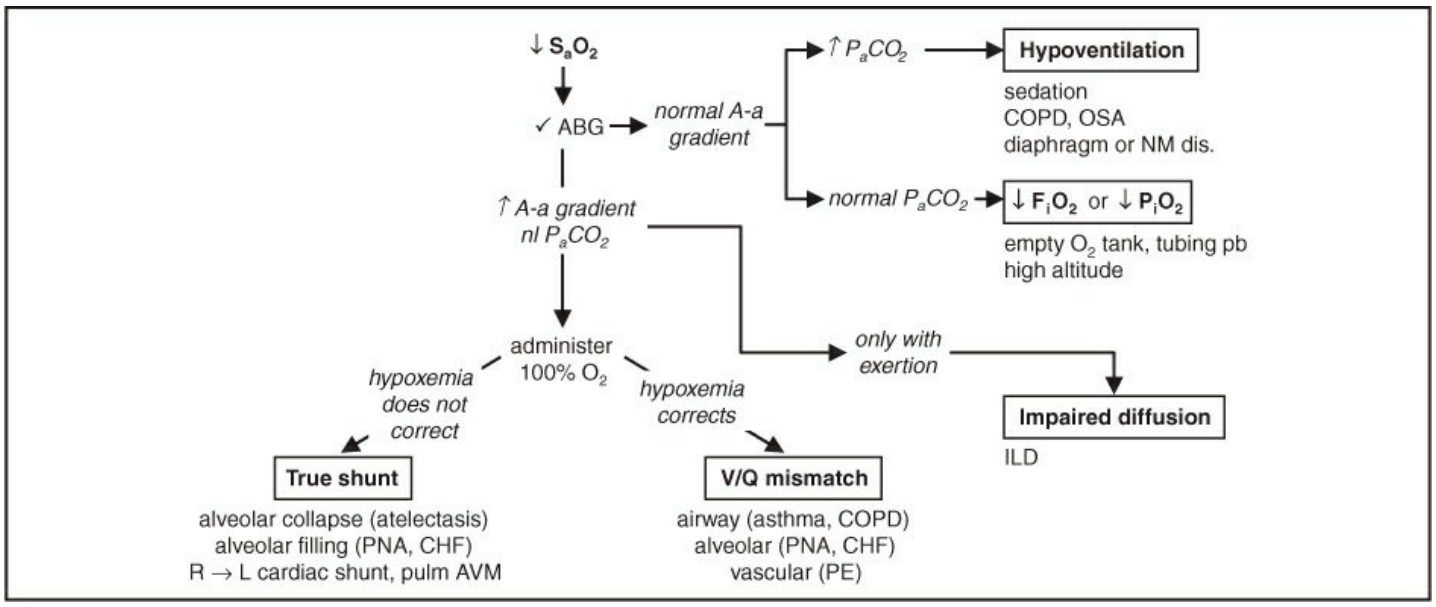
- Lung transplant: 1-y survival 66–75%; 5-y survival 45–55% (*Chest* 2004;126:63S)

RESPIRATORY FAILURE

$$\textbf{Hypoxema} \rightarrow P_AO_2 = F_iO_2 = (760 - 47)\frac{P_aCO_2}{R}$$

- A-a gradient = $P_AO_2 - P_aO_2$: normal (*on room air*) = "4 + age/4" or "2.5 + (0.2 × age)"
- Hypoxemia + nl A-a gradient: problem is ↓ P_iO_2/F_iO_2 or ↑ P_aCO_2 (ie, hypoventilation)
- Hypoxemia + ↑ A-a gradient: problem is either
  - R → L shunt, anatomic (congenital heart dis) or severe pathophys (alveoli filled w/ fluid; eg, PNA, pulm edema); cannot overcome w/ 100% O_2 b/c of sigmoidal Hb-O_2 curve
  - V/Q mismatch where "shunt-like" areas (↓ V & nl Q) cause unoxygenated blood to mix with oxygenated blood; can be overcome w/ ↑ O_2 delivery
  - Diffusion limitation: generally seen with exercise/↑CO

Figure 2-6 Workup of acute hypoxemia



- Cyanosis: seen when >4 g/dL of reduced Hb in blood vessels of skin/mucous membranes central: ↓ S_aO_2 (pulm disease, shunt); abnl Hb [metHb, sulfHb, COHb (not true cyanosis)] peripheral: ↓ blood flow → ↑ O_2 extraction (eg, ↓ CO, cold, arterial or venous obstruction)

Chemical Causes of Cellular Hypoxia						
Condition	**Causes**	**Classic Features**	**P_aO_2**	**Pulse Ox**	**CO-Ox sat**	**Treatment (+ 100% O_2)**
Carbon monoxide	Fires, portable heaters, auto exhaust	Cherry-red skin (COHb color)	nl	nl	↓	Hyperbaric O_2
Methemo-globinemia	Nitrates, sulfonamide, benzocaine, dapsone	Chocolate brown blood	nl	mild ↓	↓	Methylene blue
Cyanide	Nitroprusside, fires, industrial	Bitter almond odor; pink skin	nl	nl (↑ S_vO_2)	nl	Hydroxy-cobalamin

CO binds to Hb more avidly than does O_2. Pulse oximeter (Ox) misreads COHb as HbO_2 → falsely nl sat.

Oxidizing drugs Δ Hb (ferrous) to MetHb (ferric), which cannot carry O_2. Pulse ox misreads MetHb as HbO_2.

Cyanide inhibits mitochondrial O_2 use → cellular hypoxia but pink skin and ↑ *venous* O_2 sat.

$$\textbf{Hypercapnia} \rightarrow P_aCo_2 = \frac{k \times Vco_2}{RR \times \left(1 - \frac{V_D}{V_T}\right)}$$

Etiologies of High ↑ P_aCO_2			
"Won't Breathe"	**"Can't Breathe"**		
↓ RR	**↓ V_T**		**↑ V_D and/or ↓ V_T**
Respiratory Drive	**NM System**	**CW/Pleura**	**Lung/Airways**
Voluntary hyperventilation Nl PI_{max} & A-a grad	↓ PI_{max} ↓ PE_{max}	Abnl PEx Abnl CT	Abnl PFTs ↓ End tidal CO_2
Metabolic alkalosis **1° neurologic:** brain-stem stroke, tumor, 1° alveolar hypovent **2° neurologic:** sed-atives, CNS infxn, hypothyroidism	**Neuropathies:** cervical spine, phrenic nerve, GBS, ALS, polio **NMJ:** MG, LE **Myopathies:** diaphragm PM/DM; ↓ PO_4 musc dystrophies	**Chest wall:** obesity, kyphosis, scoliosis **Pleura:** fibrosis effusion	**Lung parenchyma:** emphysema, ILD/fibrosis, CHF, PNA **Airways:** asthma, COPD, OSA, CF bronchiectasis

↑ VCO_2 typically transient cause of ↑ P_aCO_2; Ddx: exercise, fever, hyperthyroidism, ↑ work of breathing, ↑ carbs.

MECHANICAL VENTILATION

Indications

- Improve gas exchange: ↑ oxygenation, ↑ alveolar vent and/or reverse acute resp acidosis
- Relieve respiratory distress: ↓ work of breathing (can account for up to 50% of total O_2 consumption), ↓ respiratory muscle fatigue
- Apnea, airway protection, pulmonary toilet

SUPPORTIVE STRATEGIES PRIOR TO INTUB. OR AFTER EXTUB.

Oxygen Delivery Systems (*Lancet* 2016;387:1867)		
System or Device	O_2 Flow[a]	F_iO_2 Range & Comments
Low-flow nasal cannula	1–6	24–40%, 1L adds ~3% F_iO_2
Standard face mask	5–10	35–50%, minimum 5 L/min
Partial rebreather mask	>10	40–70%
Nonrebreather mask	>10	60–80% (not 100% b/c air leaks)
Air-entrainment mask (Venturi or Venti mask)	10–15[b]	24–50%, F_iO_2 stays constant
High-flow nasal O_2 (*NEJM* 2015;372:2185; *JAMA* 2015;313:2331 & 2016;315:1354)	≤40	21–100%. In nonhypercapnic acute hypoxemic Resp failure, ± ↓ intub. (espec if P_aO_2/F_iO_2 ≤200) & ↓ 90-d mort vs. stnd O_2 or NPPV. Routine use after extub. ↓ need for reintub.

[a]L/min. [b]Total airflow >60L/min. (Adapted from Marino P. *The ICU Book*, 4th ed, Philadelphia: LWW, 2014:431)

Noninvasive Positive Pressure Ventilation (NPPV) (*NEJM* 2015;372:e30)	
Indications (*Lancet* 2009;374:250)	*Clinical:* mod–severe dyspnea, RR >24–30, signs of ↑ work of breathing, accessory muscle use, abd paradox *Gas exchange:* P_aCO_2 >45 mmHg (& significantly worse than baseline), hypoxemia, P_aO_2/F_iO_2 <200
Contraindications *Crit Care Med* 2007;35:2402	Claustrophobia, poor mask fit, ΔMS, vomiting, cannot protect airway, extrapulm organ failure, HD instab, sev UGIB, ↑ secretions
Continuous positive airway pressure (CPAP)	≈ PEEP. Pt breathes spont at own rate while vent maintains constant positive airway pressure throughout respiratory cycle. No limit on O_2 delivered (ie, can give hi-flow → F_iO_2 ≈1.0) Used if primary problem *hypoxemia* (eg, CHF)
Bilevel positive airway pressure (BiPAP)	≈ PSV + PEEP. Able to set both inspiratory (usually 8–10 cm H_2O) and expiratory pressures (usually <5 cm H_2O). Used if primary problem *hypoventilation*; F_iO_2 delivery limited
Mask ventilation (? helmet better; *JAMA* 2016;315:2435)	Tight-fitting mask connecting Pt to a standard ventilator Can receive PS ~20–30 cm H_2O, PEEP ~10 cm H_2O, F_iO_2 ~1.0 Used for short-term support (<24 h) for a reversible process

Conditions w/ strong evidence *Lancet* 2000;355:1931 *AJRCCM* 2006;173:164	Cardiogenic pulmonary edema: may ↓ intub. & mortality (*JAMA* 2005;294:3124; *Lancet* 2006;367:1155) although recent trial (w/ high crossover) did not show any mortality benefit (*NEJM* 2008;359:142) COPD exac w/ ↑ P_aCO_2: ↓ intub. & mort, but if pH <7.3 → intubate High-risk extub. (age >65, CHF, APACHE II >12): NPPV × 24 h directly after extub. → ↓ reintub. and, if P_aCO_2 >45 mmHg during SBT, ↓ mortality. Does not Δ total # vent days (*JAMA* 2018;320:1881).
JAMA 2016;315:1345 *NEJM* 2001;344:481	Hypoxemic resp failure after abdominal surgery: ↓ reintubation Immunosupp w/ infiltrates: ↓ complications & mortality

VENTILATOR MANAGEMENT

Ventilator Modes and Principles (*NEJM* 2001;344:1986; *Chest* 2015;148:340)	
Cont mandatory ventilation (CMV), aka Assist control (AC)	Vent delivers a minimum number of supported breaths Additional Pt-initiated breaths trigger *fully assisted* vent breaths ∴ Vent-triggered breaths identical to Pt-triggered breaths Tachypnea → ? resp. alkalosis, breath-stacking, & auto-PEEP May be pressure targeted or volume targeted (qv)
Pressure support vent (PSV)	Support Pt-initiated breaths w/ a set inspiratory pressure & PEEP A mode of *partial* vent support because no set rate
Other	Synch intermittent mand. vent: deliver min # supported breaths; V_T of additional Pt-initiated breaths determined by Pt's effort Proportional assist ventilation (PAV): delivers variable pressure to achieve targeted % of work of breathing

Volume or Pressure Targeted	
Volume targeted	Vent delivers a set V_T; pressures depend on airway resist. & lung/CW compl. Benefit: ↑ control over ventilation (ideal initial ventilator setting); benefit in ALI/ARDS; easy to measure mechanics (PIP, P_{plat}, airway resist., compl.) Volume control (VC) ⊕: vent delivers variable pressure (depending on real- time lung compliance) to achieve set V_T
Pressure targeted	Vent delivers a fixed inspiratory pressure regardless of V_T V_T depends on airway resistance and lung/chest wall compliance Benefit: May ↑ Pt comfort (PSV) requiring less sedation
General principles	Institutional/practitioner preference and Pt comfort usually dictate ventilator strategy; no strategy has proven superior Alarms can be set for ↑ volumes and ↑ airway pressures in pressure- targeted and volume-targeted strategies, respectively Risks: volutrauma (ie, overdistention, if set volume too high; *NEJM* 2013;369:2126), barotrauma [can happen w/ relatively high set volumes (espec if stiff lungs) or if pressure target set too high; key is to monitor transpulmonary pressure (difference between P_{plat} and esophageal ≈ intrapleural), not just airway pressure]; can result in PTX, pneumomediastinum Hypo-/hyperventilation: need to ✔ minute vent & pH/P_aCO_2

Variables on the Ventilator	
F_iO_2	Fraction of inspired air that is oxygen
V_T (tidal vol)	Volume of breath delivered; lung-protective ventilation: goal ≤6 ml/kg IBW If no ARDS, similar # of vent days at higher V_T (*JAMA* 2018;320:1872)

f (resp. rate)	Rate set by ventilator, f may be lower than RR if Pt triggering breaths. Adjust to achieve desired P_aCO_2.
Positive end-expiratory pressure (PEEP)	Positive pressure applied during exhalation via resistor in exhalation port Benefits: prevents alveolar collapse, ↓ shunt, ↑ O_2 via alveolar recruitment and improved compliance, allows severely obstructed Pt to initiate breath Cardiac effects: ↓ preload by ↑ intrathoracic pressure → ↓ venous return; ↓ afterload by ↓ cardiac transmural pressure; may ↑ or ↓ CO and may ↑ or ↓ oxygen delivery based on the above Auto-PEEP or intrinsic PEEP: inadequate exhalation time → lungs unable to completely empty before the next breath (ie, "breath stacking"); if flow at end-expiration, there must be pressure = auto-PEEP. Will ↓ preload and may ↓ CO, espec if hypovolemic Will ↑ work of breathing as must be overcome by Pt to trigger breaths; can prevent Pt from triggering ventilator, extrinsic PEEP helps Can be detected if end-expiratory flow ≠ 0 before next breath Can measure by occluding expiratory port of vent at end-expiration Can ↓ by: ↑ exp time, ↓ RR, ↓ V_T, Rx bronchospasm and secretions
Inspiratory time	Normally I:E ratio is ~1:2; however, can alter I time (and consequently flow rate, see later); use in pressure-control mode
Inspiratory flow rates	↑ flow rate → ↓ I time → ↑ E time → ∴ may improve ventilation in obstructive disease, but may affect resp rate and bronchodilation/constriction
Peak inspiratory pressure (PIP)	Dynamic measurement during inspiration; set in pressure-targeted mode Determined by airway resistance and lung/chest wall compliance ↑ PIP w/o ↑ P_{plat} → ↑ airway resist (eg, bronchospasm, plugging) ↓ PIP → ↓ airway resistance or air leak in the system
Plateau pressure (P_{plat})	Static measurement at the end of inspiration when there is no flow Determined by resp system compliance (resist. not a factor since ⌀ flow) ↑ P_{plat} → ↓ lung or chest wall compliance (eg, PTX, pulmonary edema, pneumonia, atelectasis), ↑ PEEP or auto-PEEP P_{plat} <30 cm H_2O ↓ barotrauma (↓ V_T, ↓ PEEP or ↑ compl [eg, by diuresis])

Tailoring the ventilator settings

- To improve oxygenation: options include ↑ F_iO_2, ↑ PEEP

  S_aO_2 88–92% acceptable (*AJRCCM* 2016;193:43), do not exceed 96% (*BMJ* 2018;363:k4169)

  First, ↑ F_iO_2. If >0.6 and oxygenation remains suboptimal, then try ↑ PEEP:

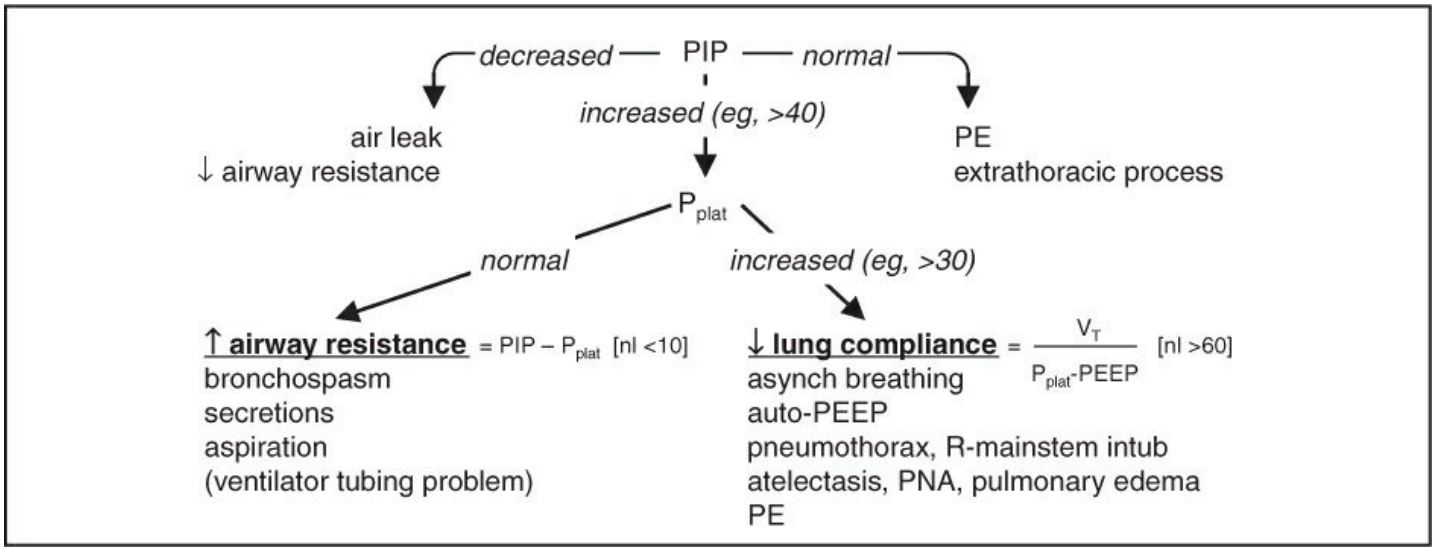
  If ↑ P_aO_2/F_iO_2 *and* P_{plat} stable, suggests recruitable lung (ie, atelectasis). If PEEP 20 & F_iO_2 1.0 and oxygenation remains suboptimal, consider rescue/expt strategies (see "ARDS").

  If ↑ PEEP yields no Δ *or* ↓ P_aO_2/F_iO_2 *or* ↑ P_aCO_2, suggests additional lung *not* recruitable and instead overdistending lung → ↑ shunt & dead space; ∴ ↓ PEEP
- To improve ventilation: ↑ V_T or inspiratory pressure, ↑ RR (may need to ↓ I time). Nb, tolerate ↑ P_aCO_2 (permissive hypercapnia) in ALI/ARDS (qv) as long as pH >7.2.

Acute ventilatory deterioration (usually ↑ PIP)

- Response to ↑ PIP: disconnect Pt from vent, bag, auscultate, suction, ✔ CXR & ABG

Figure 2-7 Approach to acute ventilatory deterioration



(Adapted from Marino PL. *The ICU Book*, 4th ed., Philadelphia: LWW, 2014)

Liberating from the ventilator (*NEJM* 2012;367:2233; *Lancet* 2016;387:1856)

- Perform daily assessment of readiness for spontaneous breathing trial (SBT)
- Clinical screening criteria: VS stable, minimal secretions, adequate cough, cause of respiratory failure or previously failed SBT reversed
- Vent parameters: P_aO_2/F_iO_2 >200, PEEP ≤5, f/V_T <105, V_E <12 L/min, VC >10 mL/kg; rapid shallow breathing index (f/V_T) >105 predicts failure, NPV 0.95 (*NEJM* 1991;324:1445)
- Daily awakening trial (d/c all sedation; *Lancet* 2008;371:126): open eyes & w/o: agitation, RR >35, S_aO_2 <88%, resp distress or arrhythmias (if fail, restart sedation at 1/2 prior dose)
- SBT = CPAP × 30 min superior to T-piece × 120 min (*JAMA* 2019;321:2175)
  failure if: deteriorating ABGs, ↑ RR, ↑ or ↓ HR, ↑ or ↓ BP, diaphoresis, anxiety
- Tolerate SBT → extubation. Fail SBT → ? cause → work to correct → retry SBT qd
- In high-risk Pts, extubation to either NPPV or high-flow O_2 equivalent (*JAMA* 2016;316:1565)
- ? acetazolamide in Pts w/ COPD & metabolic alkalosis (*JAMA* 2016;315:480)

Complications

- Oxygen toxicity (theoretical); proportional to duration + degree of ↑ oxygen (F_iO_2 >0.6)
- Ventilator-induced lung injury (see "ARDS")
- Ventilator-associated pneumonia (~1%/d, mortality rate ~30%)
  typical pathogens: MRSA, *Pseudomonas*, *Acinetobacter* and *Enterobacter* species
  preventive strategies (*AJRCCM* 2005;171:388): wash hands, HOB elevated, non-nasal intub., enteral nutrition rather than TPN?, routine suction of subglottic secretions, avoid unnecessary abx & transfusions; routine oral antiseptic controversial
- Stress ulcers/GIB: prophylaxis w/ PPI ↓ GIB, but no Δ in overall course (*NEJM* 2018;379:2199)
- Laryngeal
  edema: for Pts vent >36 h; ? predicted by ⊕ cuff leak test. Methylprednisolone 20 mg IV q4h starting 12 h pre-extub. → ↓↓ edema and 50% ↓ in reintubation (*Lancet* 2007;369:1003).
  ulceration: consider *tracheostomy* for Pts in whom expect >14 d of mech vent → ↓ duration mech vent, ↓ # ICU days (*BMJ* 2005;330:1243); no benefit to performing at ~1

wk vs. waiting until ~2 wk (*JAMA* 2010;303:1483)

- Malnutrition (for all critically ill Pts): *enteral nutrition* initiated early is safe but not necessary (*JAMA* 2012;307:795), but bolus may ↑ risk of VAP & *C diff*. (*JPEN* 2002;26:174); no clear benefit to ✔ing gastric residuals (*JAMA* 2013;309:249); permissive enteral underfeeding (~1/2 of calculated caloric req) & standard enteral feeding w/ similar outcomes (*NEJM* 2015;372:2398); *parenteral nutrition* should be delayed until after day 8 to ↓ risk of infections, cholestasis, RRT, ventilator days (*NEJM* 2011;365:506)
- Oversedation/delirium: BDZs and polypharmacy are risk factors
  propofol: HoTN in ~25%; *propofol infusion syndrome* (PRIS) ? espec w/ high (>5 mg/kg/h) & prolonged (>48 h) infusions & concom vasopressors → ↑ AG, cardiac dysfxn, rhabdomyolysis, ↑ triglycerides, & renal failure (*Crit Care* 2009;13:R169)
  dexmedetomidine: no clear benefit on vent-free days (*JAMA* 2016;315:1460 & 2017;317:1321); dosen't work as sole agent, but spares use of other (*NEJM* 2019;380:2506)

ACUTE RESPIRATORY DISTRESS SYNDROME

Berlin definition (*JAMA* 2012;307:2526)

- Acute onset within 1 week of clinical insult or worsening respiratory status
- Bilateral infiltrates without alternative explanation (eg, effusion, atelectasis, nodules)
- Edema not fully explained by fluid overload or congestive heart failure
- Hypoxemia: P_aO_2/F_iO_2 determined with 5 cm H_2O of PEEP

  P_aO_2/F_iO_2 200–300 = mild ARDS (may be on NPPV), 100–200 = mod, <100 = severe

Pathophysiology (*Lancet* 2016;388:2416)

- ↑ intrapulmonary shunt → hypoxemia (∴ Rx w/ PEEP to prevent derecruitment)
- ↑ increased dead space fraction (see Appendix), predicts ↑ mort (*NEJM* 2002;346:1281)
- ↓ compliance: $V_T/(P_{plat} - PEEP)$ <50 mL/cm H_2O

Pathology

- Diffuse alveolar damage (DAD) seen in 40% of autopsies (*AJRCCM* 2013;187:761)
- If no clear inciting event and ILD considered as alt dx, consider bx (*Chest* 2015;148:1073)

Etiologies	
Direct Injury	Indirect Injury
• Pneumonia (~40%) • Inhalation injury • Aspiration (~15%) • Lung contusion • Near drowning	• Sepsis (~25%) • Pancreatitis • Shock • Trauma/multiple fractures • DIC • Transfusion (TRALI)

Treatment (*NEJM* 2017;377:562; *ARJCCM* 2017;195:1253; *JAMA* 2018;319:698)

- Goal is to maintain gas exchange, sustain life, & avoid ventilator-induced lung injury (VILI)

Mechanisms of VILI	Ventilator Strategies (see ARDSnet.org)
Barotrauma/volutrauma: alveolar dist → mech damage	V_T ≤6 mL/kg, P_{plat} ≤30 cm H_2O, tolerate ↑ P_aCO_2 (but keep pH >7.2), ↓ mortality (*NEJM* 2000;342:1301)
Biotrauma → SIRS	Low V_T, open lung strategy w/ high PEEP
Atelectrauma: repetitive alveoli recruit & decruit	Titrate PEEP to prevent tidal alveolar collapse See below for options
Hyperoxia: ? injury; worsened V/Q matching	↑ PEEP rather than F_iO_2 (keep <0.60) O_2-induced injury only theoretical in humans

The 6 Ps

- PEEP (see below)
- Proning: if P_aO_2/F_iO_2 <150, prone positioning ≥16 h ↓ mort ~50% (*NEJM* 2013;368:2159)
- Paralysis: no benefit routinely (*NEJM* 2019;380:1997); consider if Pt-vent dyssynchrony
- Peeing (fluid balance): target CVP 4–6 cm H_2O (if nonoliguric & normotensive) → ↑ vent/ICU-free days, but no Δ mortality (*NEJM* 2006;354:2564); PA catheter unproven (*NEJM*

2006;354:2213); consider BNP >200 to trigger diuresis (UOP goal 4.5–9 mL/kg/h × 3 h)

- Pulm vasodilators: inhaled NO or prostacyclins ↑ P_aO_2/F_iO_2; no ↓ mort or vent-free days (*BMJ* 2007;334:779)
- Perfusion (V-V ECMO): may be useful if refractory (*NEJM* 2011;365:1905 & 2018;378:1965)

PEEP titration methods (best method unclear)

- No benefit at given V_T if titrated to P_aO_2 alone (*NEJM* 2004;351:327; *JAMA* 2008;299:637)
- Best PEEP trial: incremental PEEP titration using compliance, O_2, hemodynamics
  If able to ↑ PEEP w/o ↑ P_{plat}, suggests "recruitability"
  ∴↑ PEEP if → ↑ S_aO_2 (target ≥88–90%) & P_{plat} ≤30 cm H_2O → ↓ time on vent, better lung mechanics (*JAMA* 2008;299:646), ? ↓ mortality (*JAMA* 2010;303:865)
- ARDSnet "high" PEEP table for optimal F_iO_2/PEEP combo for goal S_aO_2 (ARDSnet.org)
- Recruitment maneuvers: stepwise preferred over sustained inflation, evidence insufficient to recommend routine use (*Resp Care* 2015;60:1688); recruitment maneuvers at high pressures ? ↑ mortality (*JAMA* 2017;318:1335)
- Esophageal balloon: used to estimate pleural pressure and thereby estimate trans-pulmonary pressure (ie, true airway distending pressure). Adjusting PEEP according to esoph pressure to maintain optimal transpulm. pressure does not Δ ventilator-free days or mortality, although does ↓ need for advanced rescue Rx (see above) (*JAMA* 2019;321:846).
- Driving pressure ($\Delta P = P_{plateau} - PEEP$): ↓ ΔP a/w ↑ survival; target <15 (*NEJM* 2015;372:747)

Prognosis (*JAMA* 2016;315:788)

- Mortality ~40% overall in clinical trials; 9–15% resp. causes, 85–91% extrapulm (MODS)
- Survivors: PFTs ~normal, ↓ D_LCO, muscle wasting, weakness persists (*NEJM* 2003;348:683), ↓ exercise tolerance, ↓ QoL, ↑ psych morbidity (*NEJM* 2011;364:1293); 44% of previously employed Pts jobless at 12 mos (*AJRCCM* 2017;196:1012)

SEPSIS AND SHOCK

Definitions (*JAMA* 2016;315:801; 2017;317:290 & 301)	
Sepsis	Life-threatening organ dysfxn (SOFA Δ ≥2) due to infection Quick SOFA (qSOFA): ≥2 of the following: RR ≥22, ΔMS, SBP ≤100 mmHg
Septic shock	Sepsis-induced circulatory and cellular/metabolic abnormalities severe enough to ↑ mortality; hypotension requiring pressors for MAP ≥65 and lactate >2 despite adequate fluid resuscitation
Sequential Organ Failure Assessment (SOFA): ↑ points for worsening organ dysfxn: respiration (↓ P:F ratio); coag (↓ plt); liver (↑ bili); CV (↓ MAP or ↑ pressors); CNS (↓ GCS); renal (↑ Cr or ↓ UOP)	

Systemic inflammatory response syndrome (SIRS): ≥2 of the following: (1) Temp >38 or <36°C, (2) HR >90, (3) RR >20 or $PaCO_2$ <32, (4) WBC >12k or <4k or >10% bands. No longer used.

Shock (see "PA Catheter & Tailored Therapy" for subtypes; *NEJM* 2013;369:1726)

- Tissue hypoxia due to ↓ tissue perfusion and hence ↓ tissue O_2 delivery and/or ↑ O_2 consumption or inadequate O_2 utilization
- Typical signs include HoTN (SBP <90 mmHg or drop in SBP >40 mmHg), tachycardia, oliguria (UOP <0.5 cc/kg/h), Δ mentation, metabolic acidosis ± ↑ lactate
- Hard to dx as ↑ SVR can maintain SBP, but tissue perfusion poor; shock index (HR/SBP) >0.9 and pulse pressure [(SBP – DBP)/SBP] <25% clues to significant shock

MANAGEMENT

Fluids

- Aggressive IV fluid resuscitation (30 mL/kg) admin in boluses w/in 3 h of presentation
- Crystalloid as good as colloid for resuscitation (*JAMA* 2013;310:1809; *NEJM* 2014;370:1412)
- Balanced crystalloid (LR, Plasma-Lyte) ↓ rate of major kidney events (composite of death, need for RRT, or persistent renal dysfxn) compared w/ NS (*NEJM* 2018;378:829)
- $NaHCO_3$ may ↓ mortality & need for RRT if AKI & pH <7.2 (*Lancet* 2018;392:31)
- Predictors of fluid responsiveness: pulse pressure variation >13% w/ respiration (*Chest* 2008;133:252); resp. variation in IVC diam, or >10% ↑ in pulse pressure w/ passive leg raise. Static CVP poor surrogate.
- After early resuscitation, if ALI/ARDS, target CVP 4–6 mmHg because additional fluids may be harmful → ↑ ventilator/ICU days (*NEJM* 2006;354:2564; *Chest* 2008;133:252)

Pressors & inotropes (also see "ICU Medications")

- MAP target 65–70 mmHg as good as 80–85 and ↓ AF (*NEJM* 2014;370:1583)
- Norepinephrine: ↓ arrhythmia & mortality c/w dopamine (*NEJM* 2010;362:779; *Crit Care Med* 2012;40:725) and ∴ is pressor of choice in septic shock
- Vasopressin: adding to norepi (vs. using high-dose norepi) ↓ risk of AF & RRT by ~¼ (*JAMA* 2018;319:1889)
- If targets (see below) not reached after adequate fluids and pressors, consider inotropes

Targets

- Lactate clearance (≥20%/2 h) as effective as $S_{cv}O_2$ to guide resusc. (*JAMA* 2010;303:739)
- Targeting capillary refill time ≤3 sec (check q30min) as good if not better than lactate clearance (*JAMA* 2019;321:654)

Antibiotics

- Start empiric IV abx as soon as possible following recognition of severe sepsis or septic shock; every hr delay in abx admin a/w 7.6% ↑ in mortality (*Crit Care Med* 2006;34:1589), abx admin w/in 3 h of presentation in the ED a/w ↓ in-hospital mortality (*NEJM* 2017;376:2235)
- If possible, obtain 2 sets of BCx before urgently starting abx (but do not delay abx)
- Broad gram-positive (incl MRSA) & gram-neg (incl highly resistant) coverage, ± anaerobes
- Procalcitonin-guided *cessation* (not initiation) ↓ mortality (*Crit Care Med* 2018;46:684)
- Empiric micafungin in critically ill Pts w/ Candida colonization & sepsis of unknown etiology ↓ invasive fungal infxns & tended ↑ invasive fungal infxn-free survival, espec. in Pts w/ 1,3-b-D-glucan >80 (*JAMA* 2016;316:1555)

Steroids (*Crit Care Med* 2018;46:1411)

- Hydrocortisone 50 mg IV q6 + fludrocortisone 50 µg via NGT daily in septic shock ↓ duration of shock and may ↓ mortality (*NEJM* 2018; 378:797 & 809)
- Consider in Pts w/ refractory shock on escalating doses of pressors

Early Goal-Directed Therapy (EGDT)

- Historically: IVF & pressors for MAP ≥65 mmHg, CVP 8–12 mmHg, UOP ≥0.5 mL/kg/h; inotropes & PRBCs for $S_{cv}O_2$ ≥70% in 6 h (*NEJM* 2001;345:1368)
- However, now in era of early abx and adequate fluid resuscitation, no ↓ in mortality w/ EGDT vs. current usual care, and ↑ hospital costs (*NEJM* 2017; 376:2223)

TOXICOLOGY

Drug/Toxin	Signs/Sx and Diagnostics	Management Options
Acetaminophen	Vomiting, ↑ AG & nl OG metabolic acidosis, hepatitis & hepatic failure, renal failure	N-acetylcysteine (NAC) infusion Hemodialysis if massive O/D See "Acute liver failure"
Salicylates	Tinnitus, hyperventilation, abd. pain, vomiting, ΔMS, mixed ↑ AG & nl OG metabolic acidosis + respiratory alkalosis	IVF resuscitation Alkalinization w/ $NaHCO_3$ Maintain respiratory alkalemia Consider hemodialysis
Opioids	↓ mentation, ↓ RR, miosis	IV naloxone
Benzodiazepines	↓ mentation, ataxia, ↓ RR	Flumazenil *not* rec (can precipitate withdrawal/seizures)
Calcium channel blockers	Bradycardia, AV block, hypotension, HF, hyperglycemia	IVF, vasopressors, Ca infusion, hyperinsulinemic euglycemia, ? intralipid emulsion, pacing
Beta blockers	Bradycardia, AV block, hypotension, HF, hypoglycemia	Glucagon, vasopressors, pacing
Digoxin	N/V, bradycardia, AV block, delirium, xanthopsia ✔ serum dig level (but may be inaccurate if <6 h since last dose), renal function	Correct hypokalemia Digibind if hyperkalemia, life-threatening dysrhythmia Consider hemodialysis Lidocaine for arrhythmias
Tricyclic antidepressants	Hypotension, seizures, arrhythmia, ↑ QRS, ↑ QT	IVF resuscitation, IV sodium bicarbonate, vasopressors
Lithium	N/V/D, tremor, hyperreflexia, clonus, drowsiness, seizure, ↑ QT, AV block, bradycardia	IVF (NS), maintain UOP Consider hemodialysis
Ethylene glycol	CNS depression, ↑ AG & OG metabolic acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis
Methanol (*NEJM* 2018;378:270)	CNS depression, blindness ↑ AG & OG met. acidosis	Ethanol or fomepizole, $NaHCO_3$ Consider hemodialysis
Isopropanol	CNS depression, gastritis	Supportive care
Carbon monoxide	HA, dizziness, nausea, ΔMS carboxyHb level, CO-oximetry (pulse ox invalid)	100% normobaric oxygen, hyperbaric O_2 in severe cases
Organophosphate	Salivation, lacrimation, diaphoresis, miosis, emesis, bronchospasm, ΔMS	Endotracheal intubation for respiratory failure, atropine, pralidoxime, benzodiazepines
Cyanide	Coma, seizure, metabolic acidosis, hypotension	IV Na nitrite and Na thiosulfate IV hydroxocobalamin

(*Chest* 2011;140:1072)

LUNG TRANSPLANT

Overview

- Indications: end stage, progressive decline despite max medical Rx, <2-y life expectancy; COPD, ILD (IPF), pulmonary HTN, cystic fibrosis, alpha 1-antitrypsin
- Contraindic: age >65 (rel.), uncontrolled/unRx'd infxn, malig in prior 2 y, severe non-pulm dis., BMI ≥35, active smoking, EtOH/drug depend., med noncompliance, psychosocial

Posttransplant care

- Immunosuppression: center dependent; no single best regimen. Tacro > cyclosporine (↓ incidence of acute rejection) + steroids + MMF/azathioprine
- Monitoring: clinic visits, serial PFTs, chest X-ray, bronchoscopy w/ transbronchial biopsy

Complications

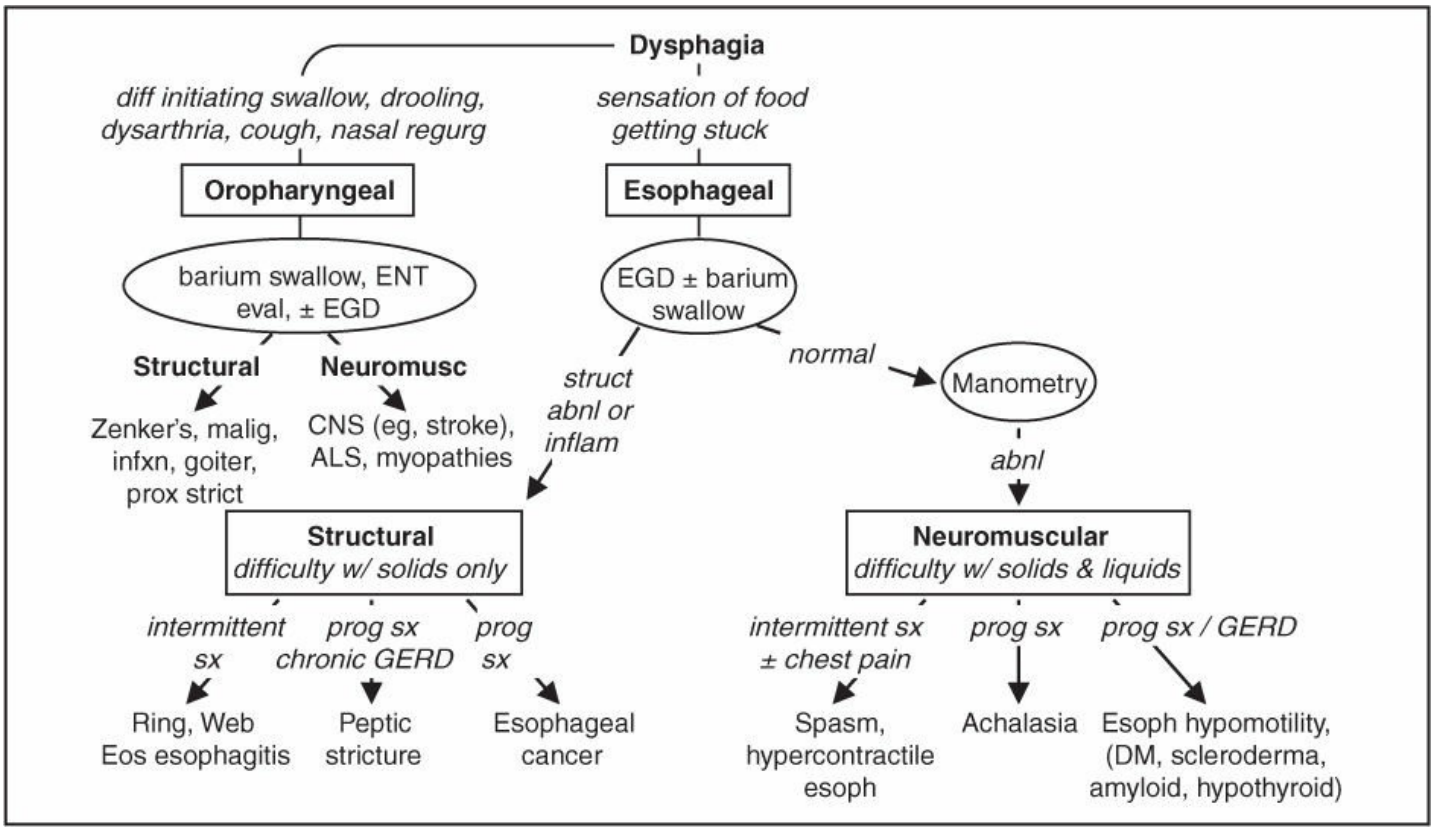
- Primary graft dysfunction (PGD): acute lung injury following txp; assoc w/ early mortality
- Anastomotic: vascular (stenosis, thrombosis) and airway (infection, necrosis, dehiscence, granulation tissue, tracheobronchomalacia, stenosis, fistula)
- Acute rejection: ↓ lung fxn, cough, SOB, fever; Dx w/ trans-bronch bx; Rx immunosupp
- Chronic rejection: bronchiolitis obliterans w/ obstruction; Dx w/ PFTs, trans-bronch bx; Rx limited (azithromycin, montelukast, Δ immunosuppressives)
- Infection: ↑ bacterial, fungal, viral pneumonia, systemic infections, CMV, OI
- Malignancy: 2× ↑ risk overall. 5.5× ↑ risk lung cancer. PTLD (assoc w/ EBV) common.
- Misc: GVHD, CKD, DM, CAD, CHF, stroke, encephalopathy, drug toxicity

ESOPHAGEAL AND GASTRIC DISORDERS

DYSPHAGIA

- Oropharyngeal: inability to propel food from mouth through UES into esophagus
- Esophageal: difficulty swallowing & passing food from esophagus into stomach

Figure 3-1 Etiologies of and approach to dysphagia (*NCP Gastrohep* 2008;5:393; *Neurogastro* 2012;24:57)



Structural dysphagia (solids > liquids; *JAMA* 2015;313:18; *Gastro* 2018;155:1022)

- Oropharyngeal
  - Zenker's divertic. (pharyngeal pouch): in elderly, a/w aspir., dx w/ video fluoro, Rx endo/surg
  - Malignancy; proximal strictures/rings/webs; infection; radiation injury; goiter; osteophytes
- Esophageal
  - Rings (intermittent dysphagia, concentric obstructing tissue, eg, Schatzki ring): near GE jxn, a/w food impaction, linked to GERD; Rx w/ PPI, dilation
  - Webs (nonconcentric): usually prox, can be a/w Fe defic. (Plummer-Vinson synd.)
  - Peptic or XRT strictures, foreign body, tumor, vascular compression (dysphagia lusoria)
  - Infxn esophagitis: odynophagia > dysphagia; often immunosupp w/ *Candida*, HSV,

CMV

Pill esophagitis: odynophagia > dysphagia; NSAID, KCl, bisphosp., doxy & tetracycline

Eosinophilic esophagitis: often young/middle-aged ♂. Dx: >15 eos/hpf on bx, esoph dysfxn (ie, dysphagia, food impaction). Rx: 1st line is PPI (½ respond); alternative (or if fail PPI) is 3Ds: 1st try elimination Diet (∅ milk, soy, eggs, wheat, nuts, fish); if no Δ, Drugs (swallow inh steroids); if ongoing sx & stricturing, Dilation.

Neuromuscular dysphagia (solids & liquids; *Neurogastero Motil* 2015;27:160 & 2016;22:6)

- Caused by aberrant motility or innervation of oropharynx/esophagus
- Oropharyngeal: consider CNS disorders (eg, stroke, ALS, myopathies, CNS tumors)
- Esophageal: motility disorder w/ dysphagia, chest pain, GERD; dx: conventional or high-res manometry w/ esophageal pressure topography. Chicago classification v3.0:
  1. Incomplete LES relaxation: *Isolated EGJ outflow obstruction or achalasia. Achalasia:* simult. ↓ amp contractions & ↓ LES relaxation; barium swallow w/ dilated esophagus & distal "bird's beak" narrowing; mostly idiopathic, although can be a/w Chagas; Rx: pneumatic dilation as effective as Heller myotomy (local expertise dependent) (*Gut* 2016;65:732); peroral endoscopic myotomy; CCB/nitrates/PDEi; Botox if ∅ surg cand.
  2. Major motility disorders: *Absent contractility; Distal spasm* (uncord. peristalsis w/ simult. contractions); *Hypercontractile* (high amp contract.; Rx w/PPI, nitrates/CCB/PDEi, TCA)
  3. Minor motility disorders: *Fragmented peristalsis; Hypomotility* (↓ amp of distal esoph contractions; seen in scleroderma, DM, hypothyroid.; Rx w/ underlying disorder & w/ PPI)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Pathophysiology

- ↑ acid exposure in esophagus, caused by ↑ transient LES relaxations. Worsened by ↑ intraabd pressure (eg, obesity, pregnancy), ↓ esophagogastric motility, hiatal hernia. Rarely caused by ↑ acid production except in ↑ secretory states (eg, Zollinger-Ellison)
- Precipitants: supine position, fatty foods, caffeine, alcohol, cigarettes, CCB, pregnancy

Clinical manifestations

- Esophageal: heartburn, atypical chest pain, regurgitation, water brash, dysphagia
- Extraesophageal: cough, asthma (often poorly controlled), laryngitis, dental erosions

Diagnosis (*Annals* 2015;163:ITC1; *Nat Rev Gastro Hepatol* 2016;13:501)

- Clinical diagnosis based on sx and response to empiric trial of PPI ("PPI test")
- EGD: if (1) ∅ response to PPI; or if (2) *alarm features*: dysphagia, vomiting, ↓ wt, anemia
- If dx uncertain & EGD nl → esoph manometry w/ 24-h pH monitoring ± impedance to dx:
  "Nonerosive reflux disease": no erosion, ulceration or Barrett's; ½ abnl pH. Unpredictable response to PPI. Most will *not* progress to erosive esophagitis or Barrett's.

"Reflux hypersensitivity": nl acid exposure on pH/impedance w/ symptom–reflux assoc.

"Functional heartburn": nl acid exposure on pH/impedance w/o symptom–reflux assoc.

Treatment (*World J Gastrointest Endosc* 2018;10:175)

- Lifestyle: avoid precipitants, lose weight, avoid large & late meals, elevate head of bed
- Medical: PPI achieve relief in 80–90% of Pts; H2 blockers for intermittent sx
- Refractory: confirm w/ pH testing (on PPI to assess need for ↑ Rx, or off PPI to verify dx).
  - If acidic or sx correlate w/ reflux episodes: surgical fundoplication (emerging Rx: LES sphincter augmentation w/ radiofrequency, implantable magnetic or electrical devices)
  - If nl pH or no sx correlation: Dx: "functional heartburn". Rx w/ TCA, SSRI or baclofen.

Complications (*Gastro Clin NA* 2015;44:203; *Gastro* 2015;149:567 & 1599)

- Reflux esophagitis (erosions/ulcers above GE jxn), strictures (caused by chronic inflamm)
- Barrett's esoph. (BE): metaplastic columnar mucosa above GE jxn replaces squam epithel.
  - Screen if chronic (>5 y) and/or frequent GERD (≥1/wk) in ♂ w/ ≥2 risk factor for Barrett's/esophageal adeno: >50 y, white, hiatal hernia, central adiposity, smoking, FHx of Barrett's/esophageal adeno. In ♂, consider only if multiple RFs. 0.1–0.3%/y risk of esoph adenocarcinoma, ↑ if ↑ dysplasia (*Am J Gastro* 2016;111:30).
  - Mgmt: PPI. W/o dysplasia: surveillance EGD q3–5y. Low-grade dysplasia: EGD q12mo; possible endoscopic eradication. High-grade dysplasia: endoscopic eradication; consider chemoprophylaxis w/ high-dose PPI & ASA (*Lancet* 2018;392:400).

PEPTIC ULCER DISEASE (PUD)

Definition & etiologies (*Lancet* 2017;390:613)

- Ulcers (break in mucosal lining >5 mm) & erosions (<5 mm) in stomach and duodenum
- Principal risk factors: *H. pylori* infection > NSAID/ASA use
- *H. pylori* infection: causes ~60–70% of duodenal ulcers (DU) & ~30–40% of gastric ulcers (GU). ~50% of world colonized w/ *H. pylori*, but only 5–10% will develop PUD.
- ASA & NSAIDs: damage to mucosa caused by ↓ prostaglandin synthesis. Cause majority of non–*H. pylori*-related DU & GU. Regular use a/w 5–6× ↑ odds of GIB.
- Other: smoking, stress, excessive EtOH, gastric cancer/lymphoma, Crohn's, viral infxn (eg, CMV/HSV in immunosupp), bisphosphonates, steroids (in combo w/ NSAIDs, but not risk factor alone); rarely gastrinoma (Zollinger-Ellison synd.), mastocytosis, idiopathic
- Stress ulcer: risk factors = ICU & coagulopathic, mech vent, h/o GIB, steroid use; Rx w/ PPI

Clinical manifestations

- Epigastric gnawing abdominal pain: relieved with food (DU) or worsened by food (GU)
- Complications: UGIB, perforation & penetration, gastric outlet obstruction

Diagnostic studies

- Testing for *H. pylori:* stool Ag, urea breath testing (UBT) or EGD + rapid urease test (RUT
  False ⊖ Ag, UBT, RUT if on abx, bismuth, PPI; ∴ stop prior to testing if possible
  Serology: ↓ utility, useful only to exclude infection in low prevalence areas (most of U.S.)
- EGD (definitive dx): if fail empiric Rx or alarm features (see "GERD"); bx GU to r/o malig & *H. pylori;* relook in 6–12 wk if >2 cm, malig features, risk factors for gastric cancer (ie, ⊕ FHx, ⊕ *H. pylori*, atrophic gastritis, dysplasia/ metaplasia on bx, >50 y), or sx persist

Treatment (*Lancet* 2016;388:2355; *Gastro* 2016;151:51; *Gut* 2017;66:6; *AJG* 2017;112:212)

- If *H. pylori* ⊕ → eradicate ("test and treat"); if ⊖ → gastric acid suppression w/ PPI
  1st line: Quad. Rx: 14d x [MNZ + TCN + bismuth + PPI] or [MNZ + amox + clarith + PPI]
  Besides PUD, test & Rx if: gastric MALT lymphoma, s/p resection for early gastric ca, FHx gastric ca, unexplained iron def. anemia, ITP, uninvestigated dyspepsia in Pt <60 y, or when initiating long-term NSAIDs
- "Test-of-cure": 4 wk after Rx, off PPI x 1–2 wk. Use stool Ag, EGD + RUT or UBT.
- Lifestyle changes: d/c smoking and probably EtOH; diet does not seem to play a role
- Surgery: if refractory to med Rx (1st r/o NSAID use) or for complications (see above)

GI prophylaxis in Pts taking ASA and/or NSAIDs (*JACC* 2016;67:1661)

- PPI if h/o PUD/UGIB and either (a) also on clopidogrel or (b) ≥2 of the following: age >60 y, steroids or dyspepsia; prior to start test & Rx *H. pylori*
- Consider Δ non-selective NSAID to selective COX-2 inhibitor (↓ PUD & UGIB but ↑ CV events) if low CV risk & not on ASA

GASTROINTESTINAL BLEEDING

Definition

- Intraluminal blood loss anywhere from the oropharynx to the anus
- Classification: upper = above the ligament of Treitz; lower = below the ligament of Treitz
- "Severe" GIB: defined as having associated shock, orthostatic hypotension, ↓ Hct by 6% (or ↓ Hb by 2 g/dL), or requiring transfusion ≥2U PRBCs. Requires hospitalization.

Clinical manifestations

- Hematemesis = blood in vomitus (UGIB)
- Coffee-ground emesis = emesis of blood exposed to gastric acid (UGIB)
- Melena = black, tarry stools from digested blood (usually UGIB, but can be from R colon)
- Hematochezia = bloody or maroon-colored stools (LGIB or rapid UGIB)

Initial management

- Assess severity: *VS including orthostatic Δs, JVP*. Tachycardia (can be masked by βB use) suggests 10% volume loss, orthostatic hypotension 20% loss, shock >30% loss. Scoring systems predict rebleeding & mortality: AIMS65 & Glasgow-Blatchford.
- History: prior GIB, tempo of current bleed, specific bleeding manifestations (see above), other GI s/s (eg, abd pain, Δ in bowel habits, weight loss, N/V), NSAID/ASA or EtOH use, anticoag/antiplt drugs, h/o or risk factors for cirrhosis, radiation, prior GI or aortic surgery
- Physical exam: localizable abd tenderness, peritoneal signs, masses, LAN, prior surgery, signs of liver disease (hepatosplenomegaly, ascites, jaundice, telangiectasias), rectal exam: masses, hemorrhoids, anal fissures, stool appearance, color
- Resuscitation: placement of 2 large-bore (18-gauge or larger) intravenous lines Volume replacement: NS or LR to achieve normal VS, UOP, & mental status
- Lab studies: Hct (*may be normal* in first 24 h of acute GIB before equilibration)
  2–3% → 500 mL blood loss; low MCV → Fe deficient and chronic blood loss; plt, PT, PTT; BUN/Cr (ratio >36 in UGIB b/c GI resorption of blood ± prerenal azotemia); LFTs
- Transfuse: type & cross; use O-neg if emerg; for UGIB (esp. w/ portal HTN) transfuse w/ more restrictive Hb goal (eg, 7 g/dL) or >8 g/dL if CAD (*JAMA* 2016;316:2025)
- Reverse coagulopathy: consider FFP to normalize PT; plts to keep count >50,000
- Triage: alert endoscopist. Consider ICU if unstable VS or poor end organ perfusion.
  Intubation for: emergent EGD, ongoing hematemesis, shock, poor resp status, Δ MS
  ? OutPt management if SBP ≥110, HR <100, Hb ≥13 (♂) or ≥12 (♀), BUN <18, ⌀ melena, syncope, heart failure, liver disease (*Clin Gastro Hepatol* 2015;13:115)

Diagnostic studies

- UGIB: EGD w/in 24 h. If severe bleed, ↑ Dx/Rx yield by gastric lavage and erythro 250 mg IV 30 min prior to endoscopy to clear stomach contents (*Am J Gastro* 2006;101:1211).

- LGIB: colonoscopy (identifies cause in >70%); if severe, colo w/in 12 h → consider rapid purge w/ PEG solution (6–8 L over 4–6 h). If hematochezia a/w orthostasis, concern for brisk UGIB → *exclude UGIB w/ EGD first.* Push enteroscopy, anoscopy, capsule endoscopy in combo w/ urgent colo results in dx >95% of cases (*GI Endo* 2015;81:889).
- Imaging: if too unstable for endo or recurrent bleeding, can then → IR procedure or surgery
  tagged RBC scan: can identify general luminal location if bleeding rate ≥0.04 mL/min
  CT angiography: faster to obtain than RBC scan, detects bleeding ≥0.3 mL/min
  arteriography: can localize exact vessel if bleeding rates ≥0.5 mL/min, *allows for IR Rx*
- Emergent exploratory laparotomy (last resort) if no localization and life-threatening bleed

Etiology UGIB		Comment & Treatment
PUD (20–67%) (*Am J Gastro* 2014;109:1005; *NEJM* 2016;374:2367; *Br J Clin Pharm* 2017;83:1619) See "PUD"		*Treatment:* PPI: 40 mg PO or IV BID. ? Octreotide if suspect varices. Endoscopic therapy: epi inj + bipolar cautery or hemoclip. Bx for ? *H. pylori* and treat if ⊕. *High-risk (for rebleeding) ulcer*: arterial spurting, adherent clot, visible vessel. Endo Rx, IV PPI × 72 h post EGD, then Δ to high-dose oral PPI. If fail, arteriography w/ embolization; surgery (last resort). *Intermediate-risk ulcer*: oozing, in o/w stable Pt. Endo Rx, can Δ to oral PPI after EGD and observe 24–48 h. *Low-risk ulcer:* clean-based or flat. Oral PPI & ? discharge. Hold anticoag & antiplatelet Rx until hemostasis; can resume after hemostasis & PPI on board (*Endoscopy* 2015;47:a1)
Erosive gastropathy (4–31%)		Precipitants: NSAIDs, ASA, EtOH, cocaine, gut ischemia, XRT Stress-related mucosal injury in ICU Pts. Risk factors include severe coagulopathy, mech vent >48 h, high-dose glucocorticoids Treatment: high-dose PPI
Erosive esopha-gitis (5–18%)		Risk factors: cirrhosis, anticoagulation, critical illness. Rx offending cause + high-dose PPI; repeat EGD later to r/o underling Barrett's.
Esophageal or gastric varices (4–20%) (*Clin Gastro Hepatol* 2015;13:2109; *J Gastro Hepatol* 2016;31:1519; *Hep* 2017;65:310) See "Cirrhosis"		2° to portal HTN. If isolated gastric → r/o splenic vein thrombosis. <u>*Pharmacologic*</u> Start octreotide pending EGD if suspect varices: 50 µg IVB → 50 µg/h (84% success). Rx for 2–5 d, but most benefit w/in 24–48 h. Abx: 20% cirrhotics p/w GIB have infxn, & ~50% develop infxn during hospitalization; Ppx w/ IV CTX, cipro, or levoflox × 7 d <u>*Nonpharmacologic*</u> Esophageal varices: endoscopic band ligation (>90% success). Covered esophageal stent placement or balloon tamponade if refractory as bridge to TIPS (consider early espec. if Child-Pugh C). Gastric varices: arteriography w/ coiling, or if available, endoscopic injection of cyanoacrylate (glue). If refractory: TIPS or balloon-retrograde transvenous obliteration.
Portal HTN gastropathy		↑ portal venous pressure → ectatic vessels, hyperemia in prox. gastric body. No endoscopic option; Rx portal HTN (octreotide), βB.
Vascular (2–8%)	Angioectasia AVMs, HHT (see below)	AVMs congenital. Angioectasia (ectatic submucosal vessels) a/w ↑ age, CKD, cirrhosis, CTD, severe CV dis. *Heyde syndrome:* GIB due to angioectasias + aortic stenosis. Endo Rx.
	Dieulafoy's lesion	Large (1–3 mm) submucosal artery protruding through fundal mucosa → sudden, massive UGIB. *Difficult to identify.* Endo Rx.
	Gastric antral vasc. ectasia (GAVE)	"*Watermelon stomach*"; ectatic gastric vessels, often a/w cirrhosis, CTD, typically older ♂. Rx w/ EGD w/ thermal hemostasis, repeat q4–8wk to eradicate lesions.

		TIPS does *not* improve outcomes.
	Aortoenteric fistula	AAA or aortic graft erodes into 3rd portion of duodenum. P/w "herald bleed"; if suspected, diagnose by endoscopy or CT.
Malignancy (2–8%)		Endoscopic hemostasis of mass temporizing measure till cancer Rx
Mallory-Weiss tear (4–12%)		GE jxn lacerations due to vomiting → ↑ intraabd pressure & shearing effect. Can self-resolve w/o endo Rx. Rx w/ antiemetics, PPI.
Cameron's lesions		Linear erosions in hiatal hernia due to mech trauma of diaphragm
Post-sphincter-otomy bleeding		Occurs in ~2% of ERCP w/ sphincterotomy; ↑ risk w/ more complic. procedure. Bleeding into duodenum. Rx w/ endo hemostasis.

(*GI Endosc Clin N Am* 2015;25:415)

Etiology LGIB	Comment & Treatment (*NEJM* 2017;376:1054)
Diverticular bleed (30%)	*Pathophysiology:* Intimal thickening and medial thinning of vasa recta as they course over dome of diverticulum → weakening of vascular wall → arterial rupture. Diverticula more common in left colon; but *bleeding diverticula more often in right colon.* *Clinical:* older, ASA/NSAIDs, usually painless hematochezia ± abd cramping *Treatment:* Usually stops spont. (~75%) but may take hrs–days; ~20% recur. Can perform endo hemostasis w/ epi injections ± electrocautery, hemoclip, banding. Intra-arterial vasopressin or embo. Surgery (partial colectomy) last resort.
Polyp/Tumor (20%)	Typically slow ooze, p/w fatigue, weight loss, iron deficiency anemia
Colitis (20%)	Infectious (see "Acute Diarrhea"), IBD, ischemic colitis, XRT
Anorectal disorders (20%)	Internal, external hemorrhoids; anal fissures, rectal ulcers, rectal varices (Rx by ↓ portal venous pressure in cirrhotics), XRT
Vascular (<10%)	Angioectasia & AVMs (see above). *Hereditary hemorrhagic telangiectasia (Weber-Osler-Rendu):* diffuse AVMs, telangiectasias throughout GI mucosa (also involve lips, oral mucosa, fingertips).
Meckel's diverticulum	Congenital blind intestinal pouch due to incomplete obliteration of vitelline duct. 2% of pop, w/in 2′ of IC valve, 2″ long, ♂:♀ 2:1, often present age 2 y (but can cause obscure GIB in adults). Dx w/ ^{99m}Tc-pertechnetate scintigraphy. Rx w/ angioembo, surgical resection.

Obscure GIB (*Am J Gastro* 2015;110:1265; *Gastro* 2017;152:497)

- Definition: continued bleeding (melena, hematochezia) despite ⊖ EGD & colo; 5% of GIB
- Etiologies: Dieulafoy's lesion, GAVE, small bowel angiodysplasia, ulcer or cancer, Crohn's disease, aortoenteric fistula, Meckel's diverticulum, hemobilia
- Diagnosis: repeat EGD w/ push enteroscopy/colonoscopy when bleeding is active
  If ⊖, video capsule to evaluate small intestine (*GIE* 2015;81:889)
  If still ⊖, consider ^{99m}Tc-pertechnetate scan ("Meckel's scan"), enteroscopy (single-balloon, double-balloon or spiral), tagged RBC scan and arteriography

DIARRHEA

ACUTE DIARRHEA (<4 WEEKS' DURATION)

Acute Infectious Etiologies (*NEJM* 2014;370:1532; *JAMA* 2015;313:71; *CDC Yellow Book* 2018)		
Noninflammatory		Predom. disruption small intestine absorp. & secretion. Voluminous diarrhea, N/V. ⊖ Fecal WBC & FOB.
Preformed toxin		"Food poisoning," <24 h dur. *S. aureus* (meats & dairy), *B. cereus* (fried rice), *C. perfringens* (rewarmed meats).
Viral (*Lancet* 2018; 392:175)	Rotavirus	Outbreak person to person (PTP), daycare; lasts 4–8 d.
	Norovirus	~50% of all diarrhea. Winter outbreaks; PTP & food/water; no immunity. Lasts 1–3 d. Vomiting prominent.
Bacterial	*E. coli* (toxigenic)	>50% of traveler's diarrhea; cholera-like toxin; <7 d.
	Vibrio cholerae	Contam H_2O, fish, shellfish; "rice water" stools w/ severe dehydration & electrolyte depletion.
Parasitic	*Giardia*	Streams/outdoor sports, travel, outbreaks. Bloating. Acute (profuse, watery) → chronic (greasy, malodorous).
(± malab for mos after Rx)	*Cryptosporidia*	In soil; water-borne outbreak; usually self-limited, can → chronic infxn if immunosupp. Abd pain (80%), fever (40%).
	Cyclospora	Contaminated produce
Inflammatory		Predom. colonic invasion. Small-vol diarrhea. LLQ cramps, tenesmus, fever, typically ⊕ fecal WBC or FOB.
Bacterial	*Campylobacter*	Undercooked poultry, unpasteurized milk; carried by puppies & kittens. Prodrome w/ abd pain, "pseudoappendicitis"; c/b GBS, reactive arthritis
	Salmonella (nontyphoidal)	Eggs, poultry, milk, hamsters. Bacteremia in 5–10%. 10–33% of bacteremic Pts >50 y may develop aortitis.
	Shigella	Abrupt onset; gross blood & pus in stool; ↑↑ WBC.
	E. coli (O157:H7 & inv/hemorrhagic non-O157:H7)	Undercooked beef, unpasteurized milk, raw produce; PTP. O157 & non-O157 sp. (40%) produce *Shiga* toxin → HUS (typically in children). Gross blood in stool.
	C. difficile	See later
	Vibrio parahaem.	Undercooked seafood
	Salmonella typhi	Travel to Asia, Africa, South America. Systemic toxicity, relative bradycardia, rose spot rash, ileus → "pea-soup" diarrhea, bacteremia.
	Other	*Yersinia:* undercooked pork; unpasteurized milk, abd pain → "pseudoappendicitis" (aka mesenteric adenitis) *Aeromonas, Plesiomonas, Listeria* (meats & cheeses)
Parasitic	*E. histolytica*	Contaminated food/water, travel (rare in U.S.); liver abscess
Viral	CMV	Immunosuppressed; dx by shell vial cx of colon bx

Evaluation (*NEJM* 2014;370:1532; *Digestion* 2017;95:293; *PLOS One* 2017;12:11)

- Ddx: hyperthyroid, adrenal insufficiency, meds (abx, antacids, checkpt inhibitors), appendicitis, diverticulitis, 1st presentation of primary bowel disorder (eg, IBD, celiac)

- History: stool freq, blood, abd pain, duration of sxs [~1 wk for viral & bacterial (except *C. diff*), >1 wk for parasitic], travel, food, recent abx, immunocompromise
- PEx: vol depletion (VS, UOP, axillae, skin turgor, MS), fever, abd tenderness, ileus, rash
- Laboratory: ✔ calprotectin, stool cx, BCx, lytes, *C. diff* (if recent hosp/abx), stool O&P (if >10 d, travel to endemic area, exposure to unpurified H_2O, community outbreak, daycare, HIV ⊕ or MSM); ± stool ELISAs (viruses, *Crypto*, *Giardia*), serologies (*E. histolytica*); PCR available (but high ⊕ rate & unclear if true vs colonized; consider if immunocompromised)
- Imaging/endoscopy: consider if *warning signs (WS)* of fever, severe abd pain, blood or pus in stool, >6 stools/d, severe dehydration, immunosupp, elderly, duration >7 d, hosp-acquired. CT/KUB if ? toxic megacolon; sig/colo if immunosupp or cx ⊖

Treatment (*Am J Gastro* 2016;111:602; *Clin Infect Dis* 2017;65:e45)

- If no WS, nl PO intake → supportive: hydrate, loperamide, bismuth subsalicylate (⌀ antichol)
- If mod. dehydration: 50–200 mL/kg/d of oral solution or Gatorade, etc. If severe: IV fluids.
- If suspect traveler's diarrhea → FQ, rifaximin, or rifamycin; if suspect protozoal → flagyl or nitazoxanide
- *Empiric* abx for non–*C. diff inflammatory* diarrhea reasonable: FQ × 5–7 d
  Abx rec for *Shigella*, cholera, *Giardia*, amebiasis, *Salmonella* if Pt >50 y or immunosupp or hospitalized, ? *Campylobacter* (if w/in 4 d of sx onset)
- *Avoid* abx if suspect *E. coli* O157:H7 (exposure hx, gross blood) as may ↑ risk of HUS

CLOSTRIDIOIDES DIFFICILE INFECTION (CDI)

Pathogenesis & epidemiology (*NEJM* 2015;372:825)

- Ingestion of *C. diff* spores → colonization when colonic flora Δd by abx or chemo → release of toxin A/B → colonic mucosal necrosis & inflammation → pseudomembranes
- Most frequently reported nosocomial infxn; community-acquired infxn may account for up to $^1/_3$ of new cases. Associated w/ *any* abx (esp. β-lactams, clinda, quinolones).
- Elderly, immunocompromised, and IBD Pts can develop CDI w/o recent abx exposure

Clinical manifestations (a spectrum of disease)

- Asx colonization: <3% healthy adults; ~20% in hospitalized patients on antibiotics
- Acute watery diarrhea (occ bloody) ± mucus, often w/ lower abd pain, fever, ↑↑↑ WBC
- Pseudomembranous colitis: above sx + pseudomembranes + bowel wall thickening
- Fulminant colitis (2–3%): toxic megacolon (colonic atony/absence of BMs, colon dilatation ≥6 cm on KUB, systemic toxicity) and/or bowel perforation

Diagnosis (*Ann Intern Med* 2018;169:49)

- Only test if *symptomatic* (diarrhea, s/s of colitis); test *liquid* stool (unless concern for ileus)
- Stool toxin immunoassay (high Sp) + glutamate dehydrogenase (GDH) (high Se)
- Stool PCR: has ↑ Se, but ⊕ if colonized in absence of active infxn; should not necessarily

Rx if ⊕ PCR w/ neg toxin assay (*JAMA IM* 2015;175;1792)

- Obtain CT abdomen/pelvis if suspect complications (toxic megacolon). Consider flex sig if dx uncertain and/or evidence of no improvement on standard Rx.

Initial treatment (*CID* 2018;66:48)

- If possible, d/c abx ASAP; stop antimotility agents & cholestyramine if using (binds vanco)
- Mild-mod: vanco 125 mg PO q6h or fidaxomicin 200 mg BID × 10 d preferred over MNZ
- Severe (any of the following: >12 BM/d, Temp >103°F, WBC >25, HoTN, ICU care required, ileus): vanco 500 mg PO (or PR) q6h + MNZ 500 mg IV q8h
- If worsening (ileus, ↑ WBC, ↑ lactate, shock, toxic megacolon, peritonitis): abd CT & urgent surgical consult re: subtotal colectomy (? diverting loop ileostomy or colonic lavage)
- If need to cont abx, cont *C. diff*. Rx for ≥7 d post-abx cessation *(Am J Gastro* 2016;111:1834)
- Stool carriage may persist 3–6 wk postcessation of sx & should not trigger further Rx (retesting for *C. diff* of limited utility during this time)

Recurrent infection (15–30% risk after d/c of abx, most w/in 2 wk of stopping abx)

- 1st recurrence: vanco 125 mg PO q6h × 10–14 d or fidaxomicin 200 mg PO bid × 10 d
- Subsequent recurrences: vanco PO pulse → taper. Consult ID physician. Fecal microbial transplant (*JAMA* 2017;318:1985; *CID* 2018;66:1) or fidaxomicin (200 mg bid × 10 d).
- Prevention: *vanco* 125–250 mg PO BID ↓ risk of recurrence 27% → 4% (*CID* 2016;65:651); consider for Pts needing abx w/ h/o severe or recurrent CDI. *Bezlotoxumab* (mAb that binds toxin B) ↓ risk of recurrence in adults receiving *C. diff* Rx & at high risk of recurrence (*NEJM* 2017; 376:305).

CHRONIC DIARRHEA (>4 WK; *JAMA* 2016;315:2712)

General evaluation

- Clinically can be organized into *watery*, *fatty*, or *inflammatory stools*
- Additional hx: timing (freq, relation to meals; *nocturnal diarrhea* a/w organic causes like IBD rather than IBS), abd pain, wt loss, prior surg, chemo/XRT, diet (incl caffeine or poorly absorbed carbs/sugars), infectious sxs, immunocompromise, travel, laxative use, etc.
- Hx offending meds: PPI, colchicine, abx, H2RA, SSRIs, ARBs, NSAIDs, chemo, caffeine
- PEx: gen appearance (BMI), signs of systemic disease, surgical scars, rectal tone/DRE
- Lab testing: CBC, metabolic profile, alb, TSH, Fe studies, ESR; *see under each category*
- Imaging/endoscopy: colonoscopy for chronic diarrhea of unknown cause. Abd CT/MRI usually warranted if systemic problem suspected.

Osmotic (watery; ⊖ fecal fat, ↑ osmotic gap, ↓ diarrhea with fasting)

- Caused by ingestion of poorly absorbed cations/anions (Mg, sulfate, phos; found in laxatives) or poorly absorbed sugars (eg, mannitol, sorbitol; found in chewing gum; or lactose if lactose intolerant). *Diarrhea resolves w/ cessation of offending substance.*

- Dx: ↑ stool osmotic gap (see Figure); stool pH <6 if unabsorbed carbohydrates
- Lactose intolerance (75% nonwhites & 25% whites lactase-deficient): can be acquired after gastroenteritis, med illness, GI surg. Clin: bloating, flatulence, discomfort, diarrhea. Dx: H+ breath test or empiric lactose-free diet. Rx: lactose-free diet & lactase tablets.

Secretory (watery; normal osmotic gap, no Δ diarrhea w/ fasting, often nocturnal diarrhea)

- Caused by secretion of anions or K+ into lumen or inhib of Na absorption → ↑ H_2O in stool. Most commonly caused by bacterial toxins from infxn (see above). Other causes:
- Endocrine: Addison's, VIPoma, carcinoid, Zollinger-Ellison, mastocytosis, hyperthyroid (↑ motility). ✔ serum peptide levels (eg, gastrin, calcitonin, VIP) & urinary histamine.
- GI neoplasm: carcinoma, lymphoma, villous adenoma
- Microscopic colitis: common cause of chronic diarrhea w/ obscure origin. Often seen in middle-aged women w/ autoimmune disorders. NSAIDs, SSRIs, PPIs notable triggers. Grossly nl on colo but bx shows lymphocytic & plasmacytic infiltration of mucosa ± thickened submucosal collagen. Rx: antidiarrheals, cholestyramine, bismuth, budesonide; consider anti-TNFs if refractory.
- Bile acid-induced diarrhea: ileal resection or disease (eg, Crohn's)→ bile acids in colon → electrolyte & H_2O secretion. Rx w/ empiric bile-acid binders (eg, cholestyramine).

Fxnal/IBS (watery; normal osmotic gap, ↓ diarrhea with fasting): see "Dysmotility"

Malabsorption (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Defective mucosal absorption of nutrients b/c Δs in: mucosal surface (surgical resection) or gen. mucosal dis. (celiac, IBD). Bloating, foul-smelling, floating stools (steatorrhea).
- Celiac disease (*JAMA* 2017;318:647; *Lancet* 2018;391:70)
  - Immune rxn in genetically predisposed Pts (~1% pop) to gliadin, a component of gluten (wheat protein) → small bowel inflammatory infiltrate → impaired absorption
  - Other s/s: Fe/folate defic anemia; osteoporosis; dermatitis herpetiformis; ↑ AST/ALT
  - Dx: IgA anti-tissue transglutaminase Ab (most Se), IgA anti-deaminated gliadin peptide Ab; IgA ɑ-endomysial Ab. Duodenal bx to confirm dx (blunted villi, crypt hyperplasia, inflamm infiltrate) but may not be necessary if serology ⊕ and Pt sx. HLA-DQ2/Q8 testing useful for high ⊖ predictive value if ⊖ serologies already on gluten-free diet.
  - Rx: gluten-free diet; 7–30% do not respond to diet → ? wrong dx or noncompliant
  - Complic: ~5% refractory sx, risk of T-cell lymphoma and small bowel adenocarcinoma
- Whipple's disease: infxn w/ *T. whipplei* (*Lancet* 2016;16:13)
  - Other s/s: fever, LAN, edema, arthritis, CNS Δs, gray-brown skin pigmentation, AI & MS, oculomasticatory myorhythmia (eye oscillations + mastication muscle contract).
  - Dx: bx/path, IHC, PCR. Rx: PCN + streptomycin or 3rd-gen ceph × 10–14 d → Bactrim ≥1 y.
- Small intestinal bacterial overgrowth (SIBO): colonic bacteria in SI → steatorrhea, B12/Fe defic, protein-losing enteropathy. A/w dysmotility (DM neuropathy, scleroderma), Δ'd anatomy (Crohn's, surgery, fistulae), immune deficiency, celiac, CF.

Dx w/ H^+ or ^{14}C-xylose breath testing or empiric abx. Rx w/ 7–10 d abx (eg, rifaximin, MNZ, FQ).

- Other: s/p short bowel resection (short bowel syndrome), chronic mesenteric ischemia, eosinophilic gastroenteritis, intestinal lymphoma, tropical sprue, *Giardia* infection

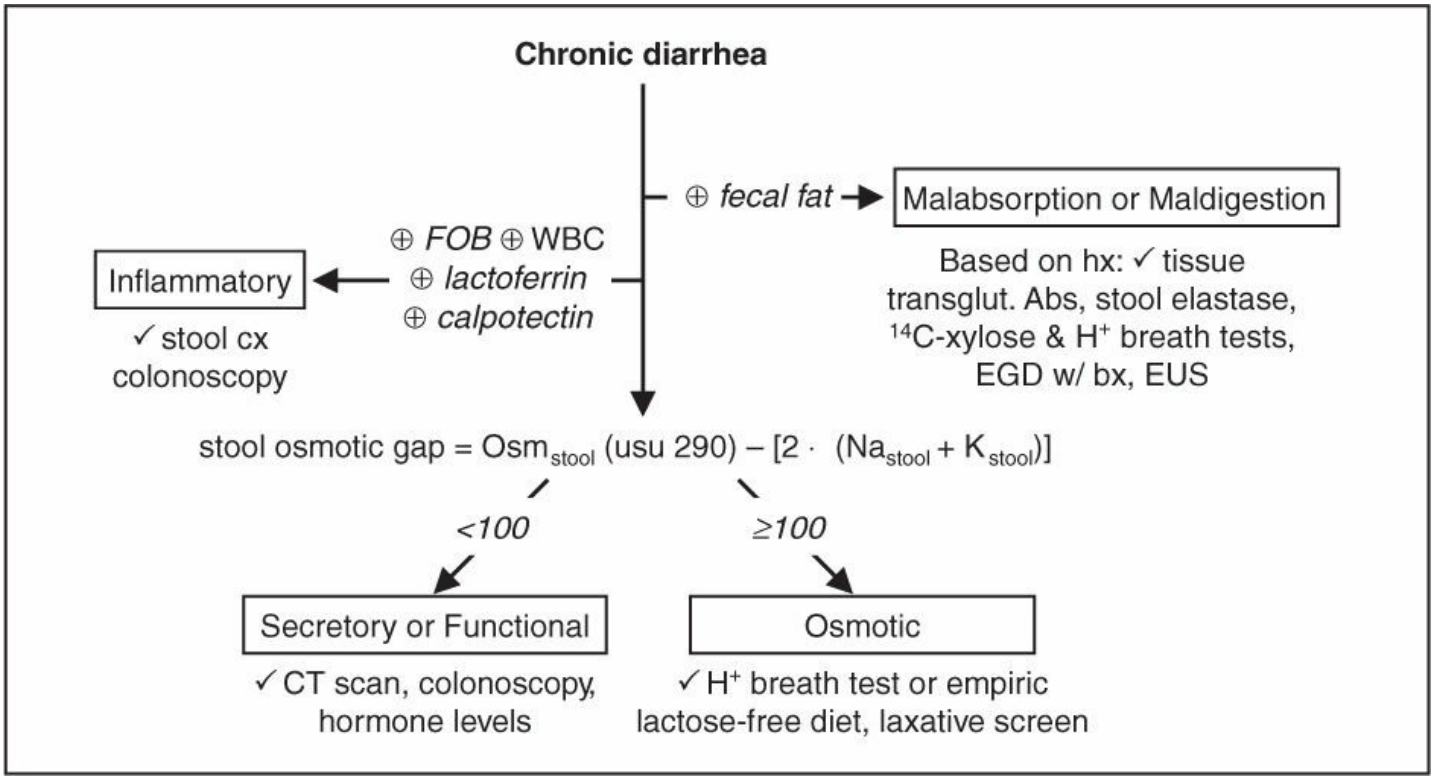
Maldigestion (fatty; ↑ fecal fat, ↑ osmotic gap, ↓ diarrhea w/ fasting)

- Defective intraluminal hydrolysis of nutrients, typ. 2/2 pancreatic/hepatobiliary pathology
- Pancreatic insufficiency: most commonly from chronic pancreatitis or pancreatic cancer. Test w/ stool elastase, chymotrypsin levels, or empiric pancreatic enzyme replacement.
- ↓ bile acids due to ↓ synthesis (cirrhosis), cholestasis (PBC), or s/p ileal resection. Test w/ empiric bile acid replacement therapy.

Inflammatory (⊕ fecal WBC, lactoferrin, or calprotectin; ⊕ FOB; fever, abd pain)

- Infections: chronic *C. diff*, *Entamoeba histolytica*, *Yersinia*, CMV, TB especially in immunocompromised hosts. CMV, *C. diff* notorious for causing exacerbations of IBD.
- Inflammatory bowel disease (Crohn's, UC)
- Radiation enteritis, ischemic colitis, neoplasia (colon cancer, lymphoma)

Figure 3-2 Workup of chronic diarrhea



DYSMOTILITY & NUTRITION

Functional GI disease (<30 types per Rome IV criteria; *Gastro* 2016;150:1257)

- Recurrent GI sx caused by disorders of gut-brain interaction rather than structural cause
- Irritable bowel syndrome (IBS) (*JAMA* 2015;313:949; *Gastro* 2015;149:1399 & 2018;154:1140)
  - Abd discomfort a/w ≥2 of following: improve w/ defecation, Δ stool frequency, Δ stool form
  - IBS-C (constipation predominant) vs. IBS-D (diarrhea predominant) vs. IBS-M (mixed) vs. IBS-U (unclassified). Sx may be affected by stress, diet, lifestyle, probably microbiome.
  - Treatment: cog. behavioral Rx, probiotics, exercise, consider gut-brain modulators (eg, TCA, SSRI), Δ diet (↓ fermentable short-chain carbohydrates)
  - IBS-C: ↑ soluble fiber in diet, laxatives (eg, lubiprostone, linaclotide, PEG), biofeedback
  - IBS-D: loperamide or rifaximin; eluxadoline, μ & κ agonist, δ antag (*NEJM* 2016;374:242)
- Cyclic vomiting syndrome (CVS): acute recurrent vomiting; a/w marijuana use, personal or FHx of migraine. Acute Rx: antiemetics, IVF, sumatriptan, BZDs; prevention: TCAs/AEDs; avoid marijuana.

Gastroparesis (*Gastro Clinics of NA* 2015;44:1; *World J Gastro* 2015;21:6842)

- Delayed gastric emptying w/o obstruction, typically p/w nausea (>90%), vomiting (>80%), early satiety (60%), postprandial fullness/pain
- Etiol: DM, post-surg, post-viral, crit. illness, Parkinson's, opiates, CCB, anti-cholin
- Dx: gastric emptying scintigraphy
- Treatment: prokinetic agents (metoclopramide or erythromycin), antiemetics for sx; feeding tube if refractory; intrapyloric botox & gastric stimulator experimental

Paralytic ileus of the colon (Ogilvie's; *ANZ J Surg* 2015;85:728) & small bowel

- Definition: loss of intestinal peristalsis in absence of mechanical obstruction
- Abd discomfort & distention, ↓ or absent bowel sounds, ± N/V, hiccups
- Typically in elderly, hospitalized, ill Pts; precipitated by: intra-abd process (surgery, pancreatitis, peritonitis, intestinal ischemia), severe med illness (eg, sepsis), meds (opiates, CCB, anticholin.), metab/endo abnl (thyroid, DM, kidney failure, liver failure, hypoK), spinal cord compression/trauma, neurologic d/o (Parkinson's, Alzheimer's, MS)
- KUB or CT w/ colonic dilatation (in ileus, dilated loops of SB) w/o mech obstruction; cecal diam >12 cm a/w high-risk perf in Ogilvie's
- Treatment: conservative measures (NPO, avoid offending meds) usually effective; IV neostigmine (monitor for bradycardia), methylnaltrexone; bowel decompression w/ NGT, rectal tube. Ogilvie's only: colonoscopy; if refractory, colostomy or colectomy.

Constipation (*Annals* 2015;162:ITC1)

- Defined as dissatisfaction w/ defecation or (per Rome IV): ≥2 of following during last 3–6 mo ≥25% of the time: straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction, manual maneuvers to facilitate defecation, stool frequency <3/wk
- Primary etiologies: slow transit vs. pelvic floor dyssynergia
- Secondary etiologies (4 Ms)
  - Mech obstruction: malignancy, compression, rectocele, strictures
  - Meds: opioids, TCAs, anticholinergics, CCB, NSAIDs, diuretics, Ca^{2+}, Fe
  - Metabolic/endo: DM, hypothyroid, uremia, preg, panhypopit, porphyria, ↑ Ca, ↓ K, ↓ Mg
  - Myopathy/Neuro: Parkinson's, Hirschsprung's, amyloid, MS, spinal injury, dysautonomia
- Dx: H&P w/ DRE. Labs: consider CBC, electrolytes w/ Ca, TSH. Colonoscopy if alarm sx. Anorectal manometry/balloon expulsion test; colonic transit study; defecography.
- Treatment: ↑ fluid & fiber intake. Emollient laxative (docusate): softens stool.
  - Bulk laxatives (psyllium, methylcellulose, polycarbophil): ↑ colonic residue, ↑ peristalsis
  - Osmotic laxatives (Mg, $NaPO_4$ [avoid in CKD], lactulose, PEG): ↑ H_2O in colon
  - Stimulant laxatives (senna, castor oil, bisacodyl): ↑ motility & secretion
  - Enema/suppository (phosphate, mineral oil, tap water, soapsuds, bisacodyl)
  - Lubiprostone (↑ secretion); methylnaltrexone and alvimopan for opioid-induced
  - Plecanitide (cGMP agonist) for chronic idiopathic constipation (*Gastroenterol* 2016;150:S317)
  - Linaclotide ↑ stool freq, ↓ straining/bloating (*Am J Gastro* 2018;113:105)

Nutrition in critical illness (also see "Mech Ventilation") (*Crit Care* 2015;19:35)

- Enteral & parenteral with similar clinical outcomes (*Lancet* 2018;391:133)
- Enteral (EN): starting w/in 48–72 hr of ICU admit may ↓ infxn & mort, but repletion of 100% caloric needs may be harmful (*Cochrane* CD0078767). Contraindic. if obstruction, major GIB. Possible complic: ischemic bowel b/c ↑ demand for splanchnic blood; aspiration PNA.
- Parenteral (PN): start after 7 d if unable to tolerate enteral feeds, late (> day 8 of ICU stay) Contraindic: hyperosmolality, severe electrolyte disturbances, severe hyperglycemia; sepsis is *relative* contraindication. Complications: hyperglycemia (due to dextrose), catheter sepsis/thrombus, refeeding syndrome, LFT abnl (steatosis, cholestasis, gallbladder sludge due to lack of enteric stimulation).

DISORDERS OF THE COLON

DIVERTICULOSIS

Definition & pathophysiology (*Aliment Pharm Ther* 2015;42:664)

- Acquired herniations of colonic mucosa & submucosa in areas where vasa recta penetrate
- Thought to occur in setting of abnormal motility and ↑ intraluminal pressure

Epidemiology

- Risk factors: ↓ fiber, ↑ red meat, obesity, smoking, physical inactivity, EtOH, NSAIDs
- Prevalence higher w/ ↑ age (10% if <40 y; 50–66% if >80 y); "Westernized" societies
- Left side (90%, mostly sigmoid) > R side of colon (except in Asia where 75–85% R-sided)

Clinical manifestations

- Usually asx, but 5–15% develop diverticular hemorrhage (see "GIB") and <5% diverticulitis
- Limited data for ↑ fiber diet or avoiding nuts/seeds (*Ther Adv Gastro* 2016;9:213)

DIVERTICULITIS

Pathophysiology (*Gastro* 2015;149:1944; *Am J Gastro* 2018;112:1868)

- Retention of undigested food and bacteria in diverticulum → fecalith formation → obstruction → compromise of diverticulum's blood supply, infection, perforation
- Uncomplicated: microperforation → localized infection
- Complicated (15%): macroperf → abscess, peritonitis, fistula (65% w/ bladder), obstrxn

Clinical manifestations

- LLQ abdominal pain, fever, nausea, vomiting, constipation or diarrhea
- PEx ranges from LLQ tenderness ± palpable mass to peritoneal signs & septic shock
- Ddx includes IBD, infectious colitis, PID, tubal pregnancy, cystitis, colorectal cancer

Diagnostic studies

- Plain abdominal radiographs to r/o free air, ileus or obstruction
- Abdominal CT (I^+O^+): >95% Se & Sp; assess complicated disease (abscess, fistula)
- Colonoscopy *contraindic.* acutely as ↑ risk of perforation; do 6–8 wk after to r/o neoplasm

Treatment (*JAMA* 2017;318:291; *Dig Surg* 2017;34:151; *NEJM* 2018;379:1635)

- Mild: outPt Rx indicated if Pt has few comorbidities and can tolerate POs
  PO abx: (MNZ + FQ) or amox/clav for 7–10 d; liquid diet until clinical improvement
  Possible that abx not needed for uncomplicated diverticulitis (*Br J Surg* 2017;104:52)
- Severe: inPt Rx if cannot take POs, narcotics needed for pain, or complications
  NPO, IVF, NGT (if ileus); IV abx (GNR & anaerobic coverage; eg, CTX/MNZ or pip-

tazo)
- Abscesses >4 cm should be drained percutaneously or surgically
- Surgery: if progression despite med Rx, undrainable abscess, free perforation
  - Resection superior to laparoscopic lavage (*JAMA* 2015;314:1364), but lavage may be suitable for perforation w/ purulent peritonitis (*Annals* 2016;164:137)
  - After source control, 4 d abx may be sufficient (*NEJM* 2015;372:1996)
  - Resection for recurrent bouts of diverticulitis on a case-by-case basis
  - Consider lower threshold for urgent & elective surgery for immunocompromised Pts

Prevention (*Cochrane* CD009839; *Am J Gastro* 2016;11:579; *Ann Gastro* 2016;29:24)
- Mesalamine + rifaximin both w/ weak evidence
- Risk of recurrence 10–30% w/in 10 y of 1st episode; more likely 2nd episode complicated

---

POLYPS & ADENOMAS

Pathophysiology & epidemiology (*NEJM* 2016;374:1065)
- Accumulation of mutations in colonic epithelial cell DNA affecting oncogenes & tumor suppressor genes → *tumor initiation* (formation of adenoma; *APC* loss of fxn) → *tumor progression* (adenoma → carcinoma; *K-ras* gain of fxn, *DCC, p53* loss of fxn)
- Risk factors: ↑ age, FHx (sporadic in 1° relatives, Lynch, FAP), IBD, ↑ dietary fat, central adiposity, ↑ EtOH, ↓ fiber, ↑ red meat, ? smoking, DM
- Protective factors: ↑ physical activity, ASA/NSAIDs, Ca^{2+} intake, HRT, ↓ BMI; possibly ↑ fiber, vitamin D, fish oil, statins, selenium
- Neoplastic polyps: adenomas (tubular, villous, tubulovillous dysplasia), sessile serrated adenomas/polyps (concern for interval CRC), carcinomas
- Nonneoplastic polyps: hyperplastic, juvenile, Peutz-Jeghers, inflammatory

Detection
- *Colonoscopy* is gold standard
- Recommended in all Pts starting at age 50 (Amer Cancer Soc. rec age 45) and then typically q10y unless pathology found
- If ⊕ FHx, start age 40, or 10 y before age of dx in youngest family member, repeat q5y

INFLAMMATORY BOWEL DISEASE

Definition

- Ulcerative colitis (UC): inflammation of the colonic *mucosa; contiguous*, starting at rectum
- Crohn's disease (CD): *transmural* inflammation anywhere along GI tract, *skip lesions*

Epidem & pathophys (*Lancet* 2016;387:156 & 2017;390:2769)

- Prevalence ~1-3:1000 in N Am; ↑ incidence in Caucasians, Jews, newly industrialized
- Age of onset 15–30 y; ? bimodal w/ 2nd peak at 50–70 y; 1:1 M:F in N America
- Smokers at ↑ risk for CD, whereas nonsmokers & former smokers at ↑ risk for UC
- Genetic predisposition + environmental risk factors → T cell dysregulation → inflammation

---

ULCERATIVE COLITIS (*Lancet* 2018;389:1756)

Clinical manifestations

- Grossly bloody diarrhea, lower abdominal cramps, urgency, tenesmus
- Extracolonic (>25%): erythema nodosum, pyoderma gangrenosum, aphthous ulcers, uveitis, episcleritis, thromboembolic events (esp. during a flare; *Lancet* 2010;375:657), AIHA, seroneg arthritis, chronic hepatitis, cirrhosis, PSC (↑ risk cholangio CA, CRC)
- Multiple scores for assessing dis. severity clinically: Truelove & Witts; SCCAI

Diagnosis

- Colonoscopy: involves rectum (95%) & extends prox., usu circumfer., & *contig. w/in colon*
- Location: proctitis (30–60%), L-sided (15–45%) and extensive (pancolitis; 15–35%)
- Appearance: vascularity loss, friable mucosa, diffuse ulceration, *pseudopolyps* (chronicity)
- Histology: superficial chronic inflammation; crypt abscesses & architectural distortion
- Barium enema with featureless and tubular appearance of colon (*leadpipe appearance*)
- Flares: ↑ ESR & CRP (not Se or Sp); ⊕ fecal calprotectin helpful in distinguishing IBD vs. IBS and monitoring for IBD flare (*Gastro Hep* 2017;13:53)

Complications

- Toxic megacolon (5%): colon dilatation (≥6 cm on KUB), colonic atony, systemic toxicity, & ↑ risk of perf. Rx w/ IV steroids & broad-spectrum abx; surgery if needed.
- Stricture (rectosigmoid), dysmotility, anorectal dysfxn after recurrent inflammation
- CRC and dysplasia (*see below*)
- For Pts s/p surgery w/ ileal pouch, may develop *pouchitis* (inflammation of ileal pouch, up to ½ of pts). Rx w/ abx (MNZ, cipro), probiotics.

Prognosis

- 50% in remission at any given time. Intermittent exacerbations in 90%; continual active disease in ~18%. Prox progression in 25% at 10 y. Rate of colectomy at 10 y is 24%.
- Mortality rate of severe UC flare is <2%, & overall life expectancy in UC = non-UC Pts

CROHN'S DISEASE (*Lancet* 2018;389:1741)

Clinical manifestations (*Nat Rev Gastro Hep* 2016;13:567)

- Abdominal pain, loose/frequent stools (up to 50% ⊕ FOBT), fever, malaise, wt loss
- Mucus-containing, nongrossly bloody diarrhea
- N/V, bloating, obstipation if presence of obstruction; extracolonic manifestations as in UC
- Multiple scoring systems: CD Activity Index (CDAI), Harvey-Bradshaw Index

Diagnosis

- Ileocolonoscopy + bx along w/ small bowel assessment (eg, MR-enterography)
- Small bowel/ileitis (~25%), ileocolonic (~50%), colonic (~25%); isolated upper tract rare
- Appearance: nonfriable mucosa, cobblestoning, aphthous ulcers, deep & long fissures
- Histology: transmural inflammation with mononuclear cell infiltrate, noncaseating granulomas (seen in <25% of mucosal biopsies), fibrosis, ulcers, fissures
- Montreal classification: age at dx, disease location & behavior (stricturing vs. nonstricturing, penetrating vs. nonpenetrating), plus modifiers for upper tract & perianal disease

Complications

- Perianal disease: fissures, fistulas, skin tags, perirectal abscesses (in 24% of Pts; perianal disease *precedes* intestinal symptomatology)
- Stricture: small bowel, postprandial abd pain; can lead to complete SBO & require surgery
- Fistulas: perianal, enteroenteric, rectovaginal, enterovesicular, enterocutaneous
- Abscess: fever, tender abd mass, ↑ WBC; *steroids mask sx*, ∴ need high-level suspicion
- Malabsorption: ileal disease/resection: ↓ bile acids abs → gallstones; ↓ fatty acid abs → Ca oxalate kidney stones; ↓ fat-soluble vitamin abs → vit D deficiency → *osteopenia*

Prognosis

- Variable at 1 y: ~50% in remission, ~20% flare, ~20% low activity, ~10% chronic active
- At 20 y, majority will have required some surgery; overall life expectancy is slightly ↓

MANAGEMENT (*Lancet* 2016;398:1756; *Mayo Clin Proc* 2017;92:1088)

Initial evaluation

- H&P (✔ for intestinal & extraintestinal manifestations) and dx studies as above
- Lab: consider CBC/diff, LFTs, iron studies, B12, folate, vit D, ESR, CRP, fecal calprotectin
- Exclude other etiologies: infectious (espec. TB), ischemic colitis, intestinal lymphoma, CRC, IBS, vasculitis, Behçet's, celiac disease, small intestinal bacterial overgrowth
- R/o infection (esp. TB, HBV, CMV) before treating with immunosuppressants and biologics (although not all acutely hospitalized Pts w/ IBD need infxn r/o prior to Rx)

Goals of treatment (*Ther Adv Gastro* 2015;8:143)

- Induce remission of acute flare → maintain remission; mucosal healing 1° goal
- Step up Rx (least → most toxic) typical approach; consider early biologic if severe disease

Medical Therapy for IBD	
Ulcerative Colitis	
Mild	5-ASA: many formulations (sulfasalazine, mesalamine, olsalazine, balsalazide) depending on disease location. Used for induction & maintenance of remission. Complications: diarrhea, abd pain, pancreatitis.
Mild- moderate	MMX-budesonide: PO budesonide released throughout colon for flare. 1st-pass metab ↓ systemic adverse effects of steroid.
Moderate-severe	PO prednisone: 40–60 mg w/ taper over several wks to induce remission AZA/6-MP: 0.5–1 mg/kg and uptitrate over several wks for maintenance; ↑ remission rate when AZA combined w/ IFX (*Gastro* 2014;146:392). Complic: BM suppression, lymphoma, pancreatitis, hepatitis; ✔ TPMT levels prior to dosing to ↓ risk of generation of toxic metabs. In selected cases, add allopurinol to boost activity in non-responders.
Severe or refractory disease (*Lancet* 2014; 384:309 & 2017;389:1218; *NEJM* 2016; 374:1754 & 2017; 76:1723; *JAMA* 2019; 321:156)	IV steroids: eg, 100 mg hydrocort q8h or 16–20 mg methylpred q8h to induce remission w/ plan to taper & switch to non-steroid maintenance. Cyclosporine: for severe flares refractory to steroids, 2–4 mg/kg infusion × 7 d w/ goal to Δ to maintenance medication (eg, AZA/6-MP) Anti-TNF (infliximab, adalimumab & golimumab): for steroid-refractory flares or to maintain remission. Complic: reactiv. TB (✔ PPD prior to Rx) or viral hepatitis; small ↑ risk NHL; lupus-like rxn, psoriasis, MS, CHF. *For TNF refractory, alternative biologic for induction & maintenance:* vedolizumab (α4β7 integrin inhibitor); tofacitinib (JAK inh) *Investigational:* fecal microbiota transplant (mixed data – efficacy may depend on mode of delivery & prep); etrolizumab (α4β7 inhib); ozanimod (sphinosine-1-phosphate receptor agonist)
Crohn's Disease	
Mild	Consider 5-ASA for colonic Crohn's disease Abx: FQ/MNZ or amo x/clav for pyogenic complic (fistulas, perineal dis.)
Mild-mod	Budesonide: PO, but pH ± time-dep release → ileum & ascending colon
Moderate-severe	PO prednisone: same as UC, for inducing remission, not maintenance AZA/6-MP: same as UC; ↑ remission w/ AZA+IFX (*NEJM* 2010; 362:1383) MTX: 15–25 mg IM/SC or PO qwk for maintenance; 1–2 mo to take effect
Severe or refractory disease (*NEJM* 2016; 375:1946)	Anti-TNF: infliximab, adalimumab or certolizumab (pegylated) If flare on infliximab, ✔ trough & presence of anti-inflixi Ab. Low & ⊖ Ab → ↑ dose/freq. If ⊕ Ab → Δ to other biologic (*Am J Gastro* 2011;106:685). Vedolizumab (anti-α4β7 integrin); ustekinumab (anti-IL 12/23) *Investigational:* tofacitinib and filgotinib (JAK-inh; *Lancet* 2017;389:266); adipose- derived stem cells (*Lancet* 2016; 388:1281)

Surgery

- UC: colectomy if sx refractory to or intolerable side effects from meds, CRC, perforation, toxic megacolon, uncontrolled hemorrhage. Often *ileal pouch-anal anastomosis* (IPAA).
- CD: resection if refractory disease; endoscopic dilation or surgery for strictures; diverting ileostomy for perineal disease

Cancer screening (*NEJM* 2015;372:1441)

- Colon cancer: risk in UC ~2% at 10 y, ~8% at 20 y, ~18% at 30 y. Similar for colonic

CD, plus risk of small bowel cancer as well. Dysplasia best marker for risk. Other risk factors include: PSC, ⊕ FHx, greater extent of disease, stricture, & pseudopolyps.

- Surveillance: *colonoscopy* w/ random bx 8 y after dx to eval for dysplasia, q1–3y thereafter based on risk factors. *Chromoendoscopy* using dye to stain high-risk lesions for targeted bx is emerging technique. If high-grade dysplasia or dysplasia-assoc. lesion/mass → colectomy.

INTESTINAL ISCHEMIA

ACUTE MESENTERIC ISCHEMIA

Definition and causes (*NEJM* 2016;374:959)

- Reduced or absent blood flow to small intestine, typically caused by *arterial* (ie, SMA or its branches) occlusion or transient hypoperfusion or less often by *venous* occlusion
- Arterial embolism (~40–50%): embolic occlusion to SMA (has narrow take-off angle), often in setting of AF, valvular disease incl. endocarditis, atherosclerotic plaque in aorta
- SMA thrombosis (~20–30%): typically due to atherosclerosis at origin of SMA; other risk factors incl. vascular injury from abd trauma, infxn, or mesenteric dissections/aneurysms
- Nonocclusive mesenteric ischemia (~10%): transient intestinal hypoperfusion due to ↓ CO, athero, sepsis, drugs that ↓ gut perfusion (pressors, cocaine, amphetamines)
- Mesenteric venous thrombosis (MVT, ~5%): a/w hypercoag. states, portal hypertension, IBD, malignancy, inflammation (pancreatitis, peritonitis), pregnancy, trauma, surgery
- Focal segmental ischemia of small bowel (<5%): vascular occlusion to small segments of small bowel (vasculitis, atheromatous emboli, strangulated hernias, XRT)

Clinical manifestations

- Total arterial or venous occlusion: sudden abd pain out of proportion to abdominal tenderness on exam, progressing to frank infarction w/ peritoneal signs if untreated
- Nonocclusive: abd distention & pain, n/v, lower GI bleeding due to mucosal sloughing; often occurring after episode of hypoperfusion (eg, cardiac event or shock)
- Exam ranges: unremarkable ± abd distention to peritoneal (infarction); ⊕ FOBT ~75%

Diagnostic studies

- Dx relies on high level of suspicion; rapid dx essential to avoid infarction (occurs w/in hrs)
- Mortality 20 to >70% if bowel infarcted; dx prior to infarction strongest predictor of survival
- Laboratory: often nl; ~75% ↑ WBC; ↑ amylase, LDH, PO_4, D-dimer; ~50% ↑ lactate (late)
- KUB: nl early before infarct; "thumbprinting," ileus, pneumatosis in later stages
- CT angiography (arterial phase): noninvasive test of choice; *venous* phase for dx MVT
- Angiography: gold standard; potentially therapeutic; indicated if vasc occlusion suspected

Treatment (*NEJM* 2016;374:959; *World J Emerg Surg* 2017;12:38)

- IVF, NPO, optimize hemodynamics (minimize pressors), broad-spectrum abx, anti-coagulation w/ heparin ± tPA (for occlusive disease), IV papaverine (vasodilator; for non-occlusive mesenteric ischemia)
- If evidence of peritonitis: to OR for surgical endovascular therapies & bowel resection
- SMA thrombosis: percutaneous (stenting) or surgical revascularization

- SMA embolism: embolectomy (catheter-based aspiration vs. surgical)
- Nonocclusive: correct underlying cause (esp. cardiac)
- Mesenteric venous thrombosis: 3–6 mo warfarin after initial heparinization. Fibrinolysis or thrombectomy typically reserved for Pts w/ hemodynamic instability or refractory sx.
- Focal segmental ischemia: typically surgical resection

CHRONIC MESENTERIC ISCHEMIA

- Definition and causes: ↓ blood flow to gut typically because of mesenteric atherosclerosis
- Sx: "intestinal angina" = postprandial abd pain, early satiety, & ↓ wt due to fear of eating. If pain becomes constant → could represent acute thrombosis (see above).
- Dx: duplex U/S or CTA; angiography gold std; gastric tonometry exercise testing
- Treatment: surgical revascularization (1st line); could also consider angioplasty ± stenting

ISCHEMIC COLITIS

Definition & pathophysiology

- Nonocclusive disease 2° to Δs in systemic circulation or anatomic/fxnal Δs in local mesenteric vasculature; often underlying etiology unknown, frequently seen in elderly
- "Watershed" areas (splenic flexure & rectosigmoid) most susceptible; 25% involve R side; confers worse prognosis (*Clin Gastroenterol Hepatol* 2015;13:1969)

Clinical manifestations, diagnosis, & treatment

- Usually p/w cramping LLQ pain w/ overtly bloody stool; fever and peritoneal signs should raise clinical suspicion for infarction
- Disease spectrum: reversible colopathy (35%), transient colitis (15%), chronic ulcerating colitis (20%), resulting stricture (10%), gangrene (15%), fulminant colitis (<5%)
- Dx: flex sig/colonoscopy or CT abd/pelvis to make diagnosis; r/o IBD, infectious colitis
- Treatment: bowel rest, IV fluids, broad-spectrum abx, serial abd exams; surgery for infarction, fulminant colitis, hemorrhage, failure of med Rx, recurrent sepsis, stricture
- Resolution w/in 48 h w/ conservative measures occurs in >50% of cases

PANCREATITIS

ACUTE PANCREATITIS

Pathogenesis

- Pancreatic duct and acinar injury via direct or indirect toxicity → impaired secretion and premature activation of digestive enzymes → autodigestion and acute inflammation

Etiologies (*NEJM* 2016;375:1972)

- Gallstones (40%): ♀ > ♂; usually due to small stones (<5 mm) or microlithiasis/sludge
- Alcohol (30%): ♂ > ♀; 4–5 drinks/day over ≥5 yrs; usually chronic w/ acute flares
- Metabolic: hypertrig. (2–5%; TG >1000; type I & V familial hyperlipemia); hyperCa
- Drugs (<5%): 5-ASA, 6-MP/AZA, ACEI, cytosine, didanosine, dapsone, estrogen, furosemide, isoniazid, MNZ, pentamidine, statins, sulfa, thiazides, tetracycline, valproate
- Anatomic: divisum, annular pancreas, duodenal duplication cysts, Sphincter of Oddi dysfxn
- Autoimmune (qv)
- Familial: suspect if early onset (age <20 y); cause acute and chronic pancreatitis (qv)
- Infections: ascaris, clonorchis, coxsackie, CMV, EBV, HIV, mumps, mycoplasma, TB, toxo
- Ischemia: shock, vasculitis, cholesterol emboli
- Neoplastic: panc/ampullary tumors, mets (RCC most common, breast, lung, melanoma)
- Post ERCP (5%): Ppx w/ PR indomethacin can ↓ sx; temporary panc duct stent if high risk
- Trauma: blunt abdominal trauma, post-pancreatic/biliary surgery

Clinical manifestations

- Epigastric abdominal or LUQ pain (90%), only ½ w/ bandlike pain radiating to back
- 10% pain-free (due to analgesic/steroid use, immunosuppressed, ΔMS, ICU, post-op), ∴ ✔ amylase/lipase in unexplained shock
- N/V (90%), abd tenderness/guarding, ↓ bowel sounds, jaundice if biliary obstruction
- Ddx: acute cholecystitis, perforated viscus, SBO, mesenteric ischemia, IMI, AAA leak, distal aortic dissection, ruptured ectopic pregnancy
- Early phase (<1 wk): possible SIRS ± organ failure; late (>1 wk): local complications (qv)

Diagnostic studies (*Am J Gastro* 2013;108:1400)

- Dx requires 2 of 3: characteristic abd pain; lipase or amylase >3× ULN; ⊕ imaging
- Laboratory: levels of amylase & lipase do *not* correlate w/ severity of disease
  - ↑ amylase: rises w/in hrs, normalizes w/in 3–5 d (faster than lipase)
    - false ⊖: 20% EtOH pancreatitis; 50% hypertriglyceridemia (assay interference)
    - false ⊕: other abd or salivary gland process, acidemia, ↓ GFR, macroamylasemia

↑ lipase: longer $t_{½}$ than amylase
>3× ULN 99% sensitive, 99% specific for acute pancreatitis
>10k has 80% PPV for biliary dx, 99% NPV for EtOH (*Dig Dis Sci* 2011;56:3376)
false ⊕: renal failure, other abd process, DKA, HIV, macrolipasemia
ALT >3× ULN has 95% PPV for gallstone pancreatitis (*Am J Gastro* 1994;89:1863)

- Imaging studies (*Am J Gastro* 2013;108:1400)
  Abd U/S: typically not useful to visualize pancreas (obscured by bowel gas), but *should be ordered for all Pts to r/o biliary etiology* (ie, gallstones, BD dilatation)
  Abd CT: not rec for initial eval unless dx unclear (local complic. not yet visible & concern for AKI w/ IV contrast). However, if persistent pain and/or clinical deterioration after 48–72 h, CT(I^+) useful to r/o local complications (necrosis, fluid collections).
  MRI/MRCP: Can detect necrosis; also used to assess for stones & ductal disruption
  Endoscopic U/S (EUS): useful for occult biliary disease (microlithiasis)

Severity (*Gut* 2013;62:102)

- Severity defined by presence of organ failure (AKI, resp failure, GIB, shock) & local or systemic complic. (panc necrosis, fluid collections, gastric outlet obstrxn, splenic & PVT).
  Mild: 80% of cases; no organ failure or local/systemic complications; low mortality
  Moderate: transient (<48 h) organ failure ± local/systemic complications, high morbidity
  Severe: persistent (>48 h) organ failure, very high mortality

Prognosis (*NEJM* 2016;375:1972)

- Ranson's, APACHE II: predict severity at 48 h using multiple physiolog. criteria; poor PPV
- BISAP: simple 5-point scoring system (BUN >25, impaired MS, SIRS, age >60 y, pleural effusion) used w/in first 24 h; score ≥3 predicts ↑ risk of organ failure, mortality
- CTSI: CT data at 48–72h (fluid collect., necrosis) to predict mortality; can lag behind clinical

Treatment (*NEJM* 2016;375:1972; *Am J Gastro* 2017;112:797)

- Fluid resuscitation: *aggressive in 1st 24 hrs, even if mild.* 20 ml/kg IVB → 3 ml/kg/hr. Goal to ↓ BUN & Hct over 12–24 h. ✔ UOP. LR may be superior to NS (↓ SIRS; avoid if ↑ Ca).
- Nutrition (*NEJM* 2014;317:1983)
  Early enteral feeding encouraged, though not superior to oral feeding at 72 h
  Mild: Start feeding once without N/V or ileus; may not need to be completely pain free. Low-fat low-residue diet as safe as liquid diet and a/w shorter LOS.
  Severe: early (w/in 48–72 h) enteral nutrition indicated and preferred over TPN b/c ↓ infectious complications, organ failure, surgical interventions, and mortality.
- Analgesia: IV opioids (monitor respiratory status, adjust dosing if ↑ renal impairment)
- Gallstone pancreatitis: urgent (w/in 24 h) ERCP w/ sphincterotomy if cholangitis, sepsis, or Tbili ≥5. If mild, CCY during initial hosp to ↓ risk of recurrence (*Lancet* 2015;386:1261);

defer surgery if necrotizing panc. until improvement in inflam. & fluid collections.
- Hypertriglyceridemia: insulin gtt (activates lipoprotein lipase), fibrates, ± apheresis
- No role for ppx abx in absence of infectious complications (*World J Gastro* 2012;18:279)

Complications
- Systemic: ARDS, abdominal compartment syndrome, AKI, GIB (pseudoaneurysm), DIC
- Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia
- Fluid collections:
  Acute fluid collection: seen early, not encapsulated, most resolve w/in 1–2 wk w/o Rx
  Pseudocyst: ~4 wk after initial attack, encapsulated. No need for Rx if asx (regardless of size/location). If sx → endoscopic (*Gastro* 2013;145:583) vs. perc/surg drainage.
- Pancreatic necrosis: Nonviable pancreatic tissue. CT-guided FNA if infection suspected.
  Sterile necrosis: if asx, can be managed expectantly, no role for ppx abx
  Infected necrosis (5% of all cases, 30% of severe): high mortality. Rx w/ carbapenem or MNZ+FQ. If stable, defer drainage to >4 wk to allow liquefication and WOPN (qv). If sx or unstable, perc drainage & minimally invasive surg debridement or endoscopic necrosectomy superior to open necrosectomy (*NEJM* 2010;362:1491).
  WOPN (walled off panc. nec.): fibrous wall surrounds necrosis over ≥4 wk; endoscopic or perc. drainage (preferred over open necrosectomy) if infected or symptomatic

---

CHRONIC PANCREATITIS

Pathogenesis & etiology (*Gastro* 2013;144:1292; *BMJ* 2018;361:k2126)
- Often recurrent acute attacks → inflam infiltrate → fibrosis → loss of exocrine & endocrine tissue. Pancreatic insufficiency (DM, fat/protein malabsorption) when 90% panc fxn lost.
- TIGAR-O: Toxins (60–80% due to EtOH; smoking), Idiopathic, Genetic (PRSS1, SPINK1, CFTR, CTRC, CASR), Autoimmune, Recurrent panc., Obstruction

Clinical manifestations
- Epigastric pain, N/V; over time can be painless; signs of exocrine insuff (steatorrhea, wt loss) or endocrine insuff (DM: polydipsia, polyuria)

Diagnostic studies (*Pancreas* 2014;43:1143)
- Labs: amylase/lipase ↑ early, may be nl later. ⊕ fecal fat, ↓ stool elastase & A1AT. Mixed TG breath test alternative to stool elastase. ✔ A1c, consider IgG4/ANA & genetic testing if young or ⊕ FHx. If dx w/ CP, measure baseline fat-soluble vitamins (ADEK).
- Imaging: Ca^{2+} on KUB/CT. ERCP/MRCP/EUS: high sens for dx; may show stricture, dilated ducts. IV secretin stim w/ MRI may ↑ dx yield. Panc fxn test not widely available.

Treatment (*Gastro* 2011;141:536; *Lancet* 2016;387:1957)
- Pancreatic enzyme replacement (may ↓ pain by reducing CCK). Rx routine vitamin D & Ca.
- Pain control: smoking & EtOH cessation, analgesics, pregabalin, endoscopy (stone removal or stenting strictures), celiac nerve plexus block, surgery

Complications
- Pseudocysts, pseudoaneurysms, pancreatic ascites or pleural eff., 13× ↑ risk of panc Ca

---

AUTOIMMUNE PANCREATITIS

Pathogenesis (*Am J Gastro* 2018;113:1301)
- Type 1: lymphoplasmacytic sclerosing panc. w/ dense fibrosis; ↑ IgG4; high relapse
- Type 2: idiopathic duct-centric pancreatitis; minimal IgG4; a/w IBD; fewer relapses

Clinical manifestations
- Abdominal pain, can p/w obstructive jaundice and panc mass mimicking panc Ca
- Can be primary, or in a/w IgG4 cholangitis, salivary gland disease (eg, Sjögren's), mediastinal or RP fibrosis, interstitial nephritis, autoimmune thyroiditis, UC/PSC, RA

Diagnosis
- Labs: cholestatic LFTs (↑ Aφ > AST/ALT), ↑ γ-globulins and IgG4, ⊕ ANA, RF
- HISORt criteria: Histology, Imaging ("sausage pancreas", bile duct stricture), Serology, other Organ involvement, Response to therapy

Treatment
- Corticosteroids 1st-line; immunomod. (AZA, MMF, cyclophosphamide, rituximab) if relapse

ABNORMAL LIVER TESTS

Tests of hepatocellular injury or cholestasis (*J Clin Transl Hepatol* 2017;5:394)

- Aminotransferases (AST, ALT): intracellular enzymes released 2° necrosis/inflammation
  ALT more specific for liver than is AST (heart, skeletal muscle, kidney, brain, RBC/WBC)
  ↑ levels seen w/ most types of hepatocellular injury; skeletal musc. injury, MI (AST > ALT)
- Alkaline phosphatase (Aϕ): enzyme bound in hepatic canalicular membrane ↑ levels seen w/ biliary obstrxn or intrahepatic cholestasis also found in bone, intestines, kidney, placenta; confirm from liver w/: ↑ GGT (or ↑ 5′-NT)
- Bilirubin: product of heme metab (unconjugated, "indirect") carried by alb to liver where taken up for conjugation ("direct") to make soluble, then excreted into bile.
  ↑ direct hyperbili seen with cholestasis, enzymatic disorders (eg, Dubin-Johnson, Rotor's)
  ↑ indirect hyperbili seen with hemolysis, enzymatic disorders (eg, Crigler-Najjar, Gilbert's)
  jaundice seen when bili >2.5 mg/dL (esp. in sclera or under tongue); if hyperbili conjugated then ↑ urine bilirubin

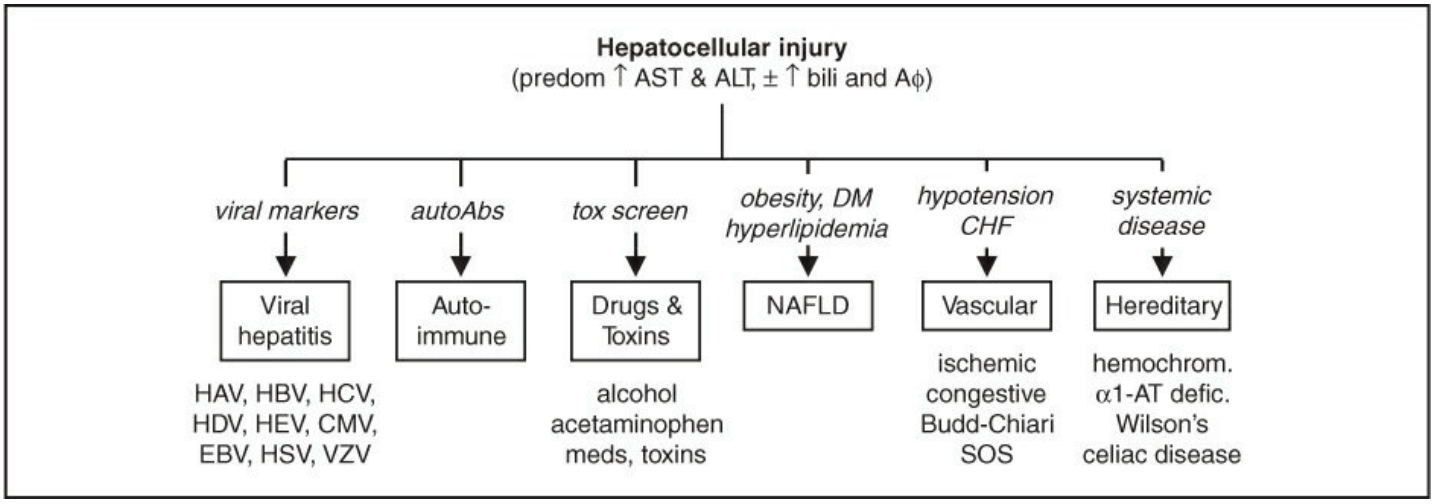
Tests of hepatic function

- Albumin: marker for liver protein synthesis, ↓ slowly in liver failure ($t_{1/2}$ ~15–18 d)
- Prothrombin time (PT): depends on synthesis of coag factors by liver (except FVIII); b/c t½ of some factors (eg, V, VII) is short, ↑ PT can occur w/in hrs of liver dysfxn

Patterns of LFTs				
Pattern	**ALT**	**AST**	**Aϕ**	**Bilirubin**
Hepatocellular	↑↑	↑↑	±↑	±↑ (direct)
Viral hepatitis, NASH	Often ALT > AST		±↑	±↑ (direct)
Alcoholic hepatitis	AST:ALT ≥ 2:1		±↑	±↑ (direct)
Ischemic injury	↑↑↑	↑↑↑	↑↑	↑↑ (direct)
Wilson's disease	↑	↑	Aϕ:Tbili < 4	
Cholestatic	±↑	±↑	↑↑	↑↑ (direct)
Infiltrative	near nl	near nl	↑↑	±↑
Nonhepatic				
Skeletal muscle injury	AST >> ALT (early)		nl	nl
Bone disease	nl	nl	↑ (w/ nl GGT)	nl
Hemolysis	nl	nl	nl	↑ (indirect)

- R-value = ratio of ALT:Aϕ normalized to ULN for each = (ALT/ULN) ÷ (Aϕ/ULN)
  R >5 suggests hepatocellular injury, <2 suggests cholestatic injury, 2–5 suggests mixed

Figure 3-3 Approach to abnormal liver tests with hepatocellular pattern



- Workup for *acute* enzyme elevation (often symptomatic)
  Severe ALT & AST elevation (>1000):
    toxins (usu. acetaminophen) → ✔ tox screen, EtOH, acet. levels. Other toxins: INH, disulfiram, pyrazinamide, OTC/herbal, fenofibrate, niacin, amiodarone, MDMA.
    ischemia (eg, sepsis, hypotension, Budd Chiari) → ✔ liver U/S w/ Doppler. Etiologies usually lead to ↑ LDH, ∴ usually ratio ALT:LDH <1.5 (vs. >1.5 w/ toxins, viruses).
    viruses (Hep A-E; HSV, CMV, VZV) → ✔ viral serologies
    other (AIH, acute Wilson Disease, acute biliary obstrxn) → see ALF & cirrhosis sections
  Acute mild-moderate ALT & AST elevation: as above, think meds/toxins (*see list at end of section*), viruses, ischemia/vascular issues in hospitalized Pts, obstruction (if mixed picture), systemic disease (*see "Workup for chronic enzyme elevation,"* below)
- Workup for *chronic* enzyme elevation (often asymptomatic)
  Screen for common causes: hep serologies, EtOH, liver U/S (? NAFLD, cirrhosis), meds
  If suspect underlying systemic disease: iron studies (HFE); ANA, ASMA, Ig levels (AIH); ceruloplasmin, urinary copper (Wilson); α1-AT (can cause liver dis even w/o lung involvement); celiac screening; thyroid studies; see "Cirrhosis"
  If ⊖ evaluation → lifestyle modification (wt loss, DM control) & repeat testing 3–6 mo
  If evidence of chronic liver disease or persistent lab abnl, consider liver bx

Figure 3-4 Approach to abnormal liver tests with cholestatic pattern

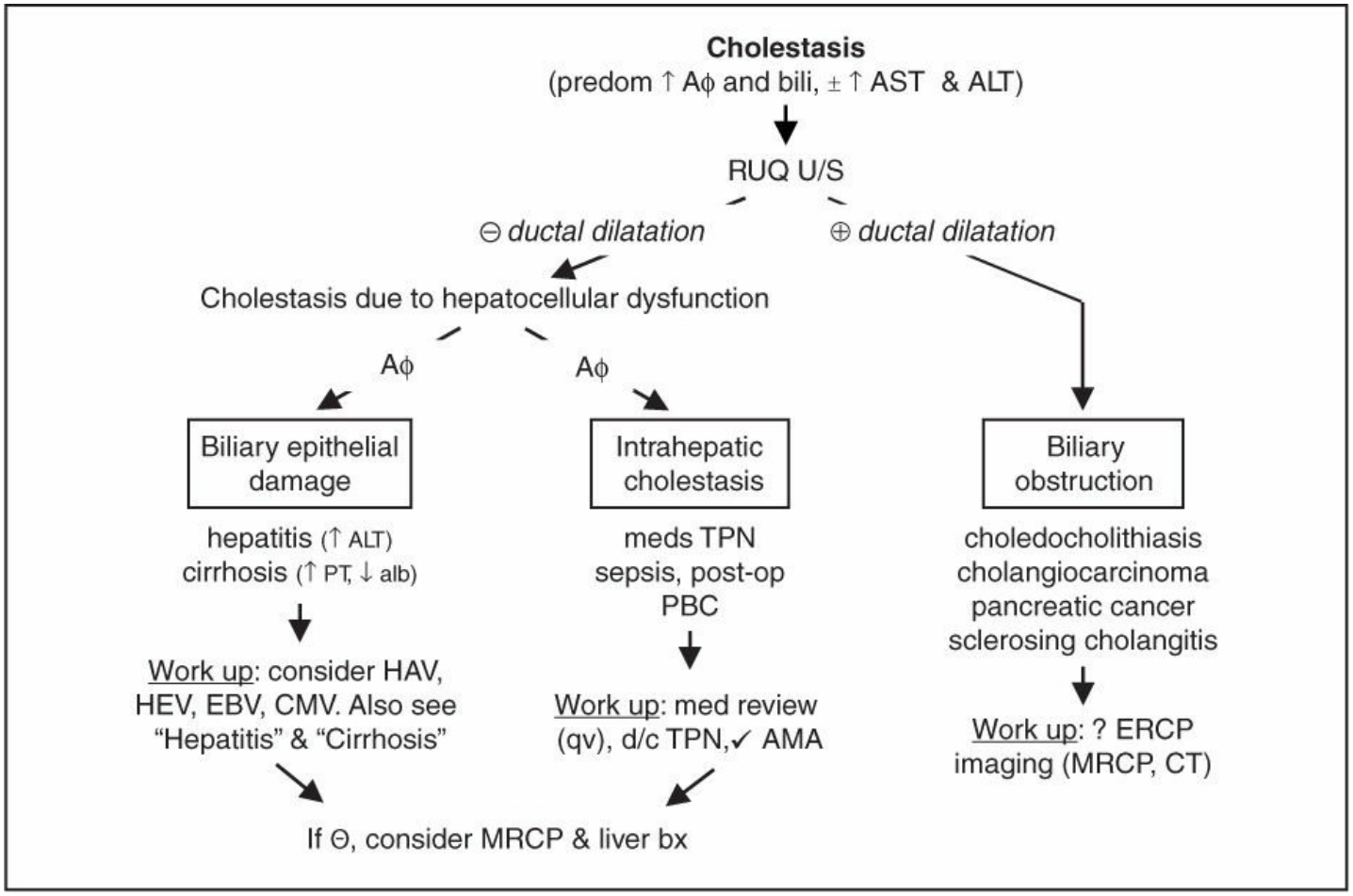
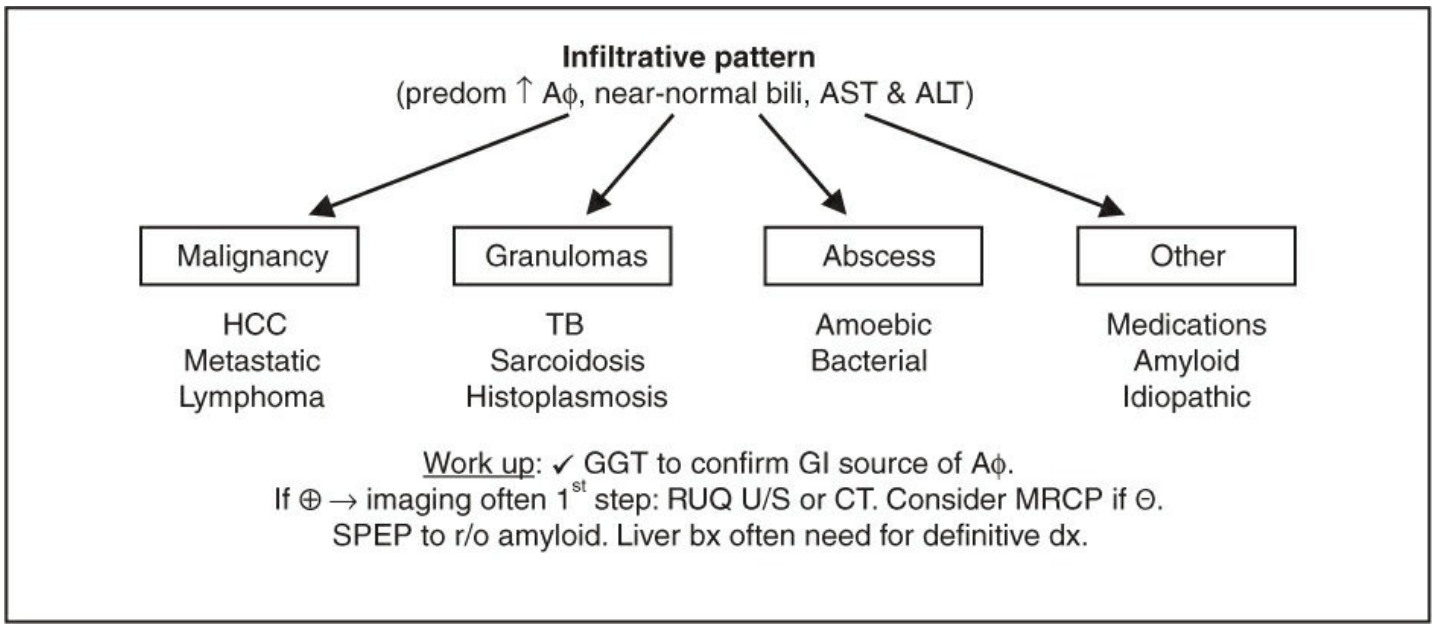


Figure 3-5 Approach to abnormal liver tests with infiltrative pattern



Common medications that cause abnormal liver tests *(http://livertox.nlm.nih.gov)*

Hepatocellular		Cholestatic		Mixed
acarbose acetaminophen allopurinol amiodarone azathioprine clindamycin fibrates hydralazine isoniazid ipilimumab (and other checkpt inhibitors) ketoconazole methotrexate mirtazapine nitrofurantoin (some) NSAIDs phenytoin	prednisone protease inhibitors pyrazinamide risperidone statins sulfonamides tamoxifen tetracyclines TNF-alpha inhibitors trazodone tricyclics valproic acid	ACE inhibitors anabolic steroids azathioprine chlorpromazine estrogens macrolides methimazole	6-MP OCP penicillins protease inhibitors sulfonamides terbinafine tricyclics	amox-clav azathioprine carbamazepine clindamycin mirtazapine nitrofurantoin penicillins phenobarbital phenytoin protease inhibitors sulfonamides trazodone tricyclics valproic acid verapamil

HEPATITIS

VIRAL

Hepatitis A (ssRNA; 30–45% of acute viral hepatitis in U.S.; *MMWR* 2018;67:1208)

- Transmission & RFs: fecal–oral route; contam. food, water, shellfish; daycare ctr; intl travel
- Incubation: 2–6 wk; no chronic carrier state
- Sx: ↓ appetite, malaise, fever, N/V, RUQ pain, jaundice; rarely ALF (↑ w/ chronic HCV)
- Diagnosis: acute hepatitis = ⊕ IgM anti-HAV; past exposure = ⊕ IgG anti-HAV (⊖IgM)
- Rx for acute HAV: supportive care; refer to liver txplnt center if acute liver failure
- Postexposure ppx: age 1–40 y → vaccine; age <1 y or >40 y, immunosupp, liver dis. → Ig

Hepatitis B (dsDNA; ~45% of acute viral hepatitis in U.S.; *JAMA* 2018;319:1802)

- Transmission: blood (IVDU, transfusion), sexual, perinatal
- Incubation: 6 wk–6 mo (mean 12–14 wk)
- Acute infxn: 70% subclinical, 30% jaundice, <1% acute liver failure (up to 60% mortality)
- Chronic infxn: HBsAg ⊕ >6 mo in <5% of adult-acquired (↑ if immunosupp), >90% of perinatal; ~40% chronic HBV → cirrhosis (↑ risk w/ HCV, HDV, or HIV coinfxn, EtOH)
- HCC: ↑ risk if cirrhotic, ⊕ FHx HCC, African >20 y old, Asian ♂ >40 y old or ♀ >50 y old, or >40 y old w/ ↑ ALT ± HBV DNA >2000. Screen w/ AFP & U/S q6mo.
- Extrahepatic syndromes: PAN (<1%), membranous nephropathy, MPGN, arthritis
- Serologic and virologic tests (see *Annals* 2017;167:794 for screening guidelines)
  - HBsAg: appears before sx; used to screen blood donors; persists >6 mo = chronic HBV
  - HBeAg: evidence of viral replication and ↑ infectivity
  - IgM anti-HBc: 1st Ab to appear; indicates acute infection window period = HBsAg becomes ⊖, anti-HBs not yet ⊕, anti-HBc only clue to infxn
  - IgG anti-HBc: indicates previous (HBsAg ⊖) or ongoing (HBsAg ⊕) HBV infection
  - anti-HBe: indicates waning viral replication, ↓ infectivity
  - anti-HBs: indicates resolution of acute disease & immunity (sole marker after vaccination)
  - HBV DNA: presence in serum correlates w/ active viral replication in liver

Diagnosis	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	⊕	⊖	IgM	⊕	⊖	⊕
Window period	⊖	⊖	IgM	±	±	⊕
Recovery	⊖	⊕	IgG	⊖	±	⊖
Immunization	⊖	⊕	⊖	⊖	⊖	⊖
Chronic hepatitis *HBeAg* ⊕	⊕	⊖	IgG	⊕	⊖	⊕
Chronic hepatitis *HBeAg* ⊖	⊕	⊖	IgG	⊖	⊕	±*

*Precore mutant: HBeAg not made, but anti-HBe can develop due to x-reactivity w/ HBcAg; a/w ↑ HBV DNA

- Rx for acute HBV: supportive; hospitalize for Δ MS or ↑ INR (liver transplant center); consider antiviral therapy if severe

Phases of Chronic HBV Infection					
Phase	**ALT (ULN*)**	**HBV DNA (IU/mL)**	**HBeAg**	**Liver Histology (inflam/fibrosis)**	**Rate of cirrhosis**
HBeAg ⊕ HBV infxn (Immune-tolerant)	Nl	≥10^6	⊕	Minimal	<0.5%/y
HBeAg ⊕ hepatitis (Immune-active)	≥2×	≥20k	⊕	Moderate to severe	2–5.5%/y
HBeAg ⊖ HBV infxn (Inactive)	Nl	≤2k	⊖	Min necroinflam.; variable fibrosis	0.05%/y
HBeAg ⊖ hepatitis (Immune reactivation; precore mutant)	≥2×	≥2k	⊖	Moderate to severe	8–10%/y

*ALT ULN <30 U/L for ♂, <19 U/L for ♂. Adapted from *Hepatology* 2016;63:261.

5th phase: chronic HBsAg ⊖ HBV infxn: HBeAg ⊖, anti-HBs ± ALT nl, "occult" HBV

- Rx of chronic HBV: Rx in immune active or immune reactivation phases or cirrhotics w/ elevated HBV DNA or decomp. Consider liver bx if ALT 1–2× ULN or in immune tolerant phase if age >40 y; Rx if mod-to-severe inflammation or fibrosis on bx.
- Entecavir or tenofovir: nucleo(s/t)ide analogs, well tolerated, low resistance; at 5 y, HBeAg seroconversion is 30–40% & loss of HBsAg is 5–10% (*Dig Dis Sci* 2015;60:1457; *Gastro Hep* 2016;1:185). Tenofovir preferred if h/o lamivudine resistance.
- Rx duration: (1) HBeAg ⊕ immune active w/o cirrhosis: if seroconversion (HBeAg ⊖, anti-HBe ⊕), can stop after 1 y if ALT nl & HBV DNA suppressed or until HBsAg clears; (2) HBeAg ⊖ immune reactivation: indefinite; (3) cirrhotic: indefinite
- If undergo liver transplant: HBIG + nucleo(s/t)ide analogue effective in preventing reinfection

- HIV/HBV *coinfection:* Rx w/ 2 drugs active against both HBV & HIV (https://aidsinfo.nih.gov)
- Immunosuppression: prior to initiating chemoRx, anti-TNF, rituximab, steroids (>20 mg/d > 1 mo), screen for HBV; Rx if mod-to-high risk of reactive. (incl HBsAb ⊕ getting rituximab)
- Postexposure (risk infxn ~30%) ppx: HBIG → vaccine (if unvac or known nonresponder)

Hepatitis C (ssRNA; ~10% of acute viral hepatitis in U.S.; *Lancet* 2015;385:1124)

- Transmission: blood (IVDU, transfusion rare cause) > sexual; 20–30% w/o clear precipitant
- Incubation: 1–5 mo; mean 6–7 wk
- Acute infxn: 80% subclinical; 10–20% sx hepatitis w/ jaundice; acute liver failure rare; prob of spont clearance a/w *IL28B* & HLA class II genotypes (*Annals* 2013;158:235)
- Chronic: up to 85% → chronic hepatitis, 20–30% of whom develop cirrhosis (after ~20 y) ↑ risk of cirrhosis in men, EtOH, HIV; HCC in 1–4% of cirrhotics/y
- Extrahepatic syndromes: mixed cryoglobulinemia, porphyria cutanea tarda, lichen planus, leukocytoclastic vasculitis, thyroiditis, MPGN, IPF, NHL and monoclonal gammopathies
- Serologic, virologic, & genetic tests
  - anti-HCV (ELISA): ⊕ in 6 wk, does *not* = recovery or immunity; can be ⊖ after recovery
  - HCV RNA: ⊕ w/in 2 wk, marker of active infection
  - HCV genotype (1–6): guides duration & predicts response to Rx; geno. 3 a/w ↑ risk HCC
- Dx: *acute* hepatitis = ⊕ HCV RNA, ± anti-HCV; *resolved* = ⊖ HCV RNA, ± anti-HCV; *chronic* = ⊕ HCV RNA, ⊕ anti-HCV
- Treatment indications (www.hcvguidelines.org) (*Hep* 2018;68:827; *Lancet* 2019;393:1453)
  - Acute: if no spont. clearance at 12–16 wk, can Rx w/ same regimens for chronic HCV
  - Chronic: ↓ HCC & mortality. Recommended for all except if ↓ life expectancy.

Recommended Oral Direct-Acting Antiviral (DAA) Regimens	
Regimen	Indication
sofosbuvir & ledipasvir	Genotypes 1 and 4
grazoprevir & elbasvir	Genotypes 1 and 4
sofosbuvir & daclatasvir	Alternative for genotypes 1–4
sofosbuvir & velpatasvir	Genotypes 1–6
sofosbuvir, velpatasvir, & voxilaprevir	DAA-experienced genotypes 1–6
glecaprevir & pibrentasvir	Genotypes 1–6, DAA-experienced genotype 1
Individual components: *RNA polymerase inhibitor* ("…buvir"); *NS5a inhibitor* ("…asvir"); *NS3/4A protease inhibitor* ("…previr")	

Based on the American Association for the Study of Liver Diseases/Infectious Diseases Society of America 2018 Guidance. www.hcvguidelines.org. *Clin Infect Dis* 2018;67:1477

- Monitoring on Rx: CBC, INR, LFTs, GFR, HCV VL prior to starting Rx. PIs contraindicated if decomp. liver dx (ascites, encephalopathy) or CTP score ≥7. D/c Rx

if jaundice, N/V, weakness, 10x ↑ in ALT, or significant ↑ in bili, Aϕ, INR after 4 wk.
- Goal is *sustained virologic response* (SVR) = ∅ viremia 12 wk after completion of Rx. Success depends on genotype but SVR rates >90% with current regimens.
- Special populations (HCV/HIV coinfection, decompensated cirrhosis, s/p liver transplant, renal impairment): www.hcvguidelines.com for updated recs on mgmt
- Vaccinate all chronic HCV patients against HBV and HAV if not immune
- Postexposure (needlestick risk ~3%) ppx: none, although sofosbuvir-velpatasivir under investigation in clinical trial; if HCV RNA → ⊕, consider Rx w/in 3 mo

Hepatitis D (RNA)
- Transmission: blood or sexual; endemic in Africa & E. Europe. Generally requires host to already have HBV infxn in order to cause co-infection or superinfection; in rare cases (immunosupp s/p liver txplt) can replicate autonomously.
- Natural hx: acute HBV-HDV coinfection resolves in >80% of cases; however acute HDV superinfection leads to chronic HBV-HDV in most cases (↑ progression to cirrhosis, HCC)

Hepatitis E (ssRNA; *World J Gastro* 2016;22:7030; *Gastro Clin N Am* 2017;46:393)
- Most common cause of acute viral hepatitis in endemic areas
- Transmission: fecal–oral; travelers to central & SE Asia, Africa and Mexico, exp. to swine. ↑ rates of cases in Europe.
- Natural hx: acute hepatitis w/ ↑ mort. (10–20%) if pregnant; rare chronic in transplant Pts
- Dx: IgM anti-HEV (through CDC), HEV RNA
- Extrahepatic sx: arthritis, pancreatitis, anemia, neuro (GBS, meningoencephalitis)

Other viruses (human pegivirus, CMV, EBV, HSV, VZV)

AUTOIMMUNE HEPATITIS (AIH)

Classification (*J Hep* 2015;62:S100, *World J Gastro* 2015;21:60)
- Type 1: anti-smooth muscle Ab (ASMA), ANA; anti-soluble liver antigen (anti-SLA), a/w more severe disease and relapsing disease
- Type 2: anti-liver/kidney microsome 1 (anti-LKM1); anti-liver cytosol type 1 (ALC-1);
- Overlap syndrome: AIH + PBC (suspect if ⊕ antimitochondrial Ab or ⊕ histology → "autoimmune cholangitis") or PSC (suspect if ↑ Aφ, IBD, pruritus, or ⊕ radiology/histology)
- Drug-induced: minocycline, nitrofurantoin, infliximab, hydralazine, α-methyldopa, statins

Diagnosis and treatment (*J Hepatol* 2015;63:1543, *Clin Liver Dis* 2015;19:57)
- 70% female; 40% present w/ severe AIH (3% ALF) w/ ALT >10 × ULN; 34–45% asx
- Extrahepatic syndromes: thyroiditis, arthritis, UC, Sjögren's, Coombs' ⊕ hemolytic anemia
- Dx: scoring system combining serologies, ↑ IgG, ∅ viral hepatitis, & liver bx (interface hepatitis & lymphoplasmacytic infiltrate) has high Sp & mod Se (*Dig Dis* 2015;33[S2]:53)
- Rx: (1) ALT 10× ULN; (2) ALT 5× ULN & IgG 2× ULN; or (3) bridging/multiacinar necrosis
- Induction Rx: (1) prednisone monoRx; (2) prednisone + AZA, or (3) budesonide (if non-

cirrhotic) + AZA → 65–80% remission (asx, nl LFTs, bili, & IgG, none-to-minimal interface hepatitis); taper steroids as able; relapse rate of 50–80% (*J Hep* 2015;62:S100)
- Nonresponders or AZA intolerant: cyclosporine, tacrolimus, MMF, rituximab, infliximab
- HCC screening and liver transplant referral for ESLD

OTHER CAUSES OF HEPATITIS OR HEPATOTOXICITY

Alcoholic hepatitis (*J Hepatol* 2016;69:154; *Am J Gastro* 2018;113:175)

- Sx: progressive jaundice, tender hepatomegaly, fever, ascites, GIB, encephalopathy
- Labs: ALT usually <300–500 w/ AST:ALT > 2:1, ↓ plt, ↑ Tbili & INR indicate severe hepatitis
- Prognosis: scoring systems include Maddrey's discriminant fxn (MDF), Lille model, MELD
  - MDF (4.6 × [PT – control] + Tb) ≥32 w/ 30–50% 1-mo mortality if unRx'd (*Gastro* 1996;110:1847)
  - Lille model: predicts nonresponse to steroids after 1st week of Rx; score >0.45 predicts poor response to further steroid Rx and a/w ↓ in 6-mo survival (*Hep* 2007;45:1348)
  - Combination of Lille + MELD scores best predictor of mortality (*Gastro* 2015;149:398)
- Rx: consider if MDF ≥32, MELD >18, or presence of encephalopathy
  - Steroids (eg, methylprednisolone 32 mg/d or prednisolone 40 mg/d × 4 wk → 4–6 wk taper) may ↓ 1-mo but not 6-mo mortality, a/w ↑ infection (*NEJM* 2015;372:1619, CD001511)
  - Contraindic.: active GIB, pancreatitis, untreated HBV, uncontrolled bact/fungal/TB infxn
  - Addition of NAC to steroids ↓ 1-mo but not 6-mo mortality (*NEJM* 2011;365:1781)
- Consider early transplantation in carefully selected Pts (*Gastro* 2018;155:422)

Acetaminophen hepatotoxicity (*Clin J Transl Hepatol* 2016;4:131; *BMJ* 2016;353:i2579)

- Pathophysiology: >90% of acetaminophen (N-acetyl-p-aminophenol, APAP) metab into nontoxic metab, but ~5% metab by CYP2E1 into NAPQI, a hepatotoxic metab detoxified by glutathione conjugation; APAP overdose (>10 g) depletes glutathione stores → injury
- CYP2E1 *induced* by fasting, alcohol, and certain anticonvulsants and anti-TB drugs, resulting in a "therapeutic misadventure" with even low doses (2–6 g) of acetaminophen
- Liver dysfunction may not be apparent for 2–6 d
- Rx: NG lavage, activated charcoal if w/in 4 h. Consider early transfer to transplant ctr
  - *N*-acetylcysteine: administer up to 72 h after ingestion, if time of ingestion unknown or chronic ingestion >4g/d; low threshold to start NAC w/ low or undetectable APAP levels
  - PO NAC (preferred): 140 mg/kg loading dose → 70 mg/kg q4h × 17 additional doses
  - IV NAC: 150 mg/kg × 1 h → 50 mg/kg × 4 h → 100 mg/kg × 16 h; risk of anaphylaxis (↓ w/ 12-h regimen; *Lancet* 2014;383:697); use if unable to tolerate POs, GIB, pregnancy, ALF

Ischemic hepatitis

- "Shock liver" w/ AST & ALT >1000 + ↑↑ LDH (ALT:LDH ratio often <1.5); delayed ↑↑ Tbili
- Seen in HoTN & CHF; often requires ↑ venous + ↓ portal/arterial pressure + hypoxia

Nonalcoholic fatty liver disease (NAFLD) (*NEJM* 2017;377:2063)

- Definition: fatty infiltration of liver *and* absence of EtOH or other cause of steatosis
  NAFL = steatosis, ∅ inflam; NASH = steatosis + inflam ± fibrosis on bx
- NAFLD: 10–30% of U.S. pop. & over 60% in T2DM & obesity
- NASH: 2–5% of NAFLD & risk of cirrhosis in NASH w/ fibrosis on bx is 30% at 10 y
- Clinical: 80% asx, ↑ ALT > AST, but nl ALT/AST does not exclude poss. of NASH on bx
- Dx: liver bx remains gold standard. VCT elastography emerging modality (*J Hepatol* 2017;66:1022). NAFLD fibrosis score predicts NASH w/ advanced fibrosis with PPV >80%
- Rx: wt loss (ideally ≥10% to reverse fibrosis, *Gastro* 2015;149:367), exercise, DM control, liraglutide (*Lancet* 2016;387:679) or pioglitazone (even w/o DM), statins (*Metabolism* 2017;71:17); vit E ↓ steatosis but not fibrosis in Pts w/o DM (*Hepatol* 2018;67:328)
- HCC a complication of NAFLD, usually but not always in setting of NASH cirrhosis

ACUTE LIVER FAILURE (ALF)

Definition

- Acute insult to liver + coagulopathy + encephalopathy; most w/o known preexisting liver dis.
- *Hyperacute* if encephalopathy <7 d from jaundice onset; *acute* if 7–21 d, *subacute* if >21 d
- Acute on chronic liver failure: acute insult to liver in Pt w/ underlying chronic liver disease

Etiology (*J Hepatol* 2015;62:S112)

- Drugs/toxins (nearly 80% of cases in U.S.; *Gastro* 2015;148:1353, *Clin Liver Dis* 2017;21:151)
  - Drugs: acetaminophen (most common cause; >40% of all cases in U.S., typically unintentional overdose); anti-TB drugs (INH, rifampin, pyrazinamide); AEDs (phenytoin, valproate, carbamazepine); NSAIDs (idiosyncratic, not dose related); abx (eg, fluoroquinolones, macrolides); MDMA (ecstasy)
  - Toxins: *Amanita phalloides* (mushroom sp. in West Coast), certain herbal preparations
- Viral (12% of cases in the U.S.): HAV, HBV, HCV (rare), HDV + HBV, HEV (esp. if pregnant). In immunosupp: HSV (50% have skin lesions), EBV, VZV, CMV, HHV6
- Vascular: Budd-Chiari, ischemic hepatitis, hepatic sinusoidal obstructive syndrome
- Other: Wilson disease, pregnancy-related ALF (acute fatty liver, preeclampsia, HELLP), initial presentation of autoimmune hepatitis; idiopathic

Clinical manifestations

- Initial presentation usually nonspecific: n/v, malaise; then jaundice & multiorgan failure
- Neurologic: encephalopathy: grade 1 = attn deficit, tremor; grade 2 = *asterixis*, lethargy, confusion, ataxia; grade 3 = somnolence, rigidity, clonus, hyporeflexia; grade 4 = coma
  cerebral edema: astrocyte swelling likely related to ↑ ammonia levels
- Cardiovascular: hypotension with low SVR, shock
- Pulmonary: respiratory alkalosis, impaired peripheral O_2 uptake, pulm edema, ARDS
- GI: bleeding (due to bleeding diathesis), pancreatitis (? due to ischemia, drugs, infxn)
- Renal: ATN, hepatorenal syndrome, hyponatremia, hypokalemia, hypophosphatemia
- Hematology: thrombocytopenia, ↑ PT/PTT, ↓ fibrinogen, bleeding diathesis (↓ synthesis of coag factors balanced by ↓ protein C/S; bleeding mostly due to low platelet count), DIC
- Infection (~90% of Pts): espec. with *Staph*, *Strep*, GNRs and fungi (↓ immune fxn, invasive procedures); SBP in 32% of Pts; *fever and ↑ WBC may be absent*
- Endocrine: hypoglycemia (↓ glc synthesis), metabolic acidosis (↑ lactate), adrenal insuf.

Workup (*Clin Liver Dis* 2017;21:769)

- CBC, PT/PTT, LFTs, lytes, BUN/Cr, NH_3, pH, *arterial* lactate, acetaminophen level, HIV,

amylase/lipase, viral serologies (qv) in all Pts, with additional labs as below if suspected
- Autoimmune hep serologies & IgG levels, ceruloplasmin & serum/urine copper, preg test
- Imaging studies (RUQ U/S or abd CT, Doppler studies of portal and hepatic veins)
- Liver biopsy if underlying etiology remains elusive after initial testing

Management (*J Clin Exp Hepatol* 2015;5:S104)
- ICU care at liver transplant center for hemodynamic & ventilatory support; CVVH for AKI
- Early listing for liver transplantation in selected Pts (see below)
- Cerebral edema: consider ICP monitoring if grade 3/4 enceph; if ↑ ICP → mannitol 0.5–1.0 mg/kg; if arterial NH_3 >150, grade 3/4 enceph, AKI or on vasopressors → prophylactic 3% saline for goal Na 145–155 mEq/L; barbiturates & hypothermia if refractory ↑ ICP
- Encephalopathy: intubate for grade 3 or 4; lactulose is of little benefit & may be detrimental
- Coagulopathy: vit K, FFP/plts/cryo if active bleeding or before invasive procedure; PPI ppx
- Infection: low threshold for abx (broad spectrum, eg, vancomycin & 3rd-gen ceph.) if suspect infection; anti-fungal coverage in high-risk Pts
- Rx of specific causes: NAC if acetaminophen; antiviral for HBV; plasma exchange can be temporizing measure for Wilson disease; IV acyclovir for HSV; PCN-G for *A. phalloides;* delivery of child for pregnancy-related; TIPS, anticoag for Budd-Chiari. Lack of data for use of steroids in autoimmune, but often given (*Hepatology* 2014;59:612).
- NAC may benefit pts w/ non-APAP ALF but data inconclusive (*Clin Drug Investig* 2017;37:473)
- Liver Tx if poor prog. but could survive surg. Extracorp liver support (molec. adsorbent recirc. system, MARS) & high-volume plasma exchange being studied (*J Hepatol* 2016;64:69).

Prognosis (*Ann Intern Med* 2016;164:724; *World J Gastro* 2016;22:1523)
- Non-acetaminophen ALF mortality ~70%, acetaminophen-induced ALF mortality ~25–30%
- Predictors of poor outcome (King's College Hospital, UK):
  Acetaminophen-induced: pH <7.25, INR >6.5 or PT>100, Cr >3.4, or grade 3/4 enceph.
  Non-acetamin.-induced: INR >6.5 or PT>100; *or* ≥3 of the following: unfavorable etiology (seronegative hepatitis or drug reaction); age <10 or >40 y; INR >3.5 or PT >50; Tbili >17.5; duration of jaundice >7 d prior to onset of encephalopathy
- ~20–25% of Pts undergo liver transplantation w/ 5-y survival rate of 75%
- BMI >30, Cr >2, age >50 y, pressors/vent support a/w poorer acute transplant outcome

CIRRHOSIS

Definition (*Dig Dis* 2016;34:374; *NEJM* 2016;375:767; *J Hep* 2016;64:717)

- Definition: fibrosis and regenerative nodules resulting from hepatocellular injury
- Decompensated = jaundice, variceal bleed, encephalopathy, ascites; worse prognosis

Etiologies

- Alcohol (~60–70%) and other toxins (eg, arsenic)
- Viral hepatitis (~10%): chronic HBV, HCV, HDV infection
- Autoimmune hepatitis: ♀, ↑ IgG, ⊕ ANA, antismooth muscle Ab, anti-LKM-1, anti-LC1
- Metabolic diseases (~5%): hemochromatosis, Wilson disease, α_1-AT deficiency
- Biliary tract diseases (~5%): primary biliary cholangitis, secondary biliary cirrhosis (calculus, neoplasm, stricture, biliary atresia), primary sclerosing cholangitis
- Vascular diseases: Budd-Chiari syndrome, R-sided CHF, constrictive pericarditis, SOS
- Nonalcoholic fatty liver dis. (NAFLD, 10–15%) cause of most "cryptogenic cirrhosis"
- Medications: amiodarone, methotrexate, vitamin A, valproate acid, isoniazid

Clinical manifestations

- Nonspecific sx (anorexia, fatigue) or jaundice, encephalopathy, ascites, variceal bleeding

Physical exam

- Liver: *initially* enlarged, palpable (L lobe predom), firm; *eventually* shrunken, nodular
- Signs of liver failure: jaundice (bili >2.5), spider angiomata & palmar erythema (↑ estradiol), Dupuytren's contractures, white nail lines (Muehrcke's lines) & proximal nail beds (Terry's nails), ↑ parotid & lacrimal glands, gynecomastia, testicular atrophy, asterixis, encephalopathy, fetor hepaticus, clubbing, hypertrophic osteoarthropathy
- Signs of portal hypertension: splenomegaly, ascites, dilated superficial abdominal veins (caput medusae), epigastric Cruveilhier-Baumgarten venous hum

Laboratory studies

- LFTs: ↑ bili, ↑ PT/INR (poor correlation w/ bleeding; factor VIII nl b/c not synthesized by liver), ↓ alb, ± ↑ aminotransferases (AST > ALT if late) and ↑ Aϕ (variable)
- Hematologic tests: anemia (marrow suppress., hypersplenism, Fe ± folate defic.), neutropenia (hypersplenism), thrombocytopenia (hypersplenism, ↓ Tpo production, EtOH tox)
- Chem: ↓ Na (↑ ADH due to ↓ EAV); ↑ Fe/TIBC, ↑ ferritin (released from hepatocytes)
- Lab indices predictive of cirrhosis: AST/plt >2; Lok index; Bonacini score (*JAMA* 2012;307:832)
- Indirect markers of fibrosis: FibroTest/FibroSURE (HBV/HCV), FIB-4 index (NAFLD, HCV), NAFLD fibrosis score

Workup (*Lancet* 2014;383:1749; *Am J Gastro* 2017;112:18)

- Abd U/S w/ Doppler: liver size & echotexture, r/o HCC, ascites, ✔ patency of

vasculature

- Determine etiology: hepatitis serologies (HBsAg, anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, anti–smooth muscle Ab), Fe and Cu studies, α_1-AT, AMA
- Assess fibrosis: biomarkers (FibroSURE = panel of 5 markers validated in HCV, ↑ score predictive of fibrosis); elastography (U/S or MR-based; measurement of liver stiffness)
- Liver bx (gold standard): percutaneous or transjugular (consider if ascites or coagulopathy), used to confirm presence of cirrhosis and dx etiology

Prognosis (www.mdcalc.com/child-pugh-score-cirrhosis-mortality)

- Modified Child-Turcotte-Pugh (CPS) score based on ascites, enceph., & labs (bili, alb & INR; see Appendix). CPS A (5-6 pts): 1-y survival 100%, B (7–9): 80%; C (10–15): 45%.
- MELD-Na (Model for End-Stage Liver Disease; *Gastro* 2011;14:1952): used to stratify liver Tx list & predict 3-mo survival in cirrhosis and some acute forms of liver dis. Based on Cr, INR, total bili, Na. Calculator: https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/.
  If MELD <21, additional predictors of mortality include refractory ascites, ↑ HVPG & ↓ QoL.
  MELD-Plus includes alb, chol, LOS, age, WBC (*PLOS One* 2017;12:e0186301).

Ascites (see "Ascites" for diagnostic eval; *Liver Int* 2016;36:S1:109; *Dig Dis* 2017;35:402)

- Due to portal HTN (defined as hepatic venous pressure gradient [HVPG] >5 mmHg)
- Develops in 60% w/in 10 y; ~50% mortality at 5 y
- Treatment: ↓ Na intake (1–2 g/d); restrict intake of free water if Na <125
  Diuretics: goal diurese ~1 L/d. Use spironolactone ± furosemide in 5:2 ratio (eg, 100 & 40 mg daily); urine Na/K >1 implies effective natriuresis if Pt compliant w/ low-Na diet
  Avoid NSAIDs in cirrhosis because interfere w/ diuretic action and are nephrotoxic
  Albumin (40 g 2×/wk × 2 wk, then weekly × 16 wk) ↓ mortality 38% (*Lancet* 2018;391:2417)
- Refractory ascites: seen in 5–10% of Pts; 2-y survival 25%
  Diuretic-resistant on 2-g Na diet, minimal weight loss on maximal diuretic doses, or diuretic-induced complications (AKI, Na <125, ↑ K, encephalopathy)
  Conflicting evid. for d/c'ing βB (*Hep* 2016;63:1968; *J Hepatol* 2016;64:574). Especially consider if SBP <90 or MAP ≤82 mmHg, serum Na <120 mEq/L, AKI, HRS, SBP, sepsis, severe alcoholic hepatitis, poor follow-up. If limited by HoTN, can add midodrine.
  Large-volume paracenteses (LVP; >5 L fluid removal): give 6–8 g albumin per L fluid removed (above 5 L) as colloid replacement a/w ↓ risk of post-para circulatory dysfxn & possibly ↓ mortality (*Hep* 2012;55:1172). Avoid LVP if SBP present because ↑ risk of AKI.
  Transjugular intrahepatic portosystemic shunt (TIPS) (*Gastro* 2017;152:157)
    ↓ ascites in 75%; ↑ CrCl, ↑ enceph, survival benefit over LVP remains controversial
    Contraindic: grade II enceph, CHF or pulm HTN, active infxn or biliary obstruction
    Complications: bleeding, fistula; stent thrombosis (1-y patency w/ coated stents ~80%); infxn ("endotipsitis"); new or ↑ enceph in 20–30% (*Am J Gastro* 2016;111:523),

hemolysis
Consider for liver transplant if above fail

- Hepatic hydrothorax: 2° diaphragmatic defect; often unilateral, R > L, ± ascites
  Treatment: avoid chest tube (↑ complications); Rx same as ascites (TIPS if refractory). Indwelling pleural catheter potential option if refractory (*Chest* 2019;155:307)
  Spontaneous *empyema* can occur (even w/o SBP) → dx thoracentesis; Rx abx

Spontaneous bacterial peritonitis (SBP; see "Ascites"; *Eur J Gastro Hep* 2016;28:e10)

- Develops in ~20%; 20% mortality; risk factors: ascitic TP <1 g/dL, hx of SBP, current GIB
- Can p/w encephalopathy, abd pain, fever, *but often* (*25%*) *asx;* perform paracentesis in all hospitalized cirrhotics w/ ascites
- Micro: GNRs (*E. coli, Klebs*) > GPCs (*S. pneumo, enterococcus*) (see "Ascites")
- Rx: 3rd-gen. ceph *or* amox/clav × 5 d. If uncomplicated (no enceph. or AKI) can use FQ but avoid in ↑ FQ resist. area. ↑ rate MDR organisms, incl. ESBL & carbapenemase. IV albumin 1.5 g/kg at time of dx & 1 g/kg on day 3 → ↑ survival (*NEJM* 1999;341:403); consider using only if Cr >1 mg/dL, BUN >30 mg/dL or Tbili >4 mg/dL (*Gut* 2007 56:597). If not improving, repeat paracentesis at 48 h: expect 25% ↓ in PMNs if Rx working.
- Indefinite Ppx if (1) h/o SBP or (2) ascitic TP <1.5 plus: Na ≤130 or Cr ≥1.2 or BUN ≥25 or [CPS ≥9 + Tbili ≥3] (*Am J Gastro* 2009;4:993) → cipro 500 mg qd or Bactrim DS qd. Short-term Ppx: CTX 1 g IV × 7d if GIB (Δ to cipro 500 bid/Bactrim DS bid when eating).

Gastroesophageal varices ± UGIB (see also "GIB"; *Hepatology* 2017;65:310)

- Presence of varices correlates w/ severity of liver dis (40% of Child A Pts → 85% Child C)
- ↑ varix size, Child B/C, & red wale marks assoc w/ ↑ risk of bleeding
- UGIB 1° prevention: screen at time of dx w/ EGD; data best for Pts w/ med-large varices
  nonselective **β**-blockers: ~50% ↓ risk of bleeding & ↓ mortality if med-large varices. Nadolol, propranolol, or carvedilol; latter ↓ MAP & HVPG more than propranolol; delays progression of varices (*Gut* 2017;66:1838); may use in Pts w/ HTN. Titrate to max tolerated dose; EGD not req. to document improvement. Hold for criteria listed above.
  endoscopic variceal ligation (EVL): superior to βB in ↓ risk of 1st bleed but no diff in mortality (*Ann Hep* 2012;11:369); risk of serious complications (esoph perf, ulcers). Repeat q1–2wk until varices gone, w/ f/u EGD at 3 mo then q6–12mo.
  βB vs. EVL: choice based on Pt/physician preference, βB often 1st (*Hepatology* 2017;65:310); using both βB and EVL for primary ppx currently not recommended
- 2° prevention: for all Pts after 1st bleed, given ~50% risk of rebleed & ~30% mortality βB + EVL > either alone; TIPS if refractory, or consider in Child B/C w/in 72 h of admission for EV bleed (↓ rebleeding, ↑ enceph., ∅ Δ mort.) (*Hepatology* 2016;63:581)

Hepatic encephalopathy (HE) (*NEJM* 2016;375:1660)

- Pathogenesis: failure of liver to detoxify NH_3 + other substances (eg, ADMA; *J Hepatol* 2013;58:38) that cause cerebral edema, ↓ O_2 consumption, ↑ ROS → brain dysfxn

- Precipitants: bleeding, infxn, med nonadherence, ↓ K, ↓ Na, dehydration, hypoxia, portosystemic shunt (eg, TIPS), meds (eg, sedatives), acute insult to liver (eg, PVT)
- Stages: see section in "Acute Liver Failure"
- Dx: NH_3 levels have poor Se for dx & monitoring Rx; remains a *clinical dx*
- Rx*:* identify/correct precipitants; lactulose (acidification of colon: $NH_3 \rightarrow NH_4^+$) w/ goal 2–4 stools/d (PEG may be more effective; *JAMA IM* 2014;174:1727); alternatively, rifaximin 550 mg bid (↓ gut bacteria → ↓ NH_3 prod; ? benefit to adding rifaximin to lactulose; *Am J Gastro* 2013;108:1458); adding albumin may speed resolution & ↓ mort. (*J Gastro Hep* 2017;32:1234)
- 2° prevention: lactulose or rifaximin 550 mg bid (*Aliment Pharmacol Ther* 2015;41:39)

Hepatorenal syndrome (HRS) (*Am J Kidney Dis* 2016;67:318; *Gastro* 2016;150:1525)

- Pathophys: splanchnic vasodilation and renal vasoconstriction w/ ↓ renal blood flow
- Criteria: (1) cirrhosis w/ ascites; (2) acute kidney injury (serum Cr ↑ ≥0.3 mg/dL w/in 48 h or ≥50% ↑ in serum Cr from baseline; *Gut* 2015;64:531); (3) ∅ improvement in Cr after d/c diuretic & volume expansion (1 g/kg/d of albumin × 2 d); (4) ∅ shock (prerenal azotemia/ATN); (5) ∅ nephrotoxic meds; (6) ∅ intrinsic kidney disease
  AKI-HRS: development in <2 wk; usually occurs in severe liver failure, often following precipitating event (see later); median survival 2 wk
  CKD-HRS: more indolent, median survival 6 mo; liver failure present < than in AKI-HRS
- Precipitants: GIB, overdiuresis, infection, serial LVP, drugs (aminoglycosides, NSAIDs)
- Rx: *if critically ill* → vasopressor (eg, norepinephrine or vasopressin) + albumin (1 g/kg, max 100 g, bolus daily) to ↑ MAP 10 mmHg. *If not critically ill* → octreotide (100–200 mcg SC tid) + midodrine (max 15 mg PO tid) + 1 g/kg (max 100 g) albumin on day of presentation followed by 20–60 g albumin qd to ↑ MAP. Serelaxin under study (*PLoS Med* 2017;14:e1002248). May need dialysis or TIPS as bridge to liver transplant.

Hepatocellular carcinoma (HCC; qv in Heme-Onc) (*Gastro* 2016;149:1226 & 150:835)

- ↑'d risk w/ cirrhosis of any type but esp. w/ viral (risk of HCC ~3–8%/y), HFE, PBC, ?α1-AT. ↑'d by concomitant EtOH (*J Hepatol* 2016;65:543).
- Clinical: asx vs. hepatic decompensation (eg, ascites, HE), PVT w/ tumor thrombus
- Dx: screen cirrhotics q6mo w/ U/S ± AFP, though many ctrs choose dual-phase CT/MRI
- Rx: see "HCC" in Heme-Onc

Other complications

- Hepatopulmonary syndrome (HPS) (*Dig Dis Sci* 2015;60:1914)
  Abnl gas exchange (A-a gradient ≥15 or P_aO_2 <80) caused by intrapulmonary vascular dilatations leading to intrapulmonary shunting
  S/S: platypnea-orthodeoxia, clubbing, cyanosis
  Dx w/ contrast echo showing "late" A-V shunting (contrast in LA 3–6 cycles after RA)
  Rx: O_2; potential embolization if large vessel on CT, ? TIPS, liver tx only definitive Rx
- Portopulmonary hypertension (POPH) (*Expert Rev Gastro Hepatol* 2015;9:983)
  Pulm HTN in Pt w/ portal HTN w/o other cause. ESLD→ ↑ endothelin→ pulm

vasoconst.
Rx w/ same therapies as for idiopathic PAH, incl prostacyclin analogs, endothelin receptor antagonists, sildenafil; liver transplant is often curative

- Cirrhotic cardiomyopathy: ↓ inotropic & chronotropic response, ↓ systolic & diastolic fxn, ↑ QT, hyperkinetic circulation; ↑ troponin, BNP (*World J Gastro* 2017;21:11503)
- Infxns: unless already immune, vaccinate for HAV, HBV, PCV13 & PPSV23; flu yearly. Cellulitis in ~20% of Pts hospitalized w/ cirrhosis, often in abd wall or LE a/w skin edema.
- Endocrine: diabetes (15–30%), ↑ frequency of adrenal insuffic. (*Dig Dis Sci* 2017;62:1067)
- Coagulopathy: balanced defects w/ ↓ synth of coag factors, hyperfibrinolysis, ↓ plt balanced by ↓ synthesis anticoag factors (protein C/S), defic. of profibrinolytic factors, ↑ levels of vWF. No support for routine administration of FFP, plt, cryo unless in DIC.
- Nutrition: monitor and supplement fat-soluble vitamins, zinc
- Meds: acetaminophen can be used up to 2 g/d; avoid ASA/NSAIDs; aminoglycosides contraindicated; oral hypoglycemics if compensated but insulin if decompensated

Liver transplantation

- Undertake evaluation when MELD ≥15. Exception points added if HCC as above, HPS
- Indic: recurrent/severe enceph, refractory ascites, recurrent variceal bleeding, HRS, HPS, PPH, HCC (if no single lesion is >5 cm *or* ≤3 lesions with largest ≤3 cm), ALF
- Contraindic: inadequate social support, active substance abuse (EtOH w/in 6 mo), sepsis, advanced cardiopulm dis., extrahepatic Ca, cholangio Ca, hemangiosarcoma, persistent noncompliance, AIDS, ALF w/ sustained ICP >50 mmHg or CPP <40 mmHg
- Survival: 1-y up to 90%, 5-y up to 80%, though lower with HCV; autoimmune liver disease, such as AIH/PBC/PSC may recur in 10–30% (or more) of allografts

OTHER ETIOLOGIES OF CIRRHOSIS

Hemochromatosis & iron overload syndromes (*Lancet* 2016;388:706)

- Recessive disorder of iron sensing or transport leading to tissue iron deposition
- HFE mutations (85% of cases): typically C282Y homozyg. (~0.5% of N. Europeans), rarely C282Y/H63D compound heterozyg. C282Y homozygotes: 28% of ♂ & 1% of ♀ develop sx (delayed since menses ↓ Fe load). C282Y/H63D: only 1.5% manifest dis.
- Non-HFE mutations: hemojuvelin, hepcidin, transferrin receptor 2, & ferroportin
- 2° causes of iron overload: iron-loading anemias (eg, thalassemia major, sideroblastic anemia, aplastic anemia), parenteral iron-overload (RBC transfusions, long-term HD), chronic liver disease (due to ETOH, HBV, HCV, NASH, etc.), dietary iron overload
- Sx: fatigue & arthralgias, loss of libido in ♂. In *advanced disease* (rare): bronze skin (melanin + iron), hypogonadism (esp. in juvenile onset), DM, arthropathy (MCP), CHF, infxns (↑ risk *Vibrio*, *Listeria*, *Yersinia*), cirrhosis (↑ risk if EtOH/fatty liver disease; 15% risk of HCC). Disease also a/w ALS (H63D homozygotes) & porphyria.
- Dx: iron sat >45% (iron/TIBC × 100%); ↑ ferritin (acute phase reactant, so poor Sp; often nl in young Pts). If ↑ iron sat. → ✔ HFE to confirm dx, imaging by MRI (black liver). If HFE ⊕ & ferritin >1000 ng/mL or ↑ LFTs → liver bx for quant Fe index & to stage

fibrosis
- Treatment: phlebotomy (250 mL = 1 unit, ~250 mg of Fe) qwk until Fe sat <50% & ferritin 50–100 µg/L, then q3–4mo; PPI ↓ intestinal Fe absorption & may ↓ need for phlebotomy; avoid vit C & uncooked seafood; deferoxamine if phleb. contraindic.; genetic counseling

Wilson disease (*World J Hepatol* 2015;7:2859)
- Recessive disorder of copper transport (mutation in *ATP7B*) → copper overload; primarily affects liver, but also other tissues (brain, eye)
- Epidemiology: 1 in ~30,000, but true allele frequency may be higher due to underdiagnosis; age of presentation generally ranges from 3 to 55 y
- Extrahepatic s/s: neuro ψ disease, parkinsonism & movement disorder (hepatolenticular disease), Kayser-Fleischer rings (⊕ in 99% w/ neuro ψ but in <50% w/ hepatic disease), Coombs ⊖ hemolytic anemia, renal disease
- Dx: ↑ 24-h urine Cu, ↓ serum ceruloplasmin (Se 90%), rarely penicillamine challenge w/ ↑ urine Cu excretion, liver bx w/ hepatic Cu content. In *acute liver failure*, Aϕ/bili <4 + AST/ALT >2.2 better Se & Sp than urine Cu or ceruloplasmin (*Hepatology* 2008;4:1167).
- Treatment: chelation w/ D-penicillamine (supplement B6 as D-pen inactivates); alternative is trientine (↓ toxicity w/ ≈ efficacy, but $$). Zinc: ↓ intestinal Cu transport & can help delay disease; best used in conjunction w/ chelation (must give 4–5 h apart from chelators). Elim. Cu-rich foods. Transplant for ALF or for chronic dis. unresponsive to Rx.

α_1-antitrypsin deficiency (α_1-AT) (*J Hepatol* 2016;65:413)
- Abnl α_1-AT → polymerization in liver (cirrhosis) & uninhibited protease activity in lung (emphysema). Affects 1/3000 of European ancestry. Varied presentations: neonatal hepatitis; cholestatic jaundice in children; ↑ AST/ALT or cirrhosis in children/adults.
- Extrahepatic disease includes: emphysema, necrotizing panniculitis, ANCA vasculitis
- Dx: serum α_1-AT level (acute phase reactant), level <50% of nl typically diagnostic;
  gold standard = phenotyping of protease inhibitor (Pi). Alleles most a/w hepatic dis.: Z (63% of ZZ adults have chronic liver dis. and liver fibrosis may be present in 35% of ZZ individuals w/o overt liver disease) & M (malton) (*J Hepatol* 2018;69(6):1357). Liver bx shows characteristic PAS ⊕ cytoplasmic inclusion bodies.
- Treatment: standard Rx for cirrhosis/chronic liver dis., including liver transplantation

Primary biliary cholangitis (PBC) (*Lancet* 2015;386:1565)
- Autoimmune destruction of *intrahepatic* bile ducts (previously "primary biliary cirrhosis")
- Epi: ♀ 40–60 y; a/w Sjögren's, Raynaud's, scleroderma, celiac & thyroid disease; may be triggered by certain infxns or toxins; a/w X monosomy, variants in IL12α & IL12R genes
- Sx (late): fatigue/sleep disturbance, pruritus, steatorrhea, xanthelasma, jaundice, cirrhosis
- Ddx: PSC, AIH, hepatic sarcoidosis, meds, idiopathic adult ductopenia, biliary stricture/Ca
- Dx: ↑ Aϕ, ↑ bili, ↑ IgM, ↑ chol, ⊕ antimitochondrial Ab (AMA) in 95%. If ⊕ AMA, liver bx not needed due to high Se & Sp. 0.5% gen pop ⊕ AMA & nl LFTs → 10% develop PBC at 6 y. If AMA ⊖, liver bx (Pts often ⊕ ANA, smooth muscle Ab; same prognosis

as ⊕ AMA).

- Rx: ursodeoxycholic acid (13–15 mg/kg/d) regardless of stage (30% of Pts untreated!)
  ~25% complete response, ↑ survival & ↓ histologic change & complications (eg, varices). Biochemical response predicts clinical outcomes (*Clin Gastro Hep* 2018;16:1342).
  Bezafibrate (not available in U.S. but fenofibrate similar) appears to be effective 2nd-line agent in combo w/ UDCA if inadequate response to UDCA (*NEJM* 2018;378:2171)
  Obeticholic acid (5 → 10 mg qd, except CPS B/C: 5 mg/wk → 10 mg twice weekly) ↓ Aφ, but no fat-soluble vitamins; screen/Rx osteoporosis fibrosis (*NEJM* 2016;375:631)
  Pruritus: cholestyramine (give 2–4 h after UDCA); if refractory sx: naltrexone, rifampin
  Fat-soluble vitamins; screen/Rx osteoporosis (risk independent of vit D deficiency)
  If ESLD: liver tx; ~20% recur but no impact on long-term survival

Primary sclerosing cholangitis (PSC) (*NEJM* 2016;375:1161; *Lancet* 2018;391:2547)

- Diffuse inflammation of *intrahepatic and extrahepatic* bile ducts leading to fibrosis & stricturing of biliary system. A/w HLA-B8 and -DR3 or -DR4, frequent ⊕ autoantibodies.
- Epi: ♂ > ♀ (20–50 y) ~70% Pts w/ PSC have IBD (usually UC); only 1–4% w/ UC have PSC. ⊕ prognostic factors: ♂, absence of IBD, small duct PSC (*Gastro* 2017;152:1829).
- Clinical: fatigue, pruritus, jaundice, fevers, RUQ pain, concomitant IBD, ESLD
- Ddx: extrahepatic obstruction, PBC, may also have overlap w/ AIH and similar presentation to IgG4 autoimmune cholangitis (steroid responsive) (*J Gastro* 2016;51:295)
- Dx: MRCP ± ERCP → *multifocal beaded bile duct strictures*, but may miss dx if confined to small intrahepatic ducts (~2% "small duct PSC":? different disease). Aφ predicts survival. Liver bx may show "onion-skin" fibrosis around bile ducts but not necessary for dx.
- Treatment: supportive care, fat-soluble vitamins; no meds have improved survival
  Ursodeoxycholic acid may ↓ colon Ca risk in Pts w/ UC & improve LFTs in Pts w/o UC
  Dominant stricture: endoscopic dilation, short-term stenting or surgical resection
  Cholangiocarcinoma (20%): ? biannual surveillance w/ MRCP/RUQ U/S and CA19-9
  Liver transplantation: ~30% recurrence, though if UC, colectomy may ↓ recurrence

HEPATIC VASCULAR DISEASE

Portal vein thrombosis (PVT) (*Clin Liver Dis* 2017;10:152)

- Definition: thrombosis, constriction or invasion of portal vein; may lead to portal HTN
- Etiologies: cirrhosis, neoplasm (pancreas, HCC), abdominal infxn, hypercoag states (qv), pancreatitis, collagen vascular diseases, Behçet's, IBD, surgery, trauma, OCPs, preg
- Clinical manifestations
  - acute: can p/w abd or lumbar pain, or asx w/ incidental finding on U/S or CT. If mesenteric vein involved may p/w intestinal infarct. If fever, consider pylephlebitis.
  - chronic: asx/incidental finding; may p/w s/s of portal HTN → hematemesis 2° variceal bleeding, splenomegaly, encephalopathy; ascites uncommon unless cirrhosis
- Dx: LFTs usually nl; begin w/ U/S w/ Doppler, confirm w/ MRA or CT (I^+), angio; consider hypercoag w/u. "Portal cavernoma": network of hepatopetal collaterals in chronic PVT—can rarely cause biliary obstruction & cholestatic LFTs = portal cholangiopathy.
- Treatment: Acute: If noncirrhotic, LMWH → warfarin × 6 mo, or indefinitely if irreversible cause. If cirrhotic, anticoag ↑ recanalziation w/o ↑ bleeding (*Gastro* 2017;153:480); screen for high-risk varices prior to Rx (*Nat Rev Gastro Hep* 2014;11:435). DOACs under investigation.
  - Chronic: Anticoag if noncirrhotic or hypercoag state. If cirrhotic, consider if sx or progression. In all, screen for varices; if present, variceal bleed ppx prior to anticoag.

Splenic vein thrombosis

- Can occur 2/2 local inflam. (eg, panc.). Can p/w isol. gastric varices. Splenectomy curative.

Budd-Chiari syndrome (*World J Hepatol* 2016;8:691)

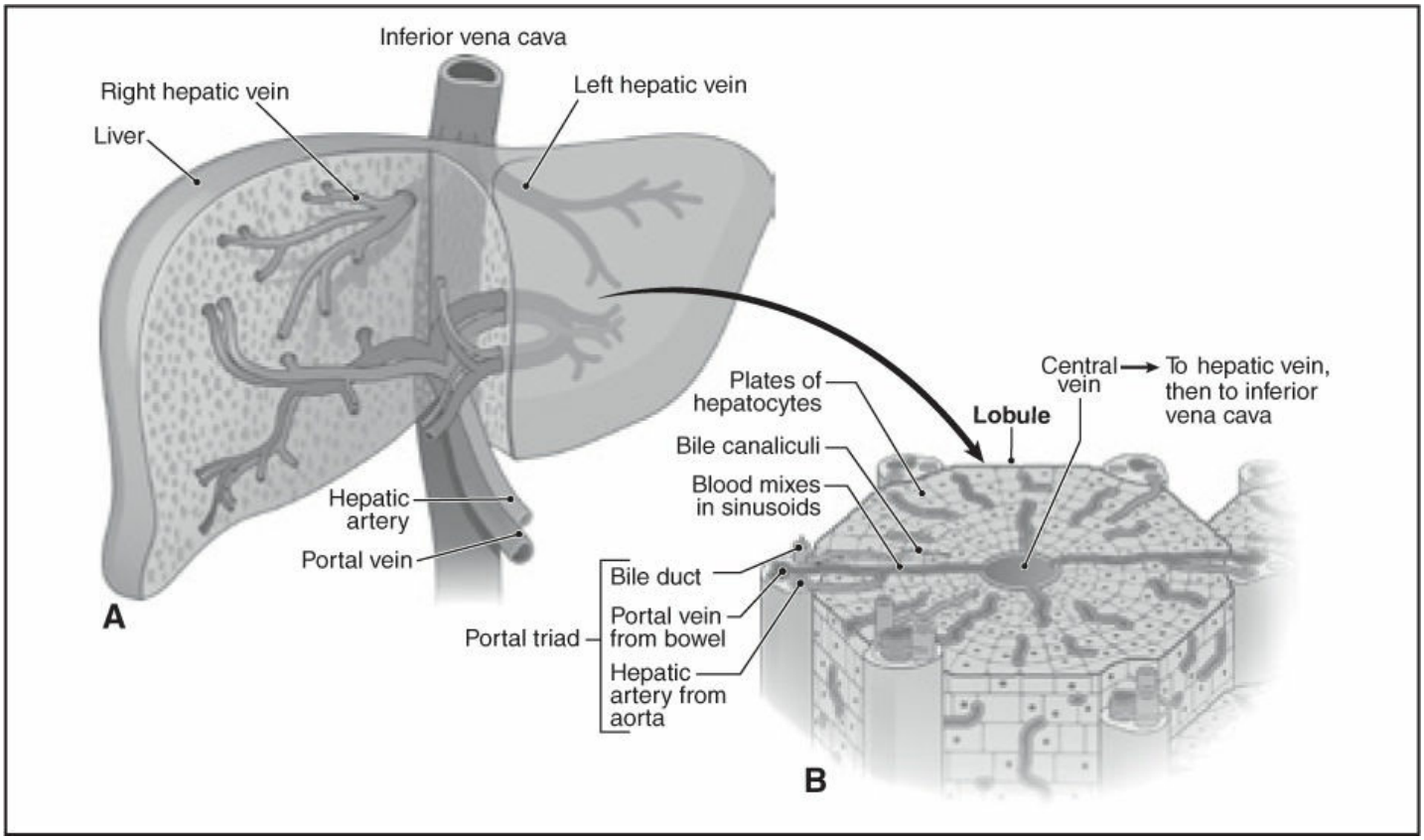
- Hepatic outflow obstruction 2/2 occlusion of hepatic vein(s) or IVC → sinusoidal congestion and portal HTN. Can be 1° (eg, thrombosis) or 2° (eg, extravascular compression).
- Etiol.: ~50% due to myeloprolif. d/o a/w *JAK2* mutations (esp. *P. vera*), other hypercoag state (qv), tumor invasion (HCC, renal, adrenal), IVC webs, trauma, 25% idiopathic
- Symptoms: hepatomegaly, RUQ pain, ascites, dilated venous collaterals, acute liver failure
- Dx: ± ↑ aminotransferases & Aϕ; Doppler U/S of hepatic veins (85% Se & Sp); CT (I^+) or MRI/MRV → vein occlusion or ↑ caudate lobe (separate venous drainage); "spider-web" pattern on hepatic venography; liver bx showing congestion (r/o right-sided CHF)
- Treatment: Rx underlying condition, anticoag (LMWH → warfarin); consider thrombolysis acutely; if short stenosis, stent may be possible; consider TIPS (↑ occlusion risk c/w side-to-side portocaval shunt); liver transplant if ALF or failed shunt (*J Gastro Surg* 2012;16:286)

Sinusoidal obstruction syndrome (SOS) (*Bone Marrow Transplant* 2015;50:781)

- Occlusion of hepatic venules & sinusoids (formerly veno-occlusive disease) 2/2 toxic insult
- Etiologies: HSCT, chemo (esp. cyclophosphamide), XRT, Jamaican bush tea
- Clinical manifestations: hepatomegaly, RUQ pain, ascites, weight gain, ↑ bilirubin
- Dx: U/S w/ reversal of portal flow, but often not helpful; dx made clinically (↑ bili, wt gain/ascites and RUQ pain) or, if necessary, by liver bx or HVPG (>10 mmHg)
- Rx (20% mort.): supportive, fluid mgmt (diuretics); ? defibrotide (adenosine agonist ↑ TPA)
- Ppx: defibrotide; ursodeoxycholic acid for high-risk HSCT pop; ? use of low-dose heparin

Figure 3-6 Normal hepatic vasculature

Modified from The Nature of Disease Pathology for the Health Professions, 2007. Hepatology 2009;49:1729.



ASCITES

Pathophysiology

- In portal hypertension → systemic vasodilatation (? due to release of NO) → ↓ effective arterial volume → renal Na retention → volume overload and ascites
- In malignant or inflammatory ascites, leaking of proteinaceous material occurs from tumor or from inflamed/infected/ruptured intraabdominal structures

Symptoms

- ↑ abd girth, wt gain, new abd hernia, abd pain, dyspnea, nausea, early satiety

Evaluation (*World J Hepatol* 2013;5:251; *JAMA* 2016;316:340)

- Physical exam: flank dullness (>1500 mL needed), shifting dullness (Se ~83%)
- Radiologic: U/S detects >100 mL; MRI/CT (also help with Ddx)
- Paracentesis (*Hep* 2013;57:1651): perform in all Pts w/ new ascites, consider in all hosp. cirrhotics w/ ascites. Low complic. rate (~1% hematoma formation). Prophylactic FFP or plts does *not* ↓ bleeding complic. Most useful tests: cell count, alb, total protein, culture.
- Serum-ascites albumin gradient (SAAG): serum alb (g/dL) – ascites alb (in g/dL)

Etiologies	
Portal HTN Related (SAAG ≥1.1)	Non–portal HTN Related (SAAG <1.1)
Presinusoidal obstruction portal or splenic vein thrombosis, schistosomiasis, sarcoidosis *Sinusoidal* obstruction: cirrhosis (81%), acute hepatitis, malignancy (HCC or mets) *Postsinusoidal* obstruction Right-sided CHF (ex: constriction, TR), Budd-Chiari syndrome, SOS	Malig: peritoneal carcinomatosis; chylous ascites from malignant lymphoma; Meigs' syndrome (ovarian tumor) Infection: TB, chlamydia/gonorrhea (ie, Fitz-Hugh-Curtis syndrome) Inflam: pancreatitis, ruptured pancreatic/biliary/lymph duct; bowel obstrxn Hypoalbuminemic states: nephrotic syndrome, protein-losing enteropathy

SAAG >1.1 diagnoses portal HTN with ~97% accuracy
If portal HTN + another cause (seen in ~5% of cases) SAAG still ≥1.1

- Ascites fluid total protein (AFTP): useful when SAAG ≥1.1 to distinguish cirrhosis (AFTP <2.5 g/dL) from cardiac ascites (AFTP ≥2.5 g/dL). Low AFTP (<1 g/dL) assoc. w/ ↑ risk of SBP (see "Cirrhosis" for guidelines on SBP Ppx based on AFTP).
- Cell count: normal limit of PMNs in ascitic fluid up to 250 PMNs/mm^3. Bloody tap (typically from traumatic para) can skew cell count; subtract 1 PMN for every 250 RBCs to correct PMN count. Ascitic PMNs ≥250 suggest infection (see below).
- Other tests: amylase (pancreatitis, gut perforation); bilirubin (test in dark brown fluid, suggests bile leak or proximal intestinal perf); TG (chylous ascites); BNP (HF); cytology (peritoneal carcinomatosis, ~95% Se w/ 3 samples). SBP a/w ↓ glc & ↑ LDH.

Treatment (see "Cirrhosis" for details)

- If 2° to portal HTN: ↓ Na intake + diuretics; if refractory → LVP or TIPS
- If non–portal HTN related: depends on underlying cause (TB, malignancy, etc.)

Bacterial peritonitis (*Gut* 2012;61:297)

Ascites PMN	⊕ Ascites Culture	⊖ Ascites Culture
≥ 250/ µL	Spontaneous bacterial peritonitis (SBP): gut bacterial translocation to ascites. In cirrhosis, ↓ ascites opsonins (esp. if ↓AFTP) ↑ risk of infxn. Cx w/ 1 org: *E. coli* (37%), *Klebs* (17%), *S. pneumo* (12%), misc. GPC (14%), misc. GNR (10%) 2° bacterial peritonitis: 2/2 intra-abd abscess, perf. Runyon's criteria: AFTP >1 g/dL, glc <50 mg/dL, LDH >ULN for serum. Cx polymicrobial. Rx 3rd-gen ceph. + MNZ; urgent abd imaging ± ex lap.	Culture-⊖ neutrocytic ascites (CNNA): cell counts suggest infxn but cx ⊖. No recent abx, w/o other explan. for counts. Rare when sens cx methods.
<250/µL	Nonneutrocytic bacterascites (NNBA): ⊕ cx w/o ↑ PMNs. Natural course may resolve w/o Rx or may progress to SBP. Cx w/ 1 org.: Misc. GPC (30%), *E. coli* (27%), *Klebs* (11%), misc. GNR (14%)	(Normal)
Peritoneal dialysis-associated: cloudy fluid, abd pain, fever, nausea. ≥100 WBCs/µL, poly predom. Cx ⊕ (typ. 1 org.): Misc. GPC (50%), misc. GNR (15%). Rx: vanc + gent (IV load, then administer in PD).		

BILIARY TRACT DISEASE

CHOLELITHIASIS (GALLSTONES)

Epidemiology & pathogenesis (*J Hepatol* 2016;65:146; *Gastro* 2016;151:351)

- Affects 10–20% of Western populations
- Bile = bile salts, phospholipids, cholesterol; ↑ cholesterol saturation in bile + accelerated nucleation + gallbladder hypomotility → gallstones
- Risk factors: ♀; South, Central, Native American; ↑ age (>40 y); obesity, TPN, rapid ↓ wt; dyslipidemia; preg., drugs (OCPs, estrogen, clofibrate, octreotide, Cftx); ileal dis., genetic
- Statin use ↓ risk of sx gallstones & cholecystectomy (*Hepatol Res* 2015;45:942)

Types of gallstones (*J Hepatol* 2016;65:146)

- Cholesterol (90%): 2 subtypes
  mixed: contain >50% cholesterol; typically smaller, multiple stones
  pure: 100% cholesterol; larger, yellow, white appearance
- Pigment (10%)
  Black: unconjugated bili & calcium; seen w/ chronic hemolysis, cirrhosis, CF, Gilbert synd
  Brown: stasis & infxn in bile ducts → bacteria deconjugate bilirubin → precipitates w/ Ca; thus found pred in bile ducts; seen w/ duod. diverticula, biliary strictures, parasites

Clinical manifestations

- Asx in ~80%. Biliary pain develops in 1–4%/y. Once sx, rate of complications ~1–3%/y.
- Biliary pain = episodic RUQ or epigastric pain; begins abruptly, continuous, resolves slowly and lasts 30 min–3 h; ± radiation to scapula; precip by fatty foods; nausea
- Physical exam: afebrile, ± RUQ tenderness or epigastric pain

Diagnostic studies

- Labs normal in large majority
- RUQ U/S: Se & Sp >95% for stones >5 mm; can show complications (cholecystitis); should be performed only after fasting ≥8 h to ensure distended, bile-filled gallbladder
- Endoscopic US (EUS) Se 94–98% in Pts w/ biliary pain but nl abd US (*J Hepatol* 2016;65:146)

Treatment (*Am Fam Physician* 2014;89:795; *J Hepatol* 2016;65:146)

- Cholecystectomy (CCY), usually laparoscopic, if symptomatic
- CCY in *asx* Pts if: GB calcification (↑ risk of cancer), GB polyps >10 mm, Native American, stones >3 cm; consider in morbidly obese undergoing bariatric surgery, cardiac Tx candidates, hemolytic anemia
- Ursodeoxycholic acid (rare) for cholesterol stones w/ uncomplicated biliary pain or if poor

surgical candidate; also reduces risk of gallstone formation with rapid wt loss
- Pain: NSAIDs drug of choice, efficacy ≈ opiates & ↓ complic.

Complications
- Cholecystitis: 20% of sx biliary pain → cholecystitis w/in 2 y
- Choledocholithiasis → cholangitis or gallstone pancreatitis
- Mirizzi syndrome: common hepatic duct obstruction by cystic duct stone → jaundice, biliary obstruction
- Cholecystenteric fistula: stone erodes through gallbladder into bowel
- Gallstone ileus: SBO (usually at term ileum) due to stone in intestine that passed thru fistula
- Gallbladder carcinoma: ~1% in U.S.

CHOLECYSTITIS (*J Hepatol* 2016;65:146; *World J Gastro Surg* 2017;9:118)

Pathogenesis
- Acute cholecystitis: stone impaction in cystic duct → inflammation behind obstruction → GB swelling ± secondary infection (50%) of biliary fluid
- Acalculous cholecystitis: GB stasis & ischemia (w/o cholelithiasis) → necroinflammation. Occurs in critically ill. A/w postop major surgery, TPN, sepsis, trauma, burns, opiates, immunosuppression, infxn (eg, CMV, *Candida*, *Crypto, Campylobacter*, typhoid fever).

Clinical manifestations
- History: RUQ/epigastric pain ± radiation to R shoulder/back, nausea, vomiting, fever
- Physical exam: RUQ tenderness, Murphy's sign = ↑ RUQ pain and inspiratory arrest with deep breath during palpation of R subcostal region, ± palpable gallbladder
- Laboratory evaluation: *may* see ↑ WBC, ± mild ↑ bilirubin, Aφ, ALT/AST, amylase; if AST/ALT >500 U/L, bili >4 mg/dL or amylase >1000 U/L → choledocholithiasis

Diagnostic studies
- RUQ U/S: high Se & Sp for stones, but need *specific signs of cholecystitis:* GB wall thickening >4 mm, pericholecystic fluid and a sonographic Murphy's sign
- HIDA scan: most Se test (80–90%) for acute cholecystitis. IV inj of HIDA (selectively secreted into bile). ⊕ if HIDA enters BD but not GB. 10–20% false ⊕ (cystic duct obstructed 2/2 chronic cholecystitis, lengthy fasting, liver disease).

Treatment (*Ann Surg* 2013;258:385; *NEJM* 2015;373:357)
- NPO, IV fluids, nasogastric tube if intractable vomiting, analgesia
- Antibiotics (*E. coli*, *Klebsiella* and *Enterobacter* sp. are usual pathogens) ([2nd- or 3rd-generation cephalosporin or FQ] + MNZ) or piperacillin-tazobactam
- CCY (typically laparoscopic) w/in 24 h ↓ morbidity vs. waiting 7–45 d
- If unstable for surgery, EUS-guided transmural, ERCP-guided transcystic duct drainage, or percutaneous cholecystotomy (if w/o ascites or coagulopathy) are alternatives to CCY
- Intraoperative cholangiogram or ERCP to r/o choledocholithiasis in Pts w/ jaundice,

cholangitis or stone in BD on U/S (see below)

Complications
- Gangrenous cholecystitis: necrosis w/ risk of empyema and perforation
- Emphysematous cholecystitis: infection by gas-forming organisms (air in GB wall)
- Post CCY: bile duct leak, BD injury or retained stones, cystic duct remnant, sphincter of Oddi dysfxn

CHOLEDOCHOLITHIASIS

Definition
- Gallstone lodged in common bile duct (CBD)

Epidemiology
- Occurs in 15% of Pts w/ gallbladder stones; can form de novo in CBD

Clinical manifestations
- Asymptomatic
- RUQ/epigastric pain 2° obstrxn of bile flow → ↑ CBD pressure, jaundice, pruritus, nausea

Diagnostic studies (*Gastro Endo* 2010;71:1; *J Hepatol* 2016;65:146)
- Labs: ↑ bilirubin, Aϕ; transient spike in ALT or amylase suggests passage of stone
- RUQ U/S: BD stones seen ~50–80% of cases; usually inferred from dilated CBD (>6 mm)
- ERCP preferred modality when likelihood high (eg, visualized stone, cholangitis, bili >4, *or* dilated CBD on U/S + bili 1.8–4 mg/dL); cholangiogram (percutaneous, operative) when ERCP unavailable or unsuccessful; EUS/MRCP to exclude BD stones when suspicion intermediate (eg, no stone, but: dilated ducts on US, bili 1.8–4 mg/dL, gallstone panc., age >55, or abnl non-bili LFT)

Treatment
- ERCP & papillotomy w/ stone extraction (± lithotripsy)
- CCY typically w/in 6 wk unless contraindication (>15% Pts will develop indication for CCY if left unRx'd)

Complications
- Cholangitis, cholecystitis, pancreatitis, stricture

CHOLANGITIS

Definition & etiologies
- BD obstruction → infection proximal to the obstruction
- Etiologies: BD stone (~85%)
  Malignant (biliary, pancreatic) or benign stricture
  Infection w/ fluke (*Clonorchis sinensis*, *Opisthorchis viverrini*)

Clinical manifestations
- Charcot's triad: RUQ pain, jaundice, fever/chills; present in ~70% of Pts
- Reynolds' pentad: Charcot's triad + shock and Δ MS; present in ~15% of Pts

Diagnostic studies

- RUQ U/S: often demonstrates dilation
- Labs: ↑ WBC (with left shift), bilirubin, Aφ, amylase; may see ⊕ BCx
- ERCP; percutaneous transhepatic cholangiogram if ERCP unsuccessful

Treatment

- Antibiotics (broad spectrum) to cover common bile pathogens (see above) ampicillin + gentamicin (or levofloxacin) ± MNZ (if severe); carbapenems; pip/tazo
- ~80% respond to conservative Rx and abx → biliary drainage on elective basis
- ~20% require urgent biliary decompression via ERCP (papillotomy, stone extraction and/or stent insertion). If sphincterotomy cannot be performed (larger stones), decompression by biliary stent or nasobiliary catheter can be done; otherwise, percutaneous transhepatic biliary drainage or surgery.

ACID-BASE DISTURBANCES

GENERAL

Definitions

- Acidemia → pH <7.36, alkalemia → pH >7.44; pH = 6.10 + log([HCO_3]/[0.03xPCO_2])
- Acidosis → process that ↑ [H^+] or ↓ pH by ↓ HCO_3 or ↑ $PaCO_2$
- Alkalosis → process that ↓ [H^+] or ↑ pH by ↑ HCO_3 or ↓ $PaCO_2$
- Primary disorders: metabolic acidosis or alkalosis, respiratory acidosis or alkalosis
- Compensation
  - Respiratory: hyper/hypoventilation alters P_aCO_2 to counteract 1° metabolic process
  - Renal: excretion/retention of H^+/HCO_3^- to counteract 1° respiratory process
  - Respiratory compensation occurs in mins-hrs; renal compensation takes days
  - *Compensation usually never fully corrects pH;* if pH normal, consider mixed disorder

Consequences of Severe Acid-Base Disturbances (*NEJM* 1998;338:26 & 107)		
Organ System	Acidemia (pH <7.20)	Alkalemia (pH >7.60)
Cardiovascular	↓ contractility, arteriolar vasodilation ↓ MAP & CO; ↓ response to catecholamines ↑ risk of arrhythmias	Arteriolar vasoconstriction ↓ coronary blood flow ↑ risk of arrhythmias
Respiratory	Hyperventilation, ↓ resp. muscle strength	Hypoventilation
Metabolic	↑ K (resp. > metab.), insulin resistance	↓ K, Ca, Mg, PO_4
Neurologic	Δ MS	Δ MS, seizures, tetany

Workup (*NEJM* 2014;371:1434)

- Traditional or physiologic approach (Brønsted-Lowry definition of acids & bases)
  - Determine primary disorder: ✔ pH, P_aCO_2, HCO_3
  - Determine if degree of compensation is appropriate

Primary Disorders				
Primary Disorder	**Problem**	**pH**	**HCO_3**	**P_aCO_2**
Metabolic acidosis	Gain of H^+ or loss of HCO_3	↓	⇓	↓
Metabolic alkalosis	Gain of HCO_3 or loss of H^+	↑	⇑	↑
Respiratory acidosis	Hypoventilation	↓	↑	⇑
Respiratory alkalosis	Hyperventilation	↑	↓	⇓

Compensation for Acid/Base Disorders (*NEJM* 2014;371:1434)	
Primary Disorder	Expected Compensation
Metabolic acidosis	↓ P_aCO_2 = 1.2 × ΔHCO_3

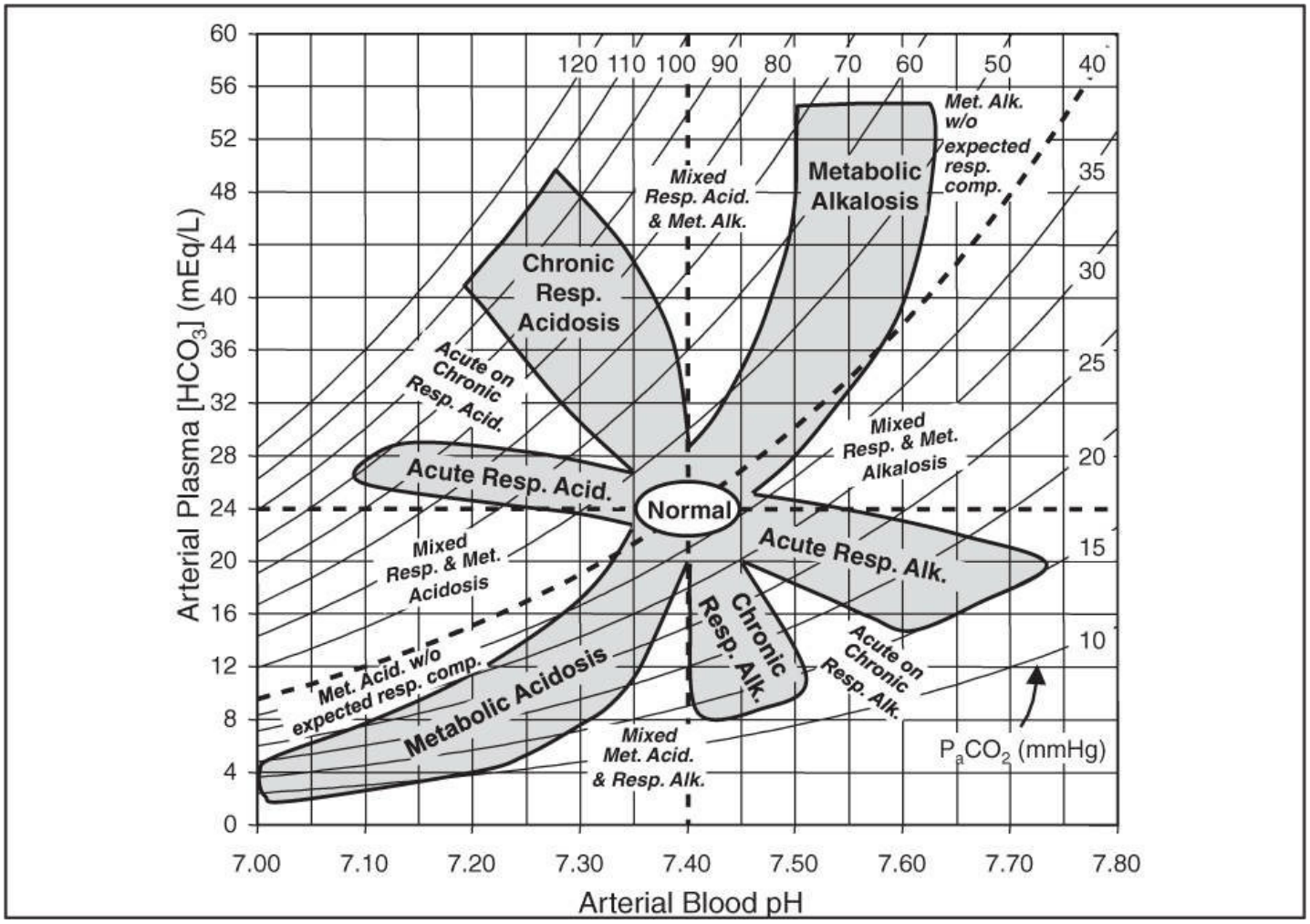
	or $P_aCO_2 = (1.5 \times HCO_3) + 8 \pm 2$ (Winters' formula) (also, $P_aCO_2 \approx$ last 2 digits of pH)
Metabolic alkalosis	$\uparrow P_aCO_2 = 0.7 \times \Delta HCO_3$ or $P_aCO_2 = 0.7\ (HCO_3\text{-}24) + 40 \pm 2$ or $HCO_3 + 15$
Acute respiratory acidosis	$\uparrow HCO_3 = 0.1 \times \Delta P_aCO_2$ (also, $\downarrow$ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory acidosis	$\uparrow HCO_3 = 0.35 \times \Delta P_aCO_2$ (also, $\downarrow$ pH = $0.003 \times \Delta P_aCO_2$)
Acute respiratory alkalosis	$\downarrow HCO_3 = 0.2 \times \Delta P_aCO_2$ (also, $\uparrow$ pH = $0.008 \times \Delta P_aCO_2$)
Chronic respiratory alkalosis	$\downarrow HCO_3 = 0.4 \times \Delta P_aCO_2$

- Alternative approaches
  - Base excess/deficit (*NEJM* 2018;378:1419)
  - Strong ion difference or "Stewart Method" (*NEJM* 2014;371:1821)

Mixed disorders (more than one primary disorder at the same time)

- If compensation less or greater than predicted, may be two disorders:
  - P_aCO_2 too low → concomitant 1° resp. alk.; P_aCO_2 too high → concomitant 1° resp. acid.
  - HCO_3 too low → concomitant 1° met. acid.; HCO_3 too high → concomitant 1° met. alk.
- Normal pH, *but*...
  - $\uparrow P_aCO_2 + \uparrow HCO_3$ → resp. acid. + met. alk.
  - $\downarrow P_aCO_2 + \downarrow HCO_3$ → resp. alk. + met. acid.
  - Normal P_aCO_2 & HCO_3, *but* ↑ AG → AG met. acid. + met. alk.
  - Normal P_aCO_2, HCO_3, & AG → no disturbance *or* non-AG met. acid. + met. alk.
- *Cannot* have resp. acid. (hypoventilation) and resp. alk. (hyperventilation) simultaneously

Figure 4-1 Acid-base nomogram



(Adapted from Brenner BM, ed., *Brenner & Rector's The Kidney*, 8th ed., 2007; Ferri F, ed. *Practical Guide to the Care of the Medical Patient*, 7th ed., 2007)

- ABG vs. VBG: concordant for pH (~0.04), HCO_3 (~2 mEq) but not PCO_2 (~8±17 mmHg)
  VBG can be used to *screen* for hypercarbia w/ PCO_2 cutoff ≥45 mmHg (100% Se), but may not accurately assess *degree* of hypercarbia (*Am J Emerg Med* 2012;30:896)

METABOLIC ACIDOSIS

Initial workup (*NEJM* 2014;371:1434)

- ✔ anion gap (AG) = $Na^+ – (Cl^– + HCO_3^–)$ = unmeasured anions – unmeasured cations
  if ↑ glc, use measured *not* corrected Na
  expected AG is [albumin] × 2.5 (ie, 10 if albumin is 4 g/dL, 7.5 if albumin is 3 g/dL)
  ↑ AG → ↑ unmeasured anions such as organic acids, phosphates, sulfates
  ↓ AG → ↓ alb or ↑ unmeasured cations (Ca, Mg, K, Li, Ig), bromide/iodine toxicity
- If ↑ AG, ✔ delta-delta (Δ/Δ = $\Delta AG/\Delta HCO_3$) to assess if there is an additional metabolic acid-base disturbance; ΔAG = (calculated AG – expected AG), $\Delta HCO_3 = (24 – HCO_3)$
  Δ/Δ = 1–2 → pure AG metabolic acidosis
  Δ/Δ < 1 → AG metabolic acidosis *and* simultaneous non-AG acidosis
  Δ/Δ > 2 → AG metabolic acidosis *and* simultaneous metabolic alkalosis
  For pure lactic acidosis Δ/Δ 1.6 b/c of slow lacatate clearance

Etiologies of AG Metabolic Acidosis	
Ketoacidosis	Diabetes mellitus, alcoholism, starvation (*NEJM* 2014;372:546)
Lactic acidosis (*NEJM* 2014; 371:2309)	Type A: hypoxic (eg, shock, mesenteric ischemia, CO poisoning, cyanide) Type B: nonhypoxic. ↓ clearance (eg, hepatic dysfxn) or ↑ generation [eg, malig, EtOH, thiamine def., meds (metformin, NRTIs, salicylates, propylene glycol, propofol, isoniazid, linezolid)] D-lactic acidosis: short bowel syndrome → precip by glc ingest → metab by colonic bacteria to D-lactate; not detected by standard lactate assay
Renal failure	Accumulation of organic anions (eg, phosphates, sulfates, etc.)
Ingestions	Glycols: *Ethylene* (antifreeze) → metab to glycolic and oxalic acids *Propylene* (pharmaceutical solvent, eg, IV diazepam, lorazepam, and phenobarbital; antifreeze) → lactic acidosis *Diethylene* (brake fluid) → diglycolic acid 5-oxoproline (pyraglutamic acid): acetaminophen → ↑ organic acid 5- oxoproline in susceptible Pts (malnourished, female, renal failure) Methanol (windshield fluid, antifreeze, solvents, fuel): metab to formic acid Aspirin: early resp alkalosis (CNS stim) + late metab acidosis (impairs oxidative phosphorylation → inorganic acids (eg, ketones, lactate)

"GOLD MARK" = Glycols, Oxoproline, Lactic, D-Lactic, Methanol, ASA, Renal, Ketoacidosis

Workup for AG metabolic acidosis

- ✔ for ketonuria (dipstick acetoacetate) or plasma β-hydroxybutyrate (βOHB)
  nb, urine acetoacetate often not present in early ketoacidosis due to shunting to βOHB; ∴ acetoacetate may later turn ⊕ but does not signify worsening disease
- If ⊖ ketones, ✔ renal function, lactate, toxin screen, and osmolal gap
- If obtunded or ↑↑ AG, check osmolal gap (OG) = measured osmoles – calculated osmoles
  calculated osmoles = (2 × Na) + (glucose/18) + (BUN/2.8) (+ [EtOH/4.6] if have EtOH level and want to test if other ingestions)
  OG >10 → suggests ingestion (see below) but lacks specificity (can be elevated in lactic acidosis, DKA, and alcoholic ketoacidosis)
  high-dose lorazepam (>10 mg/h) a/w propylene glycol intoxication
  OG & AG vary based on timing, initially OG ↑, then ↓ w/ metabolism as AG ↑

Ingestions (*NEJM* 2018;378:270) Call poison control for guidance (800-222-1222)			
AG	**OG**	**Ingestion**	**Other Manifestations**
↑	nl	Acetaminophen	Hepatitis
		Salicylates	Fever, tachycardia, tinnitus; met. acid. + resp. alkalosis
↑	↑	Methanol	ΔMS, blurred vision, pupillary dilation, papilledema
		Ethylene glycol	ΔMS, cardiopulm. failure, hypoCa. **Ca oxalate crystals** → AKI. Urine fluoresces under UV light.
		Propylene glycol	AKI, liver injury
		Diethylene glycol	AKI, N/V, pancreatitis, neuropathy, lactic acidosis
nl/↑	↑	Isopropyl alcohol	ΔMS, fruity breath (acetone), pancreatitis, lactic acidosis
		Ethanol	Alcoholic fetor, ΔMS, hepatitis; keto + lactic acidosis ± met. alk. (vomiting)

Etiologies of Non-AG Metabolic Acidosis	
GI losses of HCO_3	Diarrhea, intestinal or pancreatic fistulas or drainage
RTAs	*See section on renal tubular acidoses below*
Early renal failure	Impaired generation of ammonia
Ingestions	Acetazolamide, sevelamer, cholestyramine, toluene
Dilutional	Due to rapid infusion of bicarbonate-free IV fluids
Posthypocapnia	Respiratory alkalosis → renal wasting of HCO_3; rapid correction of resp. alk. → transient acidosis until HCO_3 regenerated
Ureteral diversion	Colonic Cl^-/HCO_3^- exchange, ammonium reabsorption

Workup for non-AG metabolic acidosis

- Evaluate history for causes (see above)
- ✔ urine anion gap (UAG) = $(U_{Na} + U_K) - U_{Cl}$
  UAG = unmeasured anions – unmeasured cations; NH_4^+ is primary unmeasured cation (represented by U_{Cl}). UAG is indirect assay for renal H^+ excretion.
- ⊖ UAG → ↑ renal NH_4^+ excretion → appropriate renal response to acidemia
  Ddx: GI causes (diarrhea, fistulas, ureteral diversion), IV NS, proximal RTA, ingestions
- ⊕ UAG → failure of kidneys to generate NH_4^+
  Ddx: distal (type 1, usually ↓ K) or hypoaldo (type IV, usually ↑ K) RTA, early renal failure
- UAG unreliable in polyuria, Na depletion (U_{Na} <20), U_{pH} >6.5 & HAGMA (causes ⊕ UAG b/c excretion of organic anions). Then use U_{Osm} gap = measured U_{Osm} – [2×(Na^+ + K^+) + BUN + glc (mmol/L)]. U_{Osm} gap <40 mmol/L indicates impaired NH_4^+ excretion.

Renal tubular acidoses (RTAs) (*Int J Clin Pract* 2011;65:350)

- Proximal (Type II): ↓ proximal reabsorption of HCO_3
  1° (Fanconi's syndrome) = ↓ proximal reabsorption of HCO_3, PO_4, glc, amino acids
  Acquired: paraprotein (MM, amyloidosis), metals (Pb, Cd, Hg, Cu), ↓ vit D, PNH, renal Tx
  Meds: acetazolamide, aminoglycosides, ifosfamide, cisplatin, topiramate, tenofovir
- Distal (Type I): defective distal H^+ secretion
  1°, autoimmune (Sjögren's, RA, SLE), hypercalciuria, meds (ampho, Li, ifosfamide); normally a/w ↓ K; if with ↑ K → sickle cell, obstruction, renal transplant
- Hypoaldo (Type IV): hypoaldo → ↑ K → ↓ NH_3 synthesis → ↓ urine acid-carrying capacity
  ↓ renin: diabetic nephropathy, NSAIDs, chronic interstitial nephritis, calcineurin inh, HIV
  ↓ aldo production: 1° AI, ACEI/ARBs, heparin, severe illness, inherited (↓ 21-hydroxylase)
  ↓ response to aldosterone

meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors
tubulointerstitial disease: sickle cell, SLE, amyloid, DM

- Combined (Type III): rarely discussed or clinically relevant, also called juvenile RTA, has distal & proximal features, can be due to carbonic anhydrase II deficiency

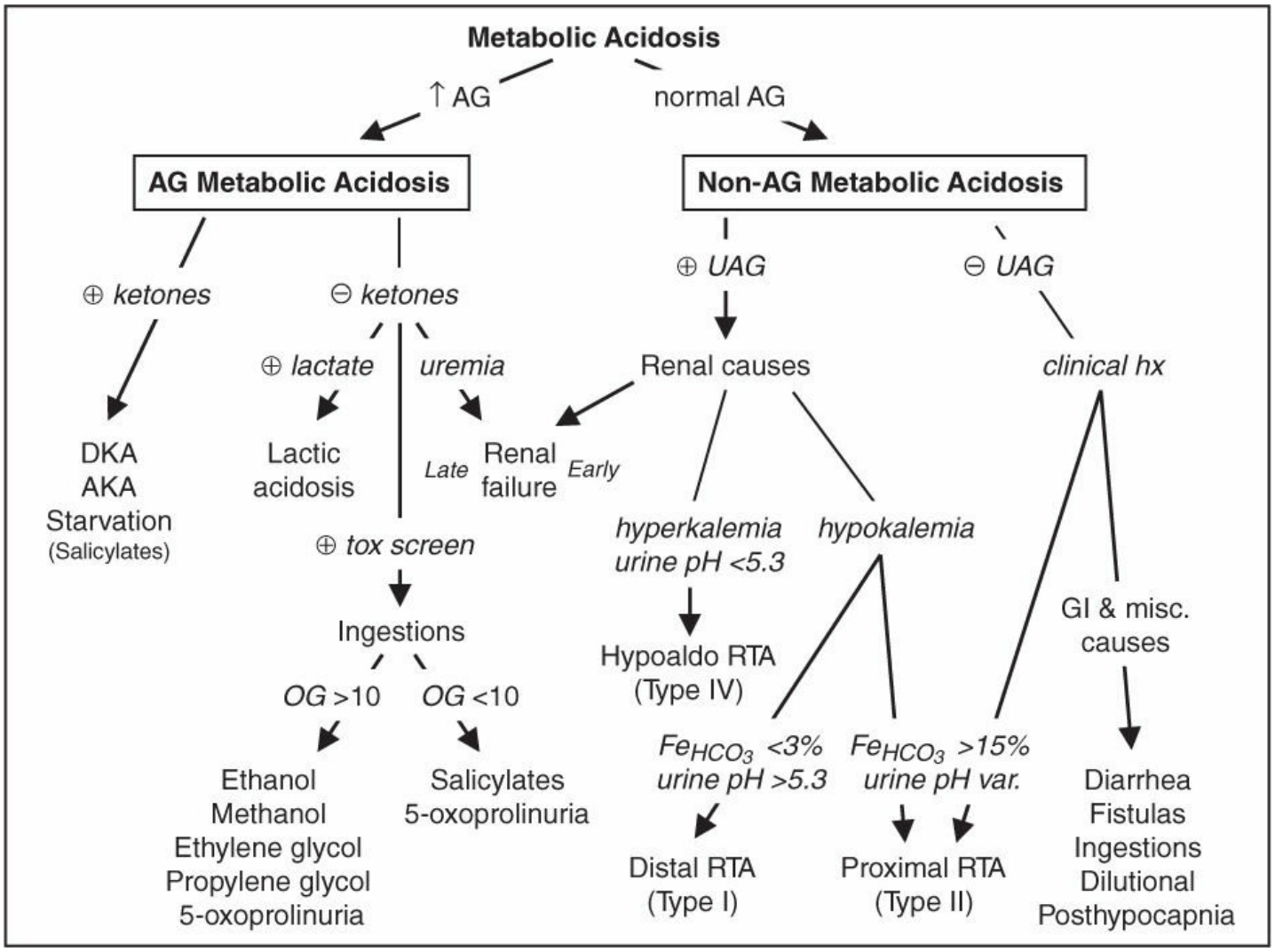
Renal Tubular Acidosis								
Location	**Type**	**Acidosis**	**UAG**	**HCO_3^-**	**UpH**	**FE_{HCO_3} [b]**	**K**	**Complications**
Proximal	II	Moderate	±	12-20	<5.3[a]	>15%	↓	Osteomalacia
Distal	I	Severe	⊕	<10	>5.3	<3%	↓[c]	Kidney stones
Hypoaldo	IV	Mild	⊕	>17	<5.3	<3%	↑	Hyperkalemia

[a]Urine pH will rise above 5.3 in the setting of HCO_3 load

[b]Fe_{HCO3} should be checked after an HCO_3 load

[c]See above for causes of distal RTA (Type I) associated with hyperkalemia

Figure 4-2 Approach to metabolic acidosis



Treatment of severe metabolic acidoses (pH <7.2) (*Nat Rev Nephrol* 2012;8:589)

- DKA: insulin, IVF, K repletion (*NEJM* 2015;372:546); AKA: dextrose, IVF, replete K, Mg, PO_4

- Lactic acidosis: treat underlying condition, avoid vasoconstrictors, avoid "Type B" meds
- Renal failure: hemodialysis
- Methanol & ethylene glycol: fomepizole (20 mg/dL), vit. B_1 & B_6 (ethylene glycol), folate (methanol), dialysis (if AKI, VS unstable, vision Δ or >50 mg/dL) (*NEJM* 2018;378:270)
- Alkali therapy: if pH <7.1 or <7.2 and co-existing AKI (*Lancet* 2018;392:21)
- $NaHCO_3$: amps by IV push or infusion of three 50-mmol amps in 1 L D_5W if less urgent
  can estimate mmol of HCO_3 needed as [desired-current $HCO_3]_{serum}$ × wt (kg) × 0.4
  side effects: ↑ volume, ↑ Na, ↓ ICa, ↑ P_aCO_2 (& ∴ intracellular acidosis; ∴ *must ensure adequate ventilation* to blow off CO_2)

METABOLIC ALKALOSIS

Pathophysiology (*Clin Physio Acid-Base* 2001; *CJASN* 2008;3:1861)

- Saline-responsive etiologies require *initiating event* and *maintenance phase*
- *Initiating event:* net HCO_3^- reabsorption (due to loss of volume, Cl^-, and/or K^+) or loss of H^+
  Loss of H+ (± Cl^-) from GI tract, kidneys, or transcellular shift in hypokalemia
  Contraction alkalosis: loss of HCO_3^--poor fluid → extracellular fluid "contracts" around fixed amount of HCO_3^- → ↑ HCO_3^- concentration
  Exogenous alkali: iatrogenic HCO_3^- (with renal impairment), milk-alkali syndrome
  Posthypercapnia: resp. acidosis → compensation with H^+ excretion and HCO_3^- retention; rapid correction of hypercapnia (eg, intubation) → transient excess HCO_3^-
- *Maintenance phase*
  Volume depletion → ↑ ATII → ↑ PCT reabsorption of HCO_3^- & ↑ aldosterone (see below)
  Cl^- depletion → ↓ Cl^- uptake in macula densa → ↑ RAS & ↑ CCD Cl^-/HCO_3^- exchanger
  Hypokalemia → transcellular K^+/H^+ exchange; intracellular acidosis → HCO_3^- reabsorption and ammoniagenesis & ↑ distal H^+-K^+-ATPase activity → HCO_3^- retention
  Hyperaldosteronism (1° or 2°) → ↑ CCD α-intercalated H^+ secretion w/ HCO_3^- retention & Na^+ reabsorption in principal cell → H^+ secretion (for electrical neutrality)

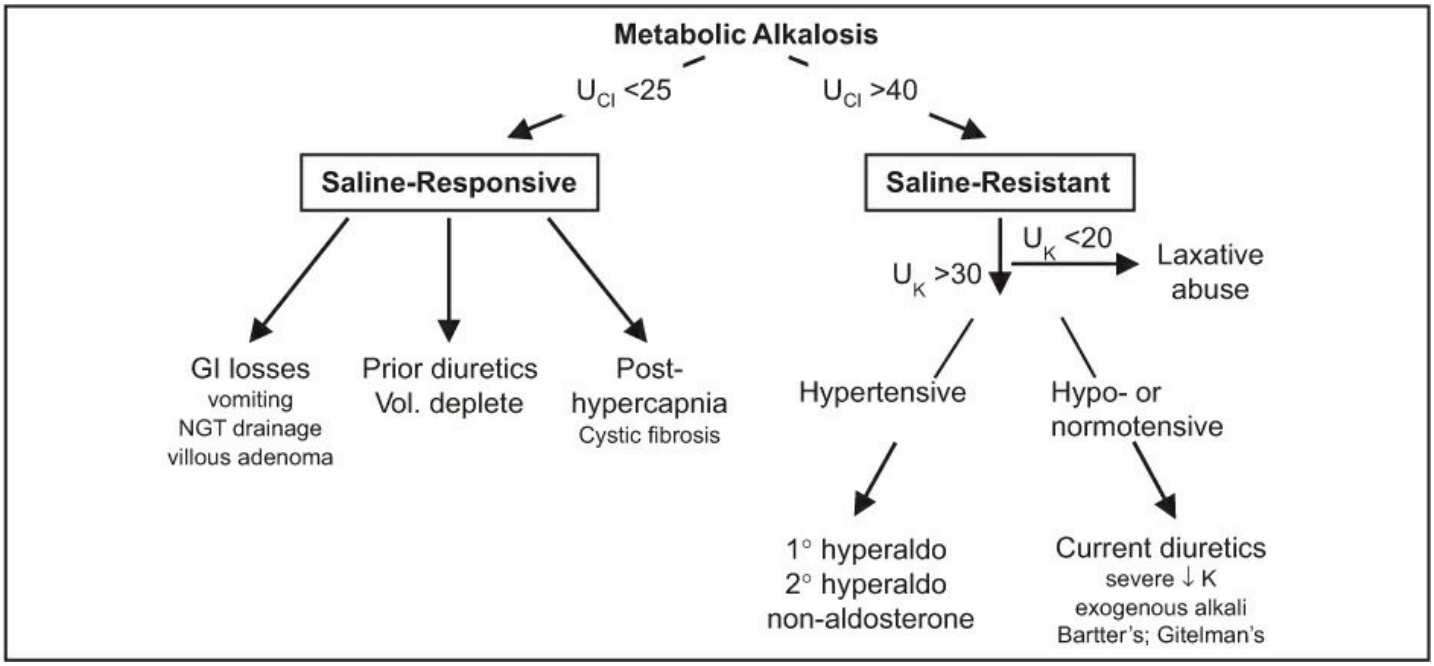
Etiologies of Metabolic Alkalosis	
Saline responsive UCl < 25	GI loss of H^+: emesis, NGT suction, villous adenoma, chloridorrhea Renal loss: loop/thiazide, ↓ Cl intake, milk-alkali, Pendred syndrome Posthypercapnia, sweat losses in cystic fibrosis
Saline resistant UCl >40	*Hypertensive* (mineralocorticoid excess) 1° hyperaldosteronism (eg, Conn's) 2° hyperaldosteronism (eg, renovascular dis., renin-secreting tumor) Non-aldo (Cushing's, Liddle's, exogenous mineralocorticoids, licorice) *Normotensive* Severe hypokalemia (K<2); exogenous alkali load (w/ AKI or ↓ vol)

	Bartter's syndrome (loop-like); Gitelman's syndrome (thiazide-like)

Workup

- Check volume status and U_{Cl}
  - U_{Cl} <25 mEq/L → saline responsive
  - U_{Cl} >40 mEq/L → saline resistant (unless currently receiving diuretics)
  - (U_{Na} unreliable determinant of volume status in alkalemia → ↑ HCO_3^- excretion → ↑ Na excretion; negatively charged HCO_3^- w/ Na^+ maintaining electrical neutrality)
  - If U_{Cl} >40 and volume replete, ✔ U_K; U_K < 20 laxative abuse; U_K >30, ✔ blood pressure

Figure 4-3 Approach to metabolic alkalosis



Treatment of severe metabolic alkalosis (pH >7.6) (*JASN* 2012;23:204)

- If saline responsive: resuscitate with Cl-rich solution (NS), replete K, d/c diuretics cardiopulmonary disease precludes hydration, can use KCl, acetazolamide, HCl
- If NGT drainage that cannot be stopped: PPI or H_2-blocker (*Clin Nephro* 2006;66:391)
- Hyperaldosteronism: treat underlying condition, K-sparing diuretic, resect adenoma if 1°

RESPIRATORY ACIDOSIS (*NEJM* 1989;321:1223; *Crit Care* 2010;14:220)

Etiologies (also see "Hypercapnia"; PaCO2 = VCO2/VE(1-VD/VT); VE= RR x VT)

- ↑ CO_2 production (↑ VCO_2): fever, thyrotoxicosis, sepsis, steroids, overfeeding (carbs)
- CNS depression (↓ RR and/or V_T): sedatives (opiates, benzos, etc.), CNS trauma, central sleep apnea, obesity hypoventilation, hypothyroidism
- Neuromuscular disorders (↓ V_T): Guillain-Barré, poliomyelitis, ALS, MS, paralytics, myasthenia gravis, muscular dystrophy, severe ↓ P & K, high spinal cord injury
- Chest wall (↓ V_T): PTX, hemothorax, flail chest, kyphoscoliosis, ankylosing spondylitis

- Upper airway (↓ V_T): foreign body, laryngospasm, OSA, esophageal intubation
- Lower airway (gas exchange) (↑ V_D and/or ↓ V_T): asthma, COPD, pulm edema, IPF
  Often hypoxia → ↑ RR → resp. alk., but muscle fatigue → resp. acid
- Post infusion of bicarbonate in acidemic Pt w/ limited ability to ↑ minute ventilation

RESPIRATORY ALKALOSIS

Etiologies (*NEJM* 2002;347:43; *Crit Care* 2010;14:220)

- Hypoxia → hyperventilation: pneumonia, CHF, PE, restrictive lung disease, anemia
- Primary hyperventilation
  CNS stimulation, pain, anxiety, trauma, stroke, CNS infection, pontine tumors
  drugs: salicylates toxicity (early), β-agonists, progesterone, methylxanthines, nicotine
  pregnancy, sepsis, hepatic failure, hyperthyroidism, fever
- Pseudorespiratory alkalosis: ↓ perfusion w/ preserved ventilation (eg, CPR, severe HoTN) → ↓ delivery of CO_2 to lungs for excretion; low P_aCO_2 but ↑ tissue CO_2

SODIUM AND WATER HOMEOSTASIS

OVERVIEW

General (*NEJM* 2015;372:55 & 373:1350)

- Disorders of serum sodium are generally due to Δs in *total body water*, not sodium
- Hyper- or hypo-osmolality → rapid water shifts → Δs in brain cell volume → Δ MS, seizures

Key hormones

- Antidiuretic hormone (ADH): primary hormone that regulates *sodium concentration*
  Stimuli: hyperosmolality (290–295 mOsm), ↓↓ effective arterial volume, angiotensin II
  Action: insertion of aquaporin-2 channels in principal cells → passive water reabsorption
  urine osmolality is an indirect functional assay of the ADH-renal axis
  U_{osm} range: 50 mOsm/L (no ADH) to 1200 mOsm/L (maximal ADH)
- Aldosterone: primary hormone that regulates *total body sodium* (and ∴ volume)
  Stimuli for secretion: hypovolemia (via renin and angiotensin II), hyperkalemia
  Action: iso-osmotic principal cell reabsorption of Na via epithelial Na channel (ENaC) in exchange for K^+ or H^+

HYPONATREMIA

Pathophysiology (*JASN* 2008;19:1076; *NEJM* 2015;372:1349)

- Free water clearance (C_{H^2O}) = solute (intake) excretion/U_{osm} normal dietary solute load ~750 mOsm/d, minimum U_{osm} = 50 mOsm/L → excrete ~15 L
- Excess H_2O relative to Na, usually due to ↑ ADH
- ↑ ADH may be *appropriate* (eg, hypovolemia or hypervolemia with ↓ EAV)
- ↑ ADH may be *inappropriate* (SIADH)
- Rarely, ↓ ADH (appropriately suppressed), but kidneys unable to maintain nl $[Na]_{serum}$
  ↑ *H_2O intake (1° polydipsia):* ingestion of massive quantities (usually >15 L/d) of free H_2O overwhelms diluting ability of kidney → H_2O retention
  ↓ solute intake ("tea & toast" & beer potomania*):* ↓↓ daily solute load → insufficient solute to excrete H_2O intake (eg, if only 250 mOsm/d, minimum U_{osm} = 50 mOsm/L → excrete in ~5 L; if H_2O ingestion exceeds this amount → H_2O retention)

Workup (*JASN* 2012;23:1140 & 2017;28:1340; *Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- History: (1) acute vs. chronic (>48 h); (2) sx severity; (3) risk for neuro complications (alcoholism, malnourished, cirrhosis, older females on thiazides, hypoxia, hypoK)
- Measure plasma osmolality

Hypotonic (P_{osm} <280) most common scenario; true excess of free H_2O relative to Na

Isotonic (P_{osm} 280–295): rare lab artifact from hyperlipidemia or hyperproteinemia

Hypertonic (P_{osm} >295): excess of another effective osmole (eg, glucose, mannitol) that draws H_2O intravascularly; for each 100 mg/dL ↑ glc >100 mg/dL → ↓ [Na] by ~2 mEq/L

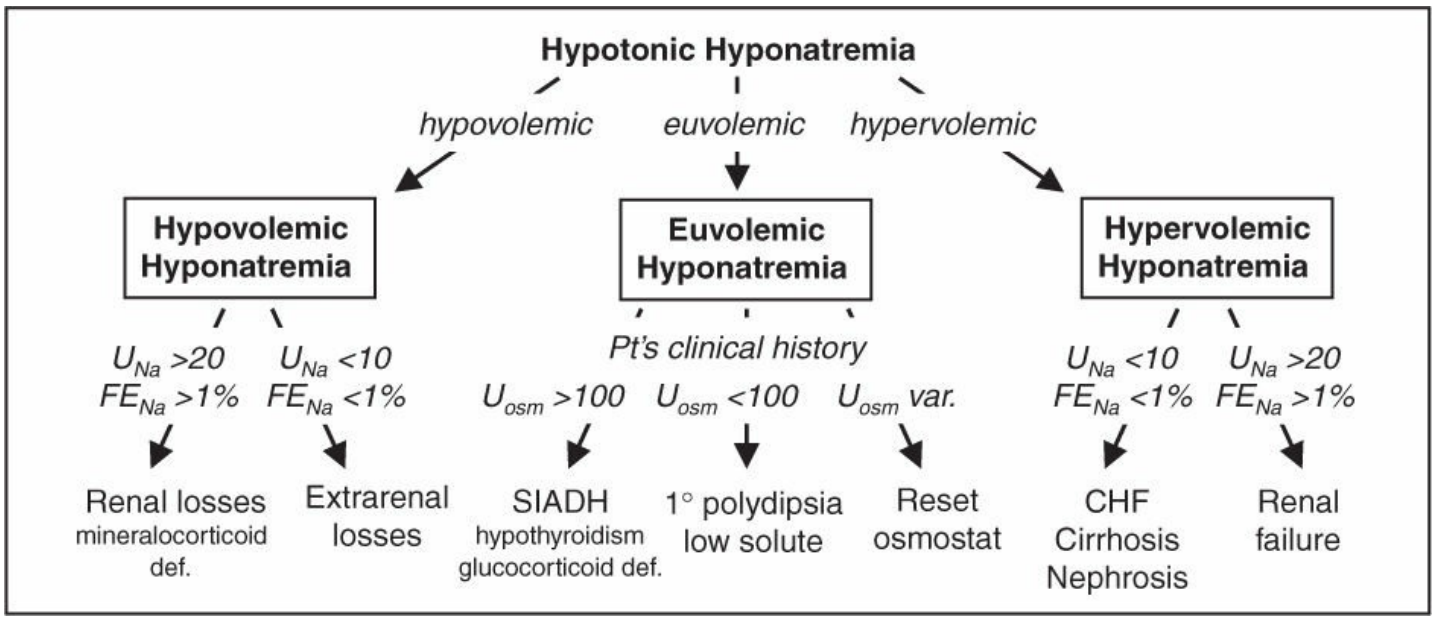
- For hypotonic hyponatremia, ✔ volume status (JVP, skin turgor, dry axilla, mucous membranes, edema, ascites), effusions, vital signs, orthostatics, BUN/Cr, $FE_{UricAcid}$, U_{Na}
- Measure U_{osm}, although useful for dx in limited circumstances, b/c almost always >300

  U_{osm} <100 in ↑ H_2O intake (1° polydipsia) or ↓ solute intake (beer potomania, "tea & toast")

  U_{osm} >300 does not mean SIADH; must determine if ↑ ADH appropriate or inappropriate

  however, U_{osm} can be important when deciding on *treatment* (see below)
- If euvolemic and ↑ U_{osm}, evaluate for glucocorticoid insufficiency and hypothyroidism
- If available, consider $FE_{UricAcid}$ as >12% suggests SIADH (*J Clinc Endo* 2008;93:2991)

Figure 4-4 Approach to hyponatremia



Hypovolemic hypotonic hyponatremia (ie, ↓↓ total body Na, ↓ TBW)

- Renal losses (U_{Na} >20 mEq/L, FE_{Na} >1%): diuretics (esp. thiazides, because loop diuretics

  ↓ tonicity of medullary interstitium, Δ for H_2O absorption, & ∴ urine concentrating ability), salt-wasting nephropathy, cerebral salt wasting, mineralocorticoid deficiency
- Extrarenal losses (U_{Na} <10 mEq/L, U_{Cl} <10 mEq/L if alkalemia, FE_{Na} <1%): hemorrhage, GI loss (diarrhea or vomiting), third-spacing (pancreatitis), ↓ PO intake, insensible losses

Euvolemic hypotonic hyponatremia (ie, ↑ TBW relative to total body Na)

- SIADH (euvolemia or mild hypervolemia, typically inapprop U_{osm} >100, U_{Na} >20 mEq/L)
  - Malignancy: lung (SCLC), brain, GI, GU, lymphoma, leukemia, thymoma, mesothelioma
  - Pulmonary: pneumonia, TB, aspergillosis, asthma, COPD, PTX, mechanical ventilation
  - Intracranial: trauma, stroke, SAH, seizure, infxn, hydrocephalus, Guillain-Barré
  - Drugs: antipsychotics, antidepress. (SSRI, TCA, MAOi), haloperidol, chemo (vincristine, cisplatin), AVP, MDMA, NSAIDs, opiates, amiodarone (*Am J Kidney Dis* 2008;52:144)
  - Miscellaneous: pain, nausea, postoperative state
- Endocrinopathies: ↑ ADH activity seen in *glucocorticoid deficiency* (co-secretion of ADH & CRH) and *severe hypothyroidism/myxedema coma* (↓ CO/SVR → ADH release & ↓ GFR)
- Psychogenic polydipsia (U_{osm} <100, ↓ $FE_{Uric\ Acid}$): usually intake >15 L/d
- Low solute (↓ U_{Na}, ↓ U_{osm}) "tea & toast"; beer potomania
- Reset osmostat: chronic malnutrition (↓ intracellular osmoles) or pregnancy (hormonal effects) → ADH physiology reset to regulate a lower $[Na]_{serum}$

Hypervolemic hypotonic hyponatremia (ie, ↑ total body Na, ↑ ↑ TBW)

- ↓ EAV → ↑ RAAS → ↑ aldosterone & ↑ adrenergic tone → ↑↑ ADH (*Am J Med* 2013;126:S1)
- CHF (↓ CO & renal venous congestion → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- Cirrhosis (splanchnic arterial vasodilation + ascites → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- Nephrotic syndrome (hypoalbuminemia → edema → ↓ EAV; U_{Na} <10 mEq/L, FE_{Na} <1%)
- Advanced renal failure (diminished ability to excrete free H_2O; U_{Na} >20 mEq/L)

Treatment (*NEJM* 2015;372:55; *JASN* 2017;28:1340; *CJASN* 2018;13:641 & 984)

- Approach: depends on *volume status*, *acuity* of hyponatremia, and if *symptomatic*
  - Acute sx: *initial* rapid correction of $[Na]_{serum}$ (2 mEq/L/h for the first 2–3 h) until sx resolve
  - Asx or chronic symptomatic: correct $[Na]_{serum}$ at rate of ≤0.5 mEq/L/h
  - Rate ↑ Na *should not exceed 6* (chronic) to *8* (acute) mEq/L/d to avoid central pontine myelinolysis/osmotic demyelination (CPM/ODS: paraplegia, dysarthria, dysphagia)
  - If severe (<120) or neuro sx: consider 3% NaCl. dDAVP 1-2 µg q8h in consultation with nephrology (to prevent rapid overcorrection) (*AJKD* 2013;61:571; *CJASN* 2018; 13:641)
- Frequent lab draws and IVF rate adjustments are cornerstones of treatment
- Rapid correction: can lead to CPM/ODS (esp if chronic or Na <120 mEq/L). Should be emergently reversed w/ dDAVP ± D_5W; partial neuro recovery possible (*CJASN* 2014;9:229).
- Effect of IV fluids (http://www.medcalc.com/sodium.html)

$$\text{initial } \Delta[Na]_{serum} \text{ per L infusate} = \frac{[Na]_{infusate} - [Na]_{serum}}{TBW + 1}$$

TBW = wt (kg) × 0.6(♂) or 0.5 (♀); if elderly use 0.5 (♂) or 0.45 (♀)

If $[Na]_s$ = 110 mEq/L in 70-kg Male:			
IVF Type	**$[Na]_{content}$**	**1 L IVF ↑ $[Na]_s$**	**Rate to ↑ $[Na]_s$ by 0.5 mEq/L/h**
5% NaCl	856 mEq/L	17.3 mEq/L	~25 mL/h
3% NaCl	513 mEq/L	9.4 mEq/L	~50 mL/h
0.9% NaCl	154 mEq/L	1 mEq/L	~500 mL/h
LR	130 mEq/L	0.5 mEq/L	~1000 mL/h

However, above assumes infusate retained *without output of Na/H*$_2$O; adjust for UOP.

If Pt euvolemic (eg, SIADH), infused Na will be excreted: for 1 L NS (154 mEq Na or 308 mOsm solute in 1 L H_2O); in SIADH with U_{osm} = 616 → 308 mOsm solute excreted in 0.5 L H_2O → net gain 0.5 L H_2O → ↓ $[Na]_{serum}$. ∴ NS *worsens* Na if U_{osm} > $infusate_{osm}$.

- Hypovolemic hyponatremia: volume repletion with isotonic 0.9% saline at a slow rate. Once volume replete → stimulus for ADH removed (w/ very short ADH $t_{½}$) → kidneys excrete free H_2O → serum Na will correct rapidly (D_5W ± ddAVP if overcorrection)
- SIADH (*NEJM* 2007;356:2064; *AJKD* 2015;65:435): fluid restrict + treat underlying cause
  hypertonic saline (± loop diuretic) if sx or Na fails to ↑ w/ fluid restriction 1 L hypertonic saline (3% NaCl) will raise $[Na]_{serum}$ by ~10 mEq (see above) ~50 mL/h will ↑ [Na] by ~0.5 mEq/L/h; 100–200 mL/h will ↑ [Na] by ~1–2 mEq/L/h formula only provides estimate; ∴ recheck serum Na frequently (at least q2h)
  NaCl tabs if chronic and no CHF. Consider urea 0.25-0.5g/kg/d (*Nephrol Dial Trans* 2014;29:ii1)
  aquaresis: vaptans (vasopressin receptor antag) for refractory SIADH (*NEJM* 2015;372:23)
  demeclocycline: causes nephrogenic DI, ↓ U_{osm} (rarely used)
- Hypervolemic hyponatremia: free water restrict (1st line), diurese w/ loop diuretics (avoid thiazides) & ↑ EAV (vasodilators to ↑ CO in CHF, colloid infusion in cirrhosis)
  vaptans sometimes used; however, no mortality benefit, hypoNa recurs after stopping drug, high risk of overcorrection, contraindicated in cirrhosis (*NEJM* 2015;372:2207)

HYPERNATREMIA

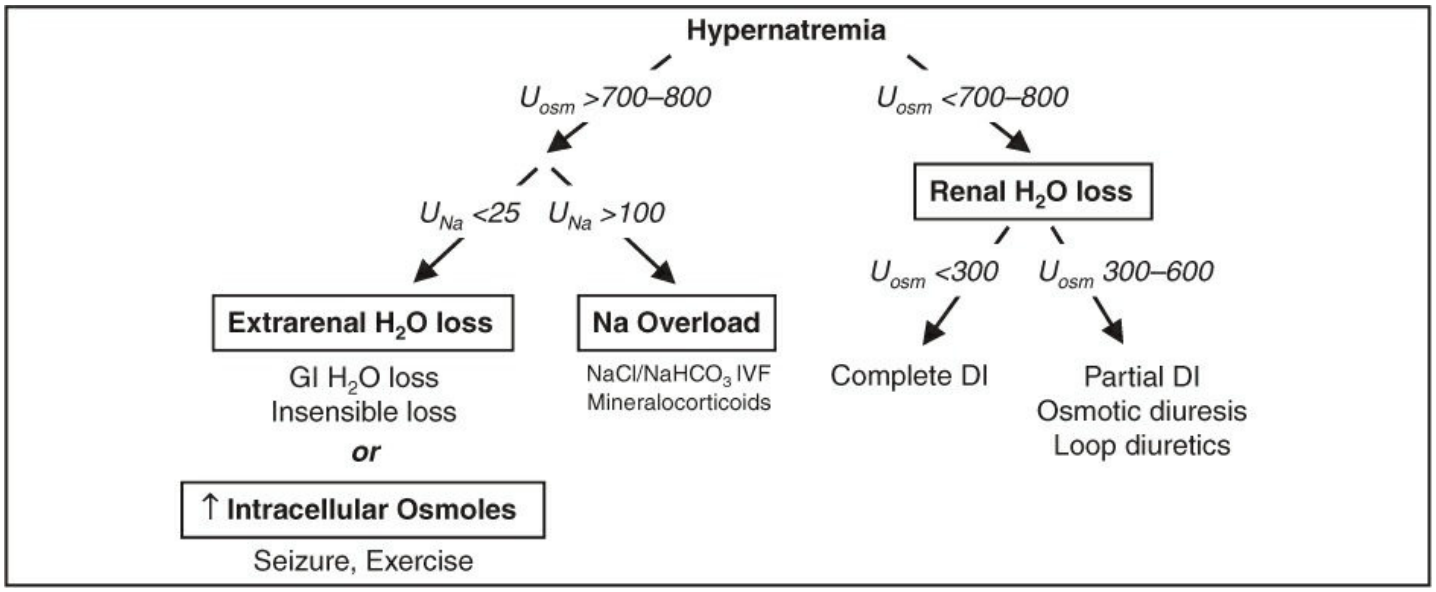
Pathophysiology (*Crit Care* 2013;17:206; *NEJM* 2015;372:55)

- Deficit of water relative to sodium; by definition, all hypernatremic Pts are hypertonic
- Usually loss of hypotonic fluid (ie, "dehydration"); occasionally infusion of hypertonic fluid, post-ATN diuresis w/ loss of low or electrolyte-free water (*Am J Neph* 2012;36:97)
- *And* impaired access to free water (eg, intubation, Δ MS, elderly): hypernatremia is a powerful thirst stimulus, ∴ usually only develops in Pts w/o access to H_2O or ill

Workup

- ✔ U_{osm}, U_{Na}, volume status (vital signs, orthostatics, JVP, skin turgor, BUN, Cr)

Figure 4-5 Approach to hypernatremia



Extrarenal H_2O loss (U_{osm} >700–800)

- GI H_2O loss: vomiting, NGT drainage, osmotic diarrhea, fistula, lactulose, malabsorption
- Insensible loss: fever, exercise, ventilation, burns

Renal H_2O loss (U_{osm} <700–800)

- Diuresis: osmotic (glucose, mannitol, urea), loop diuretics
- Diabetes insipidus (*J Clin Endocrinol Metab* 2012;97:3426)
  - ADH deficiency (central) or resistance (nephrogenic)
  - Central: hypothalamic or posterior pituitary disease (congenital, trauma/surgery, infiltrative/IgG4); also idiopathic, hypoxic/ischemic encephalopathy (shock, Sheehan's syndrome), anorexia, sarcoidosis, histiocytosis, drugs: EtOH, phenytoin, snake venom
    - tumors: craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary
  - Nephrogenic (*Annals* 2006;144:186)
    - congenital (ADH receptor V2 mutation, aquaporin-2 mutation; *Ped Nephrol* 2012;27:2183)
    - drugs: lithium, amphotericin, demeclocycline, foscarnet, cidofovir, ifosfamide
    - metabolic: hypercalcemia, severe hypokalemia, protein malnutrition, congenital
    - tubulointerstitial: postobstruction, recovery phase of ATN, PKD, sickle cell, Sjögren's, amyloid, pregnancy (placental vasopressinase)
  - DI usually presents as severe polyuria and mild hypernatremia

Other (U_{osm} >700–800)

- Na overload: hypertonic saline (eg, resuscitation w/ $NaHCO_3$), mineralocorticoid excess
- Seizures, ↑ exercise: ↑ intracellular osmoles → H_2O shifts → transient ↑ $[Na]_{serum}$

Treatment (*NEJM* 2015;372:55)

- Restore access to H_2O or supply daily requirement of H_2O (≥1 L/d)

- Replace free H_2O deficit (also replace concurrent volume deficit if appropriate):

$$\textbf{Free } H_2O \textbf{ deficit (L)} = \frac{[Na]_{serum} - 140}{140} \times TBW$$

TBW = wt (kg) × 0.6 (♂) or 0.5 (♀); if elderly use 0.5 (♂) or 0.45 (♀)

shortcut: for typical 70-kg man, free H_2O deficit (L) ~$([Na]_{serum} - 140)/3$

$$\Delta\,[Na]_{serum} \text{ per L infusate} = \frac{[Na]_{serum} - [Na]_{infusate}}{TBW + 1}$$

  eg, 1 L D_5W given to 70-kg man w/ [Na] = 160 mEq/L will ↓ $[Na]_{serum}$ by 3.7 mEq
  nb, do not forget to correct Na if hyperglycemia also present
- Rate of correction depends on acuity of onset and risk:
  chronic (>48 hr): ~12 mEq/d appears safe w/o risk of cerebral edema (*CJASN* 2019;14:656)
  acute (<48 hr): may ↓ Na by 2 mEq/L/h until Na 145
  hyperacute (min-hrs) & life threatening (ICH, seizure): rapidly infuse D_5W ± emergent HD
- *Estimate:* in 70-kg man, 125 mL/h of free H_2O will ↓ [Na] by ~0.5 mEq/L/h
- ½ NS (77 mEq/L) or ¼ NS (38 mEq/L) provides both volume & free H_2O (500 or 750 mL of free H_2O per L, respectively); can give free H_2O via NGT/OGT
- Formulas provide only estimates; ∴ recheck serum Na frequently
- DI and osmotic diuresis: see "Polyuria" section below
- Na overload: D_5W + diuretic. Consider HD if life threatening (ICH, hypertonia, seizures).

POLYURIA

Definition and pathophysiology

- Polyuria defined as >3 L UOP per day
- Due to an *osmotic* or a *water diuresis;* almost always due to osmotic diuresis in inpatients

Workup

- Perform a timed urine collection (6 h sufficient) and measure U_{osm}
- 24-h osmole excretion rate = 24-h UOP (actual or estimate) × U_{osm}
  >1000 mOsm/d → osmotic diuresis; <800 mOsm/d → water diuresis

Osmotic diuresis

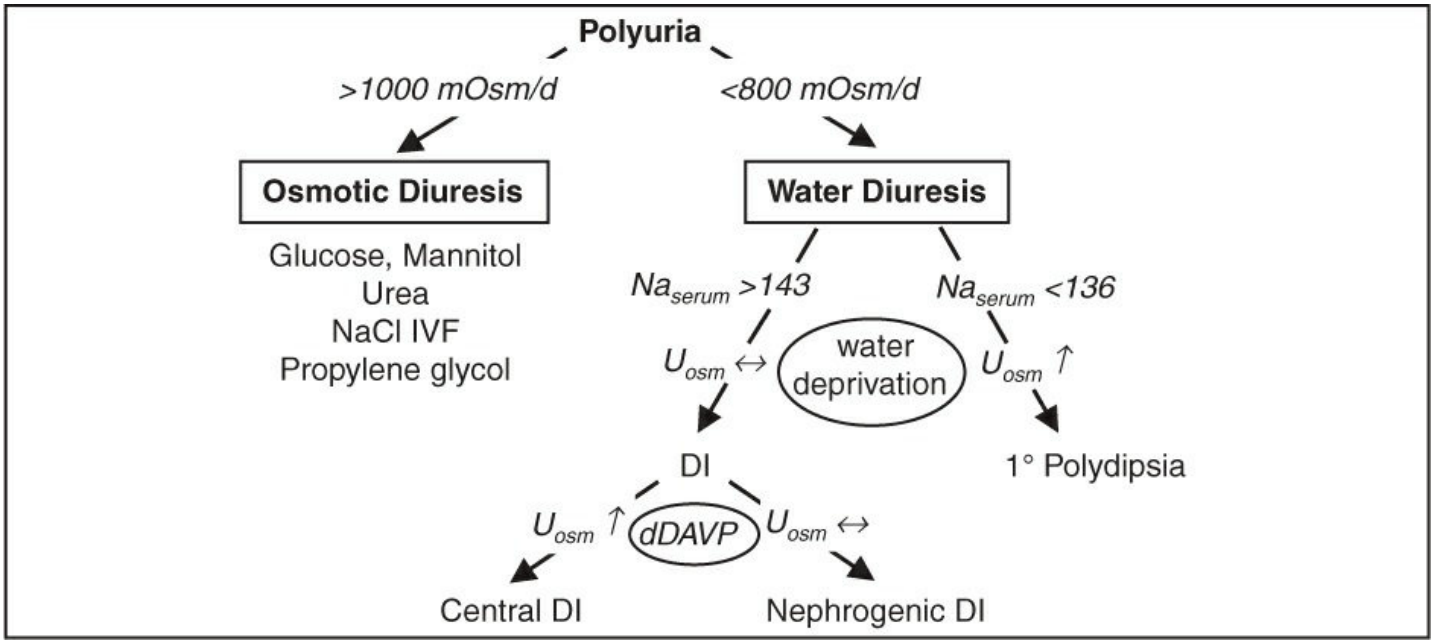
- Etiologies
  Hyperglycemia (>180 exceeds PCT reabsorption), mannitol, propylene glycol
  Na: NaCl IVF, recovering AKI (eg, post obstruction)
  Urea: ↑ protein feeds, hypercatabolism (burns, steroids), GI bleed, resolving azotemia

Water diuresis

- Etiologies: diabetes insipidus (DI) (Na_{serum} >143) or 1° polydipsia (Na_{serum} <136)
  see "Hypernatremia" above for list of causes of central and nephrogenic DI

- Workup of DI: U_{osm} <300 (complete) or 300–600 (partial)
  water deprivation test (start in a.m., ✔ Na_{serum}, P_{osm}, U_{osm}, UOP q1–2h)
  Deprive until P_{osm} >295, then ✔ U_{osm}. If U_{osm} <300, then administer vasopressin (5 U SC) or dDAVP (10 mg intranasal), then check U_{osm} in 1–2 h: U_{osm} ↑ by >50% = central DI U_{osm} unchanged = nephrogenic DI
  ✔ADH level before and after water deprivation to evaluate proper response
  Hypertonic saline-stimulated plasma copeptin >4.9 $p_{moL/L}$ indicates 1° polydipsia (97% accuracy vs. 77% for water deprivation; *NEJM* 2018;379:428)

Figure 4-6 Approach to polyuria



Treatment

- 1° polydipsia: treat psychiatric illness, check meds, restrict access to free H_2O
- Osmotic diuresis: address underlying cause, replace free H_2O deficit (see "Hypernatremia" for formula to calculate) and ongoing losses
- DI:
  Central DI: desmopressin (dDAVP, 1st line), low Na/protein diet + HCTZ, chlorpropamide
  Nephrogenic DI: treat underlying cause if possible; Na restriction + HCTZ (mild volume depletion → ↓ delivery of filtrate for free H_2O absorption), consider amiloride for Li-induced DI (*Kid Int* 2009;76:44), indomethacin (*NEJM* 1991;324:850) or trial desmopression
  Pregnancy-induced DI: due to vasopressinase from placenta, ∴ Rx w/ dDAVP

POTASSIUM HOMEOSTASIS

Overview (*NEJM* 2015;373:60)

- Renal: K excretion regulated at distal nephron (CCD) by principal & α-intercalated cells
  - Distal Na delivery & urine flow: Na absorption → lumen electronegative → K secretion
  - Metabolic alkalemia and aldosterone: increase Na absorption and K secretion
  - nb, diurnal urinary K excretion (day > night), ∴ 24-h sample preferred over spot
- Transcellular shifts: most common cause of acute Δ in serum K (98% intracellular)
  - Acid-base disturbance: K^+/H^+ exchange across cell membranes
  - Insulin → stimulates Na-K ATPase → hypokalemia (mitigates postprandial ↑ K)
  - Catecholamines → stimulate Na-K ATPase → hypokalemia; reversed by β-blockers
  - Massive necrosis (eg, tumor lysis, rhabdo, ischemic bowel) → release of intracellular K
  - Hypo- or hyperkalemic periodic paralysis: rare disorders due to channel mutations
- Diet: alone rarely causes ↑ or ↓ K (total body store ~3500 mEq, daily intake ~100 mEq)

HYPOKALEMIA

Transcellular shifts ($U_{K:Cr}$ <13 mEq/g)

- Alkalemia, insulin, catecholamines, β_2-agonists, hypothermia, hypokalemic/thyrotoxic periodic paralysis, acute ↑ hematopoiesis (megaloblastic anemia Rx w/ B_{12}, AML crisis), chloroquine; overdose: Ba/Cs, antipsychotics (risperidone, quetiapine), theophylline

GI potassium losses ($U_{K:Cr}$ <13 mEq/g)

- GI losses *plus* metabolic acidosis: diarrhea, laxative abuse, villous adenoma
- Vomiting & NGT drainage usually manifest as *renal losses* due to 2° hyperaldo & met. alk.

Renal potassium losses ($U_{K:Cr}$ >13 mEq/g)

- Hypotensive or normotensive
  - acidosis: DKA, RTA [proximal RTA (type II) and some distal RTAs (type I)]
  - alkalosis: diuretics (thiazide > loop), vomiting/NGT drainage (via 2° hyperaldosteronism)
    - Bartter's syndrome (loop of Henle dysfxn→ furosemide-like effect; *JASN* 2017;28:2540)
    - Gitelman's syndrome (DCT dysfxn→ thiazide-like effect (*KI* 2017;91:24)
  - drugs: ↑↑ acetaminophen & PCN, gent., amphotericin, foscarnet, cisplatin, ifosfamide
  - ↓ Mg: less Mg to inhibit principal cell ROMK channel, ∴ ↑ K secretion (*JASN* 2010;21:2109)
- Hypertensive: mineralocorticoid excess

1° hyperaldosteronism (eg, Conn's syndrome, glucocorticoid-remediable aldosteronism)
2° hyperaldosteronism (eg, renovascular disease, renin-secreting tumor)
Nonaldosterone mineralocorticoid (eg, Cushing's, Liddle's [↑ ENaC], exogenous, licorice)

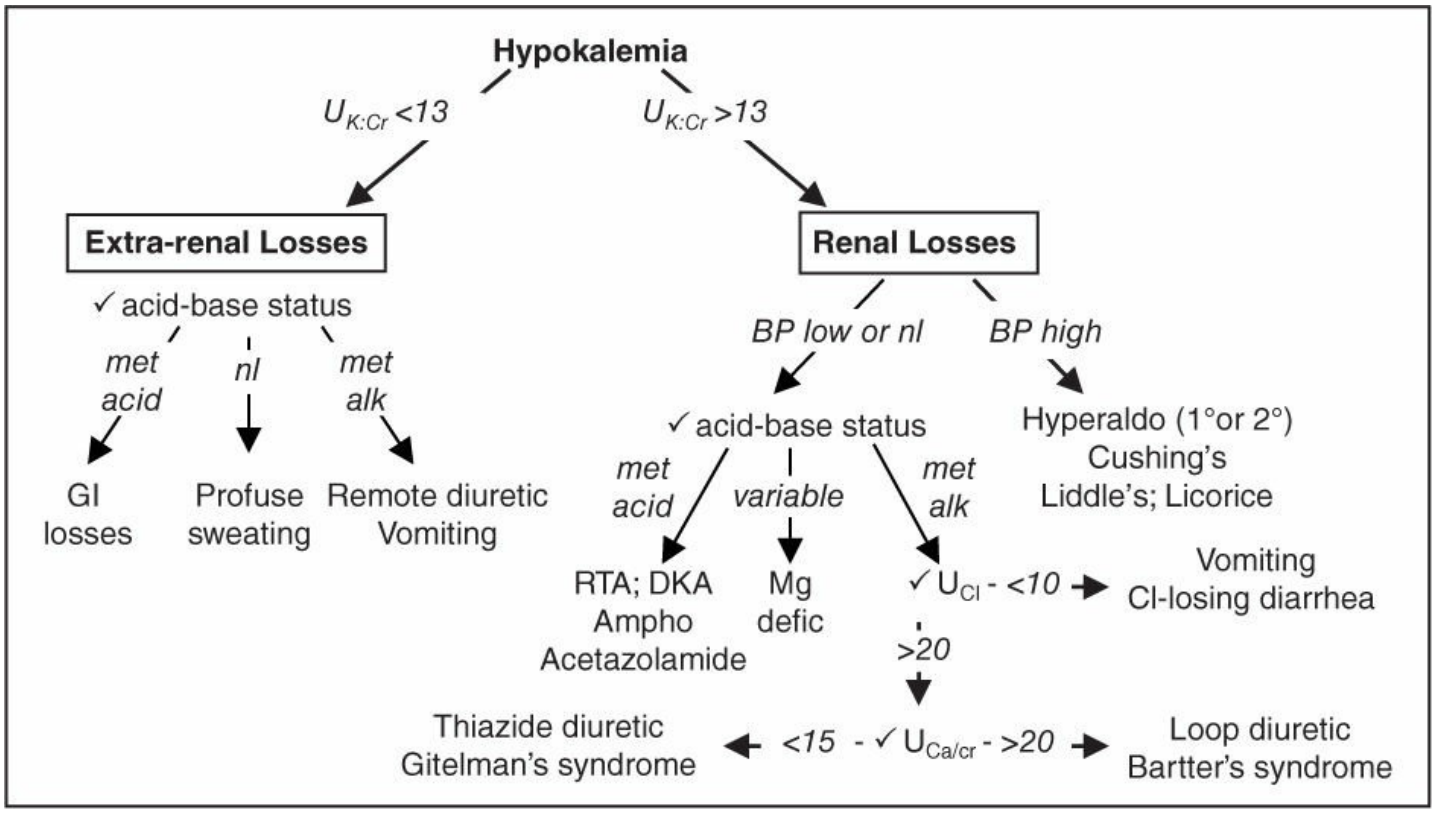
Clinical manifestations

- Nausea, vomiting, ileus, weakness, muscle cramps, rhabdomyolysis, ↓ insulin secretion
- Renal: ammoniagenesis, phosphaturia, hypocitraturia, NaCl & HCO_3 retention, polyuria
- ECG: may see U waves, ↑ QT, flat Tw, ST depression, ventricular ectopy (PVCs, VT, VF)

Workup (*Nat Rev Nephrol* 2011;7:75)

- Identify transcellular shifts & treat. TTKG validity questioned (*Curr Op Nephro* 2011;20:547).
- ✔ $U_{K:Cr}$: >13 mEq/g → renal loss; <13 mEq/g → extrarenal loss (*Archives* 2004;164:1561)
- If renal losses, ✔ BP, acid-base, U_{Cl} (U_{Na} unreliable), $U_{Ca/Cr}$, renin, aldosterone, cortisol

Figure 4-7 Approach to hypokalemia



Treatment (*JAMA* 2000;160:2429)

- *If true potassium deficit:* potassium repletion (↓ 1 mEq/L ≈ 200 mEq total body loss)
  Dosage: 40 mEq PO q4h, 10 mEq/h (IV), 20 mEq/h (central line), 40 mEq in 1L IVF
- Replete K^+ to >3 or >4 mEq/L if high-risk (HTN, CHF, arrhythmias, MI, digoxin, cirrhosis)
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Treat underlying cause (if ↓ vol: avoid dextrose as ↑ insulin → intracellular potassium shifts)

- Consider Rx that ↓ K loss: ACEI/ARB, K^+-sparing diuretics, βB
- Replete Mg if <2 mEq/L: IV Mg-SO_4 1–2 g q2h (oral Mg-oxide poorly tolerated b/c diarrhea)

  Causes of low Mg: GI loss (diarrhea, bypass, pancreatitis, malnutrition, PPI); renal loss (diuretics, nephrotoxic drugs, EtOH, ↑ Ca, 1° wasting syndromes, volume expansion)

HYPERKALEMIA

Transcellular shifts (*BMJ* 2009;339:1019)

- Acidemia, ↓ insulin (DM), cell lysis (tumor, rhabdo, ischemic bowel, hemolysis, transfusions, resorbing hematomas, hyperthermia, rewarming), hyperkalemic periodic paralysis, ↑ osmolality. Drugs: succinylcholine, aminocaproic acid, digoxin, β-blockers.

Decreased GFR

- Any cause of oliguric or anuric AKI or any cause of end-stage renal disease

Normal GFR but with ↓ renal K excretion

- Normal aldosterone function

  ↓ EAV (K excretion limited by ↓ distal Na delivery & urine flow): CHF, cirrhosis

  Excessive K intake: in conjunction with impairment in K excretion or transcellular shift

  Ureterojejunostomy (absorption of urinary K in jejunum)
- Hypoaldosteronism: same as etiologies of hypoaldo RTA (type IV)

  ↓ renin: DM, NSAIDs, chronic interstitial nephritis, HIV, multiple myeloma, Gordon's

  Normal renin, ↓ aldo synthesis: 1° adrenal disorders, ACEI, ARBs, heparin, ketoconazole

  ↓ response to aldosterone Meds: K-sparing diuretics, TMP-SMX, pentamidine, calcineurin inhibitors Tubulointerstitial disease: sickle cell, SLE, amyloid, diabetes

Clinical manifestations

- Weakness, nausea, paresthesias, palpitations; Renal: ↓ NH_4^+ secretion → acidosis
- ECG: ST depression, peaked T waves, ↓ QT, ↑ PR interval, ↑ QRS width, loss of P wave, sine wave pattern, PEA/VF (ECG: low sens., cardiac arrest can be first manifestation!)

Workup (*Crit Care Med* 2008;36:3246)

- Rule out pseudohyperkalemia (IVF w/ K, tourniquet, hemolysis, ↑ plt or WBC), rule out transcellular shift
- Assess GFR, if normal, then ✔U_K, U_{Na} (<25 mEq/d ↓ distal Na delivery). ✔ $U_{K:Cr}$ (<13 favors ↓ renal K excretion).

Treatment of Hyperkalemia			
Intervention	**Dose**	**Onset**	**Comment**
Ca gluconate **Ca chloride**[a]	1–2 amps IV	<3 min	Transient effect (30–60 min) Stabilizes cell membrane
Insulin	reg insulin 5-10 U IV + 1–2 amps $D_{50}W$	15–30 min	Peak 30-60 min, lasts 4–6 h ↓ K 0.5–1.2 mEq/L
Bicarbonate (esp. if acidemic)	1–2 amps IV 150 mEq in 1L D5W	15–30 min	Exchange K for H^+ in cells Lasts 5–6 h; ↓ K 0.7 mEq/L
β2 agonists	albuterol 10–20 mg inh. or 0.5 mg IV	30–90 min	Peak 90 min, lasts 2–6 h ↓ K 0.5–1.4 mEq/L (IV >inh)
K-binding resins	SPS[b] 15–60g PO/PR patiromer 8.4–25.2 g/d PO Na zirconium 5–10 g PO	4-24 hrs hrs-d hrs	Exchange K for cations in gut (Na, Ca, H); ↓ K 0.8–1 mEq/L/d. Edema & HTN w/ Na zirconium.
Diuretics	furosemide ≥40 mg IV	30 min	↓ total body K
Hemodialysis	Most rapid in 1st hr (1 mEq/L)		↓ total body K (*JASN* 2017;28:3441)

[a]CaCl contains more calcium and is typically reserved for codes (↑ risk of tissue necrosis) or via central line

[b]~0.4% intestinal necrosis esp. postop, ileus, SBO/LBO, bowel disease (UC), renal txp (*Clin Nephro* 2016;85:38)

- *Rate of onset* important to note when establishing a treatment plan
- Stabilize (initial): 10% CaCl (central) or gluconate (IV). ↑ memb. potential → ↓ excitability
- Redistribute: insulin + dextrose (continuous if NPO), HCO_3 (*KI* 1991;41:369), β_2-agonists
- Eliminate: SPS (Kayexalate, *NEJM* 2015;372:211), patiromer (expensive), diuretics (w/ saline if preserved renal fxn), consider emergent HD in life-threatening situations
- Patient information for diet education: http://www.kidney.org/atoz/content/potassium

RENAL FAILURE

ACUTE KIDNEY INJURY (AKI)

Definition (*KDIGO* 2012;2:1)

- Stages in ICU correspond to ↑ hospital mortality and LOS (*Crit Care Med* 2009;37:2552)
  Stage 1: Cr ≥0.3 mg/dL in 2d or ↑ Cr ≥50%, or UOP <0.5 mL/kg/h for ≥6h
  Stage 2: ↑ Cr 2–3x baseline in 7d or UOP <0.5 mL/kg/h for ≥12h
  Stage 3: ↑ 3x baseline in 7d, UOP <0.3 mL/kg/h for ≥24h, anuria ≥ 12h, or Cr >4
- *Cannot* estimate GFR using Cr in setting of AKI or Δ'ing Cr (requires steady state)

Workup (*NEJM* 2014;371:55)

- H&P: meds, contrast, or other nephrotoxins; ↓ PO intake, HoTN, infxn/sepsis; trauma, myalgias; BPH/retention. Search for insult 24–48 hr prior ↑ Cr. VS, vol status, rash.
- Urine evaluation: output, urinalysis, sediment, electrolytes, and osmolality
- Fractional excretion Na (FE_{Na}) = $(U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$; if diuretic, ✔ FE_{UN}= $(U_{UN}/P_{UN})/(U_{Cr}/P_{Cr})$
- Renal U/S or CT: r/o obstruction & cortical atrophy in chronic kidney disease
- Serologies (if indicated): see "Glomerular Disease"
- Renal biopsy (microscopy, IF, and EM): if etiology unclear (esp. if proteinuria/hematuria). Relative contraindic.: SBP>150, ASA/NSAID, anticoag, cirrhosis. DDAVP if GFR <45.

Etiologies and Diagnosis of Acute Kidney Injury (*Lancet* 2012;380:756)		
Etiologies		UA, Sediment, Indices
Prerenal	↓ Effective arterial volume (*NEJM* 2007;357:797) Hypovolemia, ↓ CO (CHF), ↓ oncotic pressure (cirrhosis, nephrotic), vasodilation (sepsis) Δ local renal perfusion: NSAIDs, ACEI/ARB, contrast, calcineurin inhib, HRS, hyperCa Large vessel: RAS (bilateral + ACEI), VTE, dissection, abd compart. synd. (renal vs. compress), vasculitis	Bland Transparent hyaline casts FE_{Na} <1%, BUN/Cr >20 FE_{UN} ≤35%
Intrinsic	Acute tubular necrosis (ATN) *Severe ischemia, sepsis, CIN* (↓ RBF + toxin) *Toxins* Drugs: vanc, AG, cisplatin, foscarnet, HES (starch), IVIG, pentamidine, amphotericin, tenofovir Pigments: Hb, myoglobin (*NEJM* 2009;361:62) Monoclonal: Ig light chains (*Blood* 2010;116:1397) Crystals: UA, ACV, MTX, indinavir, oral $NaPO_4$	Pigmented granular muddy brown casts in ~75% ± RBCs & protein from tubular damage FE_{Na} >2%, BUN/Cr <20 (except pigment, CIN) FE_{UN} >50%
	Acute interstitial nephritis (AIN) *Allergic:* β-lactams, sulfa drugs, NSAIDs, PPIs *Infection:* pyelo, viral, legionella, TB, leptospirosis *Infiltrative:* sarcoid, lymphoma, leukemia *Autoimmune:* Sjögren's, TINU syndrome, IgG4, SLE	WBCs, WBC casts, ± RBCs w/ neg UCx ⊕ urine eos in abx ⊕ lymphs in NSAIDs
	Small-med vessel: chol emboli, PAN, TMAs (TTP, HUS, atypical HUS,	± RBCs

	DIC, preeclampsia, APS, malignant HTN, scleroderma renal crisis)	⊕ urine eos in chol emboli
	Glomerulonephritis (see "Glomerular Disease")	Dysmorphic RBCs, RBC casts
Post	Bladder neck: BPH, prostate cancer, neurogenic bladder, anticholinergic meds Ureteral (bilateral or unilateral in single kidney): malig, LAN, retroperitoneal fibrosis, nephrolithiasis	Bland ± non-dysmorphic RBCs, WBC, crystals

General treatment (*CJASN* 2008;3:962)

- Prerenal: isotonic IVF ≈ alb (*NEJM* 2004;350:22). May be benefit to balanced crystalloids (LR) in ICU (*NEJM* 2018;378:829).
- Avoid nephrotoxic insults (meds and contrast); renally dose medications
- Optimize hemodynamics (both MAP & CO) and maintain euvolemia (*NEJM* 2007;357:797)
- *No* benefit to dopamine (*Annals* 2005;142:510), diuretics (*JAMA* 2002;288:2547), or mannitol

Managing complications

- May take 1–3 wk to recover from ATN; anticipate volume overload, ↑ K, ↑ PO_4, acidosis
- Episodes of AKI ↑ risk of CKD progression, even after recovery (*NEJM* 2014;371:58)
- Indications for urgent dialysis (when condition refractory to conventional therapy)
  - Acid-base disturbance: refractory acidemia
  - Electrolyte disorder: hyperK; hyperCa, hyperPO_4, tumor lysis syndrome
  - Intoxications (http://www.extrip-workgroup.org/): Poison Control (1-800-222-1222)
    - Indicated for: methanol, ethylene glycol, metformin, Li, valproic acid, salicylates, barbiturates, theophylline, thallium
    - Consider for: carbamazepine, APAP, dig (Rx Digibind), dabigatran, (Rx idarucizumab)
  - Overload: refractory hypervolemia → hypoxemia (eg, CHF)
  - Uremia: pericarditis, encephalopathy, bleeding
- No mortality benefit to early initiation of RRT (*NEJM* 2016;375:122 & *Jama* 2018;379:1431)

DISEASE-SPECIFIC MANAGEMENT

Acute interstitial nephritis (AIN) (*CJASN* 2017;12:2046)

- Commonly drug-induced: β-lactams, sulfa drugs, NSAIDs, PPIs, quinolones, allopurinol
- If suspected, prompt removal of offending drug; ? early steroids w/in 7d of dx

Cardiorenal syndrome (CRS) (*CJASN* 2017;12:1624)

- Multifactorial pathophys including: 1) ↓ CO, 2) ↑ renal venous congestion, 3) ↑ RAAS
- Bidirectionality: acute CHF → AKI, and oliguric AKI can worsen CHF (*JACC* 2008;52:1527)
- Rx: IV loop diuretics (bypass gut edema; dosing below); no diff. between high vs. low dose and bolus vs. gtt (*NEJM* 2011;364:797). No clinical benefit: dopa, nesiritide, ultrafilt.
- Prognosis: 7% ↑ mortality a/w each 10 mL/min ↓ eGFR in ADHF (*JACC* 2006;47:1987)

Contrast-induced acute kidney injury (CIAKI) (*NEJM* 2019;380:2146)

- Risk factors: CKD, DM, CHF, age, hypotension, ↑ contrast volume (*JACC* 2004;44:1393)
- AKI 24–48 h post contrast, peaks 3–5 d, resolves 7–10 d (consider chol emboli if does not)

- Prevention: consider if eGFR <60 (espec. w/ proteinuria), DM, MI, HoTN (*CJASN* 2013;8:1618)
  - Isotonic IV fluids: data mixed, but may be helpful if high risk (*Int Med* 2014;53:2265; *Lancet* 2017;389:1312). No benefit to $NaHCO_3$ over NaCl (*NEJM* 2018;378:603).
  - Outpatients: 3 mL/kg/h × 1h prior, 1–1.5 mL/kg/h × 6h after (*JAMA* 2004;291:2328)
  - Inpatients: 1 mL/kg/h × 6–12 h pre, intra, post-procedure (*Lancet* 2014;383:1814)
  - Hold ACEI/ARB (*AJKD* 2012;60:576), NSAIDs, diuretics. Min. contrast & use iso-osmolar.
  - No benefit to NAC (*NEJM* 2018;378:603) or preemptive RRT (*Am J Med* 2012;125:66)
- Nephrogenic systemic fibrosis: fibrosis of skin, joints, internal organs ~2–4 wk post gado exposure in CKD 4–5 (*JACC* 2009;53:1621). Postgado HD encouraged, though limited data.

Diabetic nephropathy (*NEJM* 2016;375:2096)

Hepatorenal syndrome (HRS; see "Cirrhosis"; *AJKD* 2013;62:1198)

- Albumin + *either* IV vasopressors (norepi, terlipressin) *or* octreotide & midodrine

Obstructive diseases

- Dx: renal U/S if undifferentiated or CT abd/pelvic (I^-) if suspect nephrolithiasis
- Rx: Foley if urethra vs. perc. nephrostomy if above ureters (eg, stones), tamsulosin/finasteride
- Watch for post-obstructive diuresis after relieving blockage, replace ½ UOP w/ ½ NS.
  - Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly.

Polycystic kidney disease (*NEJM* 2004;350:151; 2008;359:1477; 2017;377:1988)

- Mostly AD *PKD1/PKD2* mutations → renal cysts. PKD1 (85%) younger-onset ESRD.
- Rx: hydration, low-salt diet; tolvaptan reduces GFR decline. Family genetic screening.

Rhabdomyolysis (*NEJM* 2009;361:62)

- Pathophys: myoglobin-induced oxidant injury, vasoconstriction, myoglobin precipitation & pre-renal (extravasation). Can lead to ↓ Ca, ↑ K, and ↑ PO_4.
- Diagnosis: UA ⊕ for heme but 0 RBCs (ie, myoglobinuria)
- Risk of AKI when CK >20,000. Rhabdo and mortality risk score: *JAMA Int Med* 2013;173:1821.
- Aggressive IVF (tailor IVF to target UOP ~3 mL/kg). If urine pH <6.5, consider $NaHCO_3$
  - ✔ K & Ca frequently, trend CK. Monitor for compartment syndrome.

Scleroderma renal crisis (*Nature Neph* 2016;12:678)

- 5–20% diffuse cutaneous SSc w/ narrowing glomerular vessels. Sx: renal failure, severe HTN, encephalopathy. Rx: max ACEi for BP control.

Thrombotic microangiopathies (TMAs): *see "Hematology"*

CHRONIC KIDNEY DISEASE (CKD)

Definition and etiologies (*Lancet* 2012;379:165; *JAMA* 2015;313:837)

- GFR <60 for ≥3 mo *and/or* kidney damage (albuminuria, structural abnormality)
- Prevalence 15% in U.S.

- Albuminuria predicts all-cause & CV mortality, CKD progression (*NEJM* 2004;351:1296)
- Cr poor estimate of GFR, use equation (www.kidney.org/professionals/KDOQI/gfr_calculator.cfm)
  CKD-EPI preferred over MDRD because less likely to underestimate at normal GFRs
  cystatin-C–based formulae perform better than Cr-based (*NEJM* 2012;367:20)
- Etiologies: DM (45%), HTN/RAS (27%), glomerular (10%), interstitial (5%), PKD (2%) (*NEJM* 2008;359:1477; *AJKD* 2019;73:A7), congenital, drugs, myeloma (*JAMA* 2009;302:1179), repeated insults (eg, Mesoamerican nephropathy *AJKD* 2018;72:469)
- Progression to ESRD: kidney failure risk equation (*JAMA* 2016;315:164)

Stages of CKD (*Kid Int* 2013;3[Suppl]:5)		
GFR Stage	GFR mL/min/1.73 m^2	Goals
1 (nl or ↑ GFR)	>90	Dx/Rx of underlying condition & comorbidities, slow progression; cardiovascular risk reduction
2 (mild)	60–89	Estimate progression
3a (mild-mod)	45–59	Evaluate and treat complications
3b (mod-severe)	30–44	Evaluate and treat complications
4 (severe)	15–29	Prepare for renal replacement therapy (RRT)
5 (kidney failure)	<15 or dialysis	Dialysis if uremic/volume overload; Tx
Albuminuria stage based on albuminuria (mg/d) or spot urine alb (mg) to Cr (g) ratio Stages: A1 = <30 (normal/mild); A2 = 30–300 (moderate); A3 = >300 (severe)		

Signs and Symptoms of Uremia (*NEJM* 2018;379:669)	
General	Nausea, anorexia, malaise, uremic fetor, metallic taste, hypothermia
Skin	Uremic frost (white crystals in & on skin), pruritus, calciphylaxis
Neurologic	Encephalopathy (Δ MS, ↓ memory & attention), seizures, neuropathy, impaired sleep, restless leg syndrome
Cardiovascular	Pericarditis, atherosclerosis, HTN, CHF, cardiomyopathy (LVH)
Hematologic	Anemia, bleeding (due to platelet dysfunction and Epo deficiency)
Metabolic	↑ K, ↑ PO_4, acidosis, ↓ Ca, 2° hyperparathyroidism, osteodystrophy

Complications & treatment (KDIGO 2013)

- General: renal referral when GFR <30 or proteinuria, access planning (avoid subclavian lines, preserve an arm by avoiding phlebotomy, BP measurements, IVs)
- CV risk reduction: consider usual preventive Rx including statin, βB, etc.
- Dietary restrictions: Na (if HTN), K (if oliguric or hyperkalemic), PO_4, mod protein.
- Diabetes: strict glc control; SGLT2i slow CKD progression (*NEJM* 2017;377:1765 & 2019;380:2295)
- BP control: goal <130/80, a/w ↓ mortality (*NEJM* 2015;373:2103; *JASN* 2017;28:2812). ACEI or ARB (NEJM 2004;351:1952), not both (*NEJM* 2013;369:1892). For outPts, ✔ Cr & K in 1–2 wk, d/c if Cr ↑ 30% or K >5.4 (after dietary Δ & loop diuretic).
- Metabolic acidosis: sodium bicarbonate or sodium citrate if low HCO_3 (*JASN* 2015;26:515)
- Hyperkalemia: 2-g K diet, see "Potassium Homeostasis"
- Anemia: goal Hb 10–11.5 g/dL, worse outcomes if target higher (*NEJM* 2009;361:2019)
  epoetin (start 80–120 U/kg SC, divided 3×/wk) or darbepoetin (0.75 mg/kg q 2wk)

iron supplementation to keep transferrin sat >20% (often given IV in HD Pts)
- Uremic bleeding: desmopressin (dDAVP) 0.3 μg/kg IV or 3 μg/kg intranasally
- 2° hyperPTH: ↑ PO_4, ↓ Ca, ↓ calcitriol, ↑ FGF-23 → ↑ PTH → renal osteodystrophy

CKD stage	3	4	5
Target PTH (pg/mL)	35–70	70–110	150–600

Phosphorus binders (*take with meals!*) (*NEJM* 2010;362:1312)
Consider sevelamer first, Ca acetate & lanthanum other options. Non-Ca–based binders a/w ↓ mort. compared to Ca-based (*Lancet* 2013;382:1268).
If PTH above goal then start vit. D (if 25-(OH)D <30) or 1,25-(OH)D analogue (calcitriol); stop if ↑ Ca (*AJKD* 2009;53:408)
Cinacalcet (parathyroid Ca-sensing receptor agonist) if ↑ PTH despite phosphorus binders ± vit. D analogue (*CJASN* 2016;11:161); consider parathyroidectomy
- Calciphylaxis (calcific uremic arteriopathy, *NEJM* 2018;378:1704)
Pathophys: calcification of media in dermal small- to med-sized blood vessels & SC fat → ischemia and skin necrosis w/ painful lesions (*NEJM* 2007;356:1049)
Risk factors: ESRD, ♀>♂, DM, vit K def, obesity, warfarin, local trauma, thrombophilias
Dx: skin bx, but limitations (*Kidney Int* 2018;94:390); bone scan used in support of dx
Rx: ↓ risk factors, wound care/surgical debridement, Na thiosulfate (*CJASN* 2013;8:1162), manage hyperPTH, no vit D & Ca, NOACs > warfarin, pain control, palliative care
Prognosis: 60% 1-y mortality in ESRD Pts (*AJKD* 2015;66:133)
- Anticoag: ESRD at ↑ bleed risk; if using DOAC, consider apixiban > rivaroxaban > dabigatran due to protein binding/renal clearance (*JASN* 2017;28:2241)
- Transplant evaluation

DIURESIS

General considerations
- ↑ Na & H_2O excretion for treatment of HTN or edema in CHF, renal failure, and cirrhosis
- Daily wt most effective method of documenting successful diuresis

Loop diuretics (*NEJM* 2017;377:1964)
- Drugs: furosemide (Lasix), torsemide, bumetanide (Bumex), ethacrynic acid
- Mech: inhib NaK2Cl cotransporter in thick ascending limb (ThAL, site of 25% Na reabsorp) → ↓ medullary osmotic gradient & ↓ free H_2O reabsorption via ADH
Transient venodilation may aid in pulmonary congestion (*NEJM 1*973;288:1087)
Response is fxn of amt of drug excreted; ∴ ↑ dose needed in renal insufficiency, CHF
Sigmoidal dose response curve; ∴ ↑ dose until induce diuresis, ↑↑ dose beyond that point yields diminishing returns compared with ↑ frequency of dosing
- Dosing: bioavailability PO furosemide ~50%, PO torsemide & bumetanide ~90%

40 mg IV = 80 mg PO Lasix = 20 mg PO/IV torsemide = 1 mg IV/PO bumetanide
Dose furosemide bid-qid; qd dosing can yield initial diuresis, but then anti-natriuresis. Cont. vs. bolus IV similar in acute CHF (*NEJM* 2011;364:797). Ethacrynic acid if sulfa allergy.
? ↑ diuresis w/ co-administration of albumin if ↓ serum albumin (*Crit Care Med* 2005;33:1681)

- Adverse effects: ↑ Na, ↓ K, ↓ Mg, ↓ Ca, hyperuricemia, ototoxicity, hypersensitivity (sulfa)

Thiazide diuretics (*JASN* 2017;28:3414)

- Drugs: hydrochlorothiazide (HCTZ), chlorothiazide (Diuril), metolazone (Zaroxolyn)
- Mech: inhib Na-Cl cotransporter in the distal convoluted tubule (DCT); 5% Na reabsorp synergistic with loop diuretic, esp. if chronic loop use
  ↓ effect when GFR <30, *except metolazone*, which is still effective in renal insufficiency
- Dosing: give 30 min prior to loop diuretic
- Adverse effects: ↓ Na, ↓ K, ↓ Mg, ↑ Ca, HLD, pancreatitis, ↑ glc, hypersensitivity

K-sparing diuretics (*NEJM* 2017;377:1964)

- Drugs: spironolactone (Aldactone), amiloride, triamterene, eplerenone
- Mech: ↓ Na reabsorption (~1%) in collecting duct (amiloride/triamterene inhibit principal cell Na channel [ENaC]; spironolactone/eplerenone inhibit mineralocorticoid receptor). Relatively weak natriuretic activity, useful in combination with thiazide or in cirrhosis.
- Adverse effects: ↑ K (esp. w/ ACEI), metabolic acidosis, gynecomastia (spironolactone)

Approach to Diuresis (if inadequate diuresis, go to next step)	
Step	Action
1	Loop diuretic PO: ✔ response at 1–3 h, redose at 2× prior dose if needed
2	Add thiazide diuretic PO (potentiates response to loop diuretic)
3	Loop diuretic IV: bolus bid–qid ± thiazide (*may start here if inPt*) ↑ dose w/ ↑ Cr; initial effective IV Lasix dose ≈ 30 × Cr (ie, if Cr = 4 → 120 mg IV)
4	Loop diuretic infusion: bolus + continuous IV infusion ± thiazide (PO or IV)
5	RRT: consider ultrafiltration, CVVH, or HD

Disease state specific regimens

- Renal insufficiency: loop diuretic (↑ dose to achieve effective delivery to ThAL) ± thiazide
- CHF: loop diuretic (↑ frequency over ↑ dose), IV for gut edema + thiazide (watch K & Mg)
- Nephrotic syndrome: urinary albumin binds secreted loop diuretic, use 2–3× normal dose
- Cirrhosis: spironolactone (blocks 2° hyperaldosteronism) + Lasix in 2.5:1 ratio
- Severe metabolic alkalosis: acetazolamide & treat underlying cause

RENAL REPLACEMENT AND DIALYSIS

General

- Acute indications: see “AKI”; choices CVVH vs. HD

- Chronic indications: timing of RRT initiation should factor in Pt QoL, uremic sx, risk of development of urgent/acute indications; modalities PD vs. HD (no clear diff in outcomes)
- Outcomes of ESRD: death from CVD (50%), infxn (30%), withdrawal of care (20%)

Modalities			
	HD	**CVVH**	**PD**
Physiology	Diffusion	Convection	Diffusion
Access	AV fistula/graft or CVC	CVC	Peritoneal catheter
Prescription	Duration, volume goal; K, Na, Ca, HCO_3 in bath, anticoag	Volume goal, K & Ca in replacement fluid (HCO_3 vs. citrate)	PD fluid (dextrose, icodextrin), dwell time, # cycles
Complic.	HoTN, arrhythmia, disequilibrium syndrome* if very high BUN, ↑ CO HF	HoTN, ↓ PO_4, ↓ iCa (citrate toxicity in hepatic dysfxn)	Peritonitis, ↑ glc, ↓ albumin, R pleural effusion

*Disequilibrium syndrome: sx cerebral edema due to H_2O shifts after urea removal

Hemodialysis (HD) (*NEJM* 2010;363:1833)

- Solute removal across *semipermeable* membrane, countercurrent blood & dialysate flow
  Volume removal: Na/H_2O ultrafiltered via transmembrane pressure (TMP) gradient
  Solutes: Cr, urea, K diffuse from blood → dialysate, HCO_3 from dialysate → blood
  Solute removal inversely proportional to size ∴ effective removal of K, urea, Cr, not PO_4
- 6× vs. 3×/wk improved HTN, LV mass, QoL, but ↑ vasc issues (*NEJM* 2010;363:2287); w/ 3×/wk HD, ↑ mortality risk during 2-d interval (Sa–Tu or Fri–Mo) (*NEJM* 2011;365:1099)
- Fever w/ catheter: empiric abx (vanc + GNR coverage qHD). GPC > GNR > mixed/fungal. Remove/replace catheter (depends on organism), "lock" abx (*JASN* 2014;25:2927).
- Central vein stenosis: assoc. with longer HD duration, tunneled catheters. HeRO grafts bypass subclavian stenosis with flow into central vein (*J Vasc Access* 2016;17:138).

Vascular Access		
	Advantages	Disadvantages
AV fistula	Highest patency Lowest risk of bacteremia Lowest mortality (*JASN* 2013;24:465)	Long maturation time (2–6 mo) Primary nonfunction (20%)
AV graft	Easier to create than AVF Maturation time (2–3 wk)	Poor 1° patency, often requiring thrombectomy or angioplasty
Catheter	Immediate use Use as bridge to AVF/AVG	Highest risk of bacteremia ↓ blood flow → ↓ HD efficiency

Continuous veno-venous hemofiltration (CVVH) (*NEJM* 2012;367:26)

- *Hemofiltration* rather than dialysis. Blood under pressure passes down one side *highly permeable* membrane filtering H_2O and solutes via TMP gradient (convective

clearance); filtrate discarded. Replacement fluid infused (solute concentration similar to plasma, except no urea, Cr, PO_4). Fluid balance by adjusting filtrate/replacement fluid.

- Replacement fluid rate determines clearance. Choice of replacement fluid buffer:
  HCO_3 (+ heparin to prevent clotting, although can be run heparin-free)
  citrate: hepatically metabolized to HCO_3, ∴ cannot be given in cirrhosis/liver failure. Provides anticoag w/in machine via Ca chelation. Citrate toxicity: ↓ iCa but nl/ ↑ serum Ca and AG met acidosis.
  Dose adjust for solute and volume removal (*AJKD* 2016;68:645)
- Other CRRT modalities: CVVHD (dialysis), CVVHDF (filtration & dialysis) (*AJKD* 2016;68:645)
- Benefits compared w/ HD: ↓ gross fluid shift (preferred in HoTN), but slower clearance of solutes and toxins

Peritoneal dialysis (PD) (*JAMA* 2017;317:1864)

- Fluid removed via convection using oncotic pressure (eg, dextrose). ↑ concentrations and dwell times removes more fluid (less as glc equilibrates).
- PD fluid: dextrose (1.5%, 2.5%, or 4.25%), buffer (lactate), Na^+, Ca^{2+}, Mg^{2+}
- infuse 10 min, dwell 90 min–5.5 h, drain 20 min; exchanges done manually or using cycler at night (automated or cont. ambulatory peritoneal dialysis APD, CAPD)
- PD peritonitis: abd pain & cloudy drainage (WBC >100 & >50% PMNs). 60–70% GPC, 15– 20% GNR. Rx: abx IV or in PD, catheter removal for certain org (yeast, *Pseudomonas*).
- Sclerosing peritonitis, a rare long-term complication (*NEJM* 2002; 347:737)
- Hyperglycemia: exacerbated by inflammation, long dwell times, and higher [glucose]
- Benefits: lower cost, independence, preservation of residual kidney function. No Δ mortality vs. HD (*AJKD* 2018;71:344).

Kidney transplantation (*Med Clin N Am* 2016;100:435)

- Refer when GFR <20. Contraindic: active malig, infxn, ischemia, noncompl, subst use
- 5-yr survival: living donor 91%; deceased donor 70–84% (*AJKD* 2016;23:281). Donors have minor ↑ risk of ESRD (*Am J Transplant* 2014;14:2434).
- Immunosuppression: calcineurin inhib (tacrolimus>CsA) or CTLA4 inhib (belatacept) (*NEJM* 2016;374:333), antimetabolite (MMF>AZA), prednisone, mTOR inhib (sirolimus) if others contraindicated
- Rejection: Ab (ABMR) or T-cell mediated (TCMR), a/w poor graft survival; BANFF criteria (*Am J Transplant* 2018;18:293). Rx options: ↑ immunosupp., pulse steroids, IVIG, rituximab.
- Late renal dysfxn: usual AKI causes + calcineurin tox, rejection (*NEJM* 2010;363:1451), BK virus, recurrence of 1° disease; usual w/u + immunosupp levels, donor-specific antigen (DSA), BK virus load, U/S, then bx if no other cause (*CJASN* 2008;3:S56; *CJASN* 2011;6:1774)
- ↑ infxn (incl opportunistic such CMV, JC, BK viruses; *CJASN* 2012;7:2058) & cancer (PTLD)
- ↑ CVD risk due to HTN (calcineurin inhib, RAS), DM & dyslipidemia (immunosupp meds)

GLOMERULAR DISEASE

GLOMERULONEPHRITIS (GN)

Definition (*Lancet* 2016;387:2036; *JASN* 2016;27:1278)

- ↑ glomerular inflammation → endothelial & podocyte injury
- Histology: proliferative (↑ cells), sclerosing (scar), necrotizing (areas cell death). Focal (<50% of glomeruli) to diffuse to crescentic. Segmental (<50% tuft) to global (100%).
- Clinically: hematuria w/ dysmorphic RBCs or RBC casts, ± subnephrotic proteinuria often w/ AKI, HTN, edema
- Progression: acute ≈ days; rapidly progressive (RPGN) ~6 wk; chronic ≈ mos; can be asx
- Crescentic GN (pathologic description) ≈ RPGN (clinical description)

ANCA ⊕ Vasculitis (pauci-immune, minimal staining) ~40–45% of total						
Pathogen: infxn, drug (hydral, allopurinol, contam cocaine) (*CJASN* 2017;12:1680)						
Disease	**Gran**	**Renal**	**Pulm**	**Asthma**	**ANCA Type[a]**	**ANCA ⊕**
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic gran with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO (p-ANCA)	50%

[a]Predominant type; p- or c-ANCA can be in all (*NEJM* 2012;367:214); [b]GPA (Wegener's); EGPA (Churg-Strauss)

Anti-GBM Disease (linear staining) <15% of total (*CJASN* 2017;12:1162)			
Disease	**Glomerulonephritis**	**Pulm Hemorrhage**	**Anti-GBM**
Goodpasture's	⊕	⊕	⊕
Anti-GBM disease	⊕	—	⊕

Immune Complex (IC) Disease (granular staining) ~40–45% of total (*CJASN* 2018;13:128)	
Renal-limited Diseases	Systemic Diseases
Infection-related GN (*Staph & Strep;* ↓ C3, ± ASLO)	SLE (*CJASN* 2017;12:825) (⊕ ANA, ⊕ anti-dsDNA, ⊕ anti-Sm, ↓ C3, ↓ C4)
Membranoproliferative GN (MPGN) (↓ C3)	Cryoglobulinemia (⊕ cryocrit, ⊕ RF, ⊕ HCV, SPEP, ↓ C3, ↓ C4)
Fibrillary and immunotactoid GN (normal C3/C4)	Endocarditis (fever, ⊕ BCx, valvular disease, ↓ C3)
IgA nephropathy (normal C3, ±↑ IgA) (*NEJM* 2013;368:2402; *CJASN* 2017;12:677)	Henoch-Schönlein purpura (IgA nephropathy + syst. vasculitis w/ IgA deposits, nl C3, ±↑ IgA)

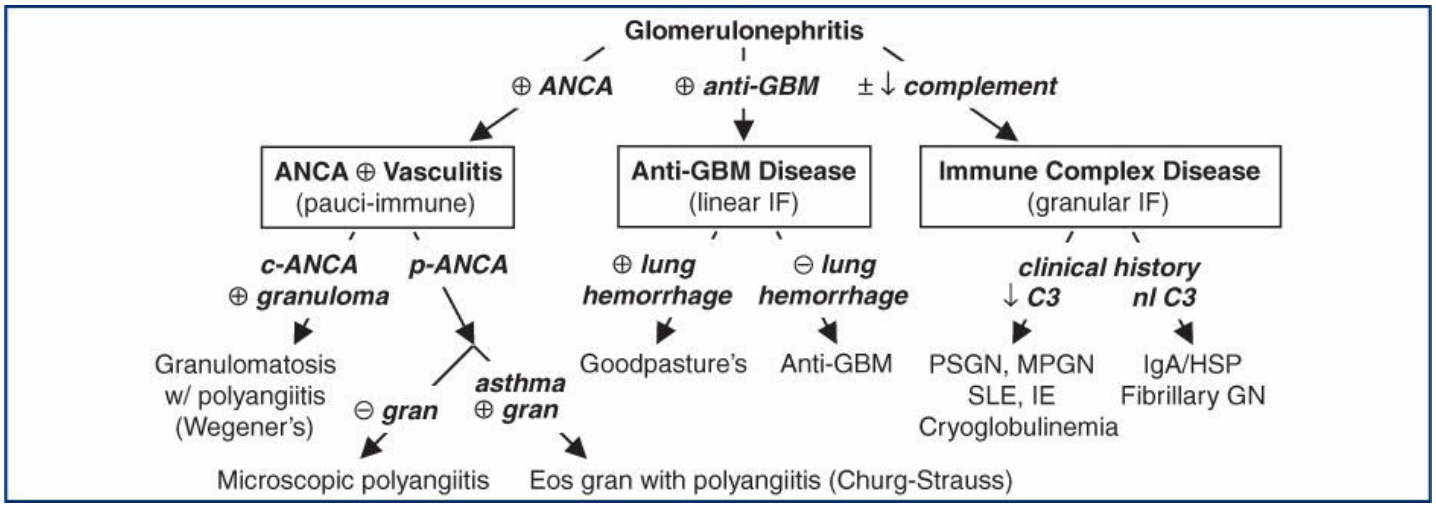
Oncology-related glomerulopathy (*CJASN* 2016;11:1681)

- Associations between malig (solid tumors & heme) and/or their Rx (HSCT & chemotherapeutics) and GN, nephrotic syndrome, and thrombotic microangiopathies (TMA)
- Most common associations: membranous (solid tumors, HSCT), MCD (Hodgkin's, solid tumors), MPGN (CLL, MM), TMA (HSCT, VEGF, anti-EGFR, CNIs, TKIs, mTOR)
- Monoclonal glomerulopathy of renal significance: Ig-mediated kidney disease by nonmalignant B or plasma cells. Workup: SPEP, sFLC, flow cytometry, IFE, BMBx.

Workup (*JAMA* 2017;318:1276)

- *Acute GN/RPGN ± lung hemorrhage is an emergency* → requires early Dx and Rx
- UA + sediment (dysmorphic RBCs) ✔ ANCA, anti-GBM, C3/C4, SPEP, serum FLC
- Depending on hx: ANA, anti-dsDNA/Sm, RF, Hep B&C, HIV, ASLO, BCx, cryocrit, skin bx
- Consider GN mimics: thrombotic microangiopathies (qv), myeloma, AIN, cholesterol emboli
- Renal biopsy with immunofluorescence (IF) ± electron microscopy (EM)

Figure 4-8 Approach to glomerulonephritis based on immunofluorescence pattern



Treatment (*CJASN* 2017;12:1680)

- If acute GN/RPGN suspected, give 500–1000 mg methylpred. IV qd × 3d *ASAP* while awaiting bx results. Consider plasmapheresis & further Rx based on underlying disease.
- SLE nephritis: induction w/ steroids + cyclophosphamide (CYC) or MMF (*CJASN* 2017;12:825)
- ANCA ⊕ or anti-GBM: pulse steroids + CYC (or rituximab). Plasma exchange if severe AKI or pulm hemorrhage (*JASN* 2007;18:2180; *NEJM* 2010;363:221; *AJKD* 2011;57:566).
- See "Vasculitis" for further disease-specific treatment details

ASYMPTOMATIC GLOMERULAR HEMATURIA

Definition and etiologies

- Hematuria ± proteinuria of glomerular origin w/o renal insufficiency or systemic disease (nonglomerular more common; see "Hematuria")

Ddx: any cause of GN (esp. IgA); also consider Alport's (X-linked, deafness, renal failure)

- thin basement membrane nephropathy (autosomal dominant, benign; *JASN* 2013;23:364)

IgA nephropathy (*NEJM* 2013;368:25; *CJASN* 2017;12:677)

- Most common cause of GN; ♂ pred; peak incidence 20–30s; can also be post-infectious
- Wide range of clinical presentations: asx hematuria (30–40%), gross hematuria ~1–3 d after URI (10–15%), chronic GN (10%), nephrotic syndrome (5%), RPGN (<5%)
- Though clinical presentation can be highly suggestive, definitive dx only w/ bx
- Prognosis: ↑Cr, HTN, proteinuria a/w poor prog. (*AJKD* 2012;59:865). 20–40% ESRD w/in 20 y.
- Rx: ACEI/ARB (*JASN* 1999;10:1772); steroids if persistent proteinuria (> 1g/d; *NEJM* 2015;373: 2225); ± cytotoxic Rx for crescentic GN or HTN & ↑ Cr (*JASN* 2012;23:1108); ? fish oil

---

NEPHROTIC SYNDROME

Definition (*JASN* 2014;25:2393)

- Podocyte injury (effacement) → loss of proteins (albumin, ATIII, Ig)
- Clinically: proteinuria >3.5 g/d, albumin <3 g/dL, edema, ↑ chol., VTE (25%), infection

Primary glomerular diseases (grouped by pathology)

- Focal segmental glomerulosclerosis (40%; *CJASN* 2017;12:502): 1° (cytokine mediated); *adaptive* (hyperfiltration, sickle cell, obesity, anabolic steroids, OSA, ↑ protein, vesico-ureteral reflux); *genetic* (*ApoL1* mutation in AA (*JASN* 2015;26:1443); *viral* (HIV most strongly associated); *meds/toxins* (IFN, bisphosphonates, NSAIDs, heroin)
- Membranous nephropathy (30%; *Lancet* 2015;385:1983; *CJASN* 2017;12:938): 1° (Ab to PLA2R [70%] or THSD7A [5%]; *NEJM* 2014;371:2277); *infection* (HBV, HCV, HIV, syphilis); *autoimmune* (eg, SLE); *carcinomas*; *drugs* (NSAIDs, penicillamine)
- Minimal change disease (20%, more common in children; *CJASN* 2017;12:332)
  allergies, NSAIDs, ampicillin, Hodgkin's disease, SLE, DM, MG, celiac disease
- Membranoproliferative GN (5%, *mixed* nephrotic/nephritic features; *CJASN* 2014;9:600)
  Immune complex mediated: infection (esp. HCV ± cryos, IE, HBV, "shunt" nephritis, other chronic infxns), SLE, cryos, Sjögren's, lymphomas, dysproteinemia, idiopathic
  Complement mediated (rare); dense deposit disease (DDD), C3GN
- Fibrillary-immunotactoid glomerulopathy (1%; *JASN* 2008;19:34)
- Mesangial proliferative GN (? atypical forms of MCD/FSGS, 5%) IgM, C1q nephropathy

Systemic diseases with secondary glomerular involvement

- Diabetes mellitus (*CJASN* 2017;12:2032): nodular glomerulosclerosis (Kimmelstiel-Wilson lesion); glomerular hyperfiltration → microalbuminuria → dipstick ⊕ → nephrotic range (10–15 y). Proliferative retinopathy seen in 90% of type 1 and 60% of type 2.
- Amyloidosis: AL or light-chain amyloid or AA amyloid secondary to inflammation
- SLE (*CJASN* 2017;12:825): typically membranous nephropathy (WHO class V)

- Cryoglobulinemia (AJKD 2016;67): a/w HCV, monoclonal gammopathy. Typically MPGN.

Workup (*BMJ* 2008;336:1185)

- U/A + sediment: usually benign; ± oval fat bodies ("Maltese crosses"; *NEJM* 2007;357:806)
- Measure proteinuria: 24-h urine or spot urine protein/Cr ratio (not accurate in AKI), renal bx
- 2° causes: ↑ Hb_{A1C} + retinop. → DM; ✔ ANA, anti-dsDNA, tox screen, C3/C4, SPEP/light chains, fat pad bx, cryocrit, HBV/HCV, HIV, RPR, APLA2R Ab, age-approp. CA screen

Treatment (*NEJM* 2013;368:10)

- General: protein suppl.; diuretics for edema; treat hyperlipidemia, Na restriction (<2 g/d)
- ACEI or ARB: ↓ proteinuria → slow nonimmunologic progression of renal disease
- 1° glomerular: steroids ± cytotoxic therapy (*KI* 2012;2:139; *CJASN* 2014;9:1386)
- Secondary causes: treat underlying disease
- Watch for malnutrition (protein loss), consider anticoag if albumin <2.5 in membranous (*KI* 2014;85:1412), infection (esp. encapsulated organisms b/c loss of Ig)

URINALYSIS

Urine Dipstick	
Metric	Significance and Uses
Specific gravity	Estimate U_{osm}: each 0.001 above 1 ≈ 30 osm (SG 1.010 → U_{osm} ≈ 300) SG and U_{osm} useful in evaluating AKI, dysnatremias, polyuria Heavy substances (glucose, contrast) ↑ SG more than U_{osm}
pH	Range: 4.5–8.5; useful in evaluation of stones, RTAs, infection (urease UTI)
Protein	Detects albuminuria (>300 mg/d); see "Proteinuria". False ⊖: dilute urine
Blood	See "Hematuria"; ⊕ from RBCs, free Hgb, or free myoglobin (eg, rhabdo) False ⊕: semen, dilute urine (→ osmotic cell lysis), ↑ pH, vaginal blood False ⊖: vit C
WBC	Suggests inflammation (UTI, interstitial nephritis, GN)
Ketones	Detects acetoacetate (ie, ketoacidosis) but *not* β-hydroxybutyrate
Leuk est	Lysed PMNs. Sn 80% for UTI. FN: proteinuria, glycosuria FP: ↓ pH or SG
Nitrite	Suggests presence of nitrate reductase ⊕ bacteria (most enteric GNRs)
Bilirubin	↑ in biliary or hepatic disease
Glucose	⊕ in hyperglycemia (>180 mg/dL), pregnancy, Fanconi's syndrome, SGLT2i

Urine Sediment (microscopic examination) (*Am J Kidney Dis* 2008;51:1052)	
Method: Centrifuge fresh sample (prox. port if Foley) × 3–5 min at 1500–3000 rpm; pour off supernatant in one motion; resuspend pellet by agitating base of tube; pour suspension onto slide w/ coverslip; view under "high dry" power; phase contrast for RBC morphology	
Cells	RBCs: assess amount & morphology (many dysmorphic → glomerular) WBCs: PMNs (UTI) vs. eosinophils (AIN; may require special stain) Epithelial cells: tubular (ATN), transitional (bladder or ureters), squamous
Casts *(see urinalysis photo inserts in appendix)*	*Proteins molded in lumen of renal tubule* ± *entrapped cellular elements* RBC → GN WBC → AIN, pyelonephritis, GN Granular ("muddy brown"): degenerating cellular casts → ATN Tubular cell → ATN Hyaline: Tamm-Horsfall protein (nonspecific) Waxy and broad → advanced chronic kidney disease
Crystals *(see urinalysis photo inserts in appendix)*	Calcium oxalate monohydrate: spindle, oval, or dumbbell shaped Calcium oxalate dihydrate: envelope shaped or octahedral Uric acid: variable shape; polychromatic under polarized light Cystine: hexagon shaped Struvite: coffin-lid shaped; seen in chronic UTI with urea-splitting organisms Drugs: sulfa, protease inhibitors: "shocks of wheat"; acyclovir: fine needles

PROTEINURIA

Etiologies of Proteinuria		
Category	Description	Etiologies
Glomerular	Disruption of filtration	Glomerulonephritis

(can be >3.5 g/d)	barrier → lose albumin	Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN; AIN Fanconi's syndrome
Overflow	↑ production of freely filtered proteins	Multiple myeloma Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)

- Urine dipstick
  1+ ≈30 mg/dL, 2+ ≈100 mg/dL, 3+ ≈300 mg/dL, 4+ >2 g/dL; interpretation depends on SG; eg, 3+ in very concentrated urine might not indicate heavy proteinuria
  Insensitive for microalbuminuria and myeloma light chains (Bence-Jones protein)
- Spot urine: protein (mg/dL)/creatinine (mg/dL) ≈ g/d of proteinuria (*NEJM* 1983;309:1543)
  unlike urine dipstick, will accurately measure myeloma light chains
  reliable surrogate for 24-hr urine, esp. 1st morning void (*JASN* 2009;20:436); inaccurate if AKI
  depends on Cr production, ∴ underestimates if muscular, overestimates if cachectic
- Moderate albuminuria (30–300 mg/d *or* mg/L *or* mg/g Cr): early sign of glomerular vascular disease; marker for ↑ risk of CV adverse outcomes (*KI* 2013;3:19)
- Orthostatic proteinuria: typically in adolescents; ~90% of young ♂ with isolated proteinuria have orthostatic proteinuria; typically resolves spontaneously

HEMATURIA

Etiologies of Hematuria	
Extrarenal (far more common)	Intrarenal
Nephrolithiasis Neoplasm: transitional cell, prostate Infxn: cystitis, urethritis, prostatitis Foley trauma BPH Schistosoma haematobium	Nephrolithiasis or crystalluria Neoplasm Trauma/exercise (? extrarenal component) Vascular: renal infarcts, renal vein thromb., sickle cell, ruptured hemangioma Glomerular: IgA, thin BM, others PKD (*NEJM* 2008;359:1477)

- Wide, overlapping ages for various etiologies, but general guide for common causes:
  <20 y: GN, UTI, congenital; 20–60 y: UTI, nephrolithiasis, cancer
  >60 y ♂: prostatitis, cancer, UTI; >60 y ♀: UTI, cancer

Workup (*JAMA* 2017;177:800)

- Urine dipstick: ⊕ if ≥3 RBCs; ⊕ dipstick and ⊖ sediment → myo- or hemoglobinuria
- Urine sediment: dysmorphic RBCs or RBC casts → GN → consider renal bx
- Dx: *CT urography*: r/o nephrolithiasis & neoplasia (Se 96%, Sp 98%); *urine cytology* (Se 70%, Sp 95%); *cystoscopy*: r/o bladder neoplasia, esp if Pt ≥35 y
- Rx: if obstruction: bladder irrigation and 3-way Foley on CBI

NEPHROLITHIASIS

Types of stones and risk factors (*Nat Rev* 2016;2:16008)

- Calcium (Ca oxalate > Ca phosphate): 70–90% of kidney stones (*NEJM* 2010;363:954)
  - Urine findings: ↑ Ca, ↑ oxalate (Ca-ox only), ↑ pH (Ca-phos only), ↓ citrate, ↓ volume
  - 2° hypercalciuria: 1° hyperparathyroidism, distal RTA, sarcoid, Li use
  - 2° hyperoxaluria: Crohn's, ileal disease w/ intact colon, gastric bypass, pancreatic insuffic.
  - Diet: ↑ animal protein, ↑ sucrose, ↑ Na, ↓ K, ↓ fluid, ↓ fruits/vegetables, ↑ vit. C, ↓ Ca
- Uric acid: 5–10% of kidney stones, radiolucent on plain film
  - Urine findings: ↑ uric acid, ↓ pH (eg, from chronic diarrhea)
- Magnesium ammonium phosphate ("struvite" or "triple phosphate")
  - Chronic upper UTI w/ urea-splitting organisms (eg, *Proteus, Klebs*) → ↑ urine NH_3, pH >7
- Cystine: inherited defects of tubular amino acid reabsorption

Clinical manifestations

- Hematuria (absence does not exclude diagnosis), flank pain, N/V, dysuria, frequency
- Ureteral obstruction (stones >5 mm unlikely to pass spont.) → AKI if solitary kidney
- UTI: ↑ risk of infection proximal to stone; urinalysis of distal urine may be normal

Workup (*Urology* 2014;84:533)

- Non-contrast CT 97% Se, 96% Sp (ureteral dilation w/o stone suggests recent passage); U/S (Se 57%, Sp 98%) may serve as initial test in stable patient (*NEJM* 2014;371:1100)
- Strain urine for stone to analyze; U/A & UCx; electrolytes, BUN/Cr, Ca, PO_4, PTH
- 24-h urine × 2 (>6 wk after acute setting) for Ca, PO_4, oxalate, citrate, Na, Cr, pH, K, vol.

Acute treatment (*CJASN* 2016;11:1305)

- Analgesia (narcotics ± NSAIDs; combination superior, *Ann Emerg Med* 2006;48:173), ensure adequate fluid repletion, antibiotics if UTI
- α-blocker > CCB to pass stone if ≤10 mm (Cochrane;2014:CD008509, *Lancet* 2006;368:1171)
- Indications for immediate urologic eval and/or hosp: obstruction (esp. solitary or transplant kidney), urosepsis, intractable pain or vomiting, significant AKI
- Urologic Rx: lithotripsy (*NEJM* 2012:367:50), ureteroscopic removal, lap/perc nephrolithotomy

Chronic treatment (*CJASN* 2016;11:1305 & 2017;12:1699)

- Increase fluid intake (>2 L/d) for goal UOP 2 L/d (*J Nephrol* 2016;29:211)
- Calcium stones: 24-h urine identifies specific urinary risk factors to treat
  - Diet: ↓ Na and meat (*NEJM* 2002;346:77), ↓ oxalate foods & sucrose/fructose
  - Meds: thiazides (↓ urine Ca), K-citrate if low urine citrate, allopurinol if high urine uric acid

Avoid low dietary Ca as ↑ oxalate absorp (*NEJM* 2002;346:77), unclear role of Ca suppl.

- Uric acid: fluid intake, urine alkalinization (K-citrate) to pH 6.5–7, allopurinol
- Magnesium ammonium phosphate (struvite): antibiotics for UTI; urologic intervention; acetohydroxamic acid; urease inhibitor reserved for experienced clinician, poorly tolerated
- Cystine: fluid, urine alkaliniz (K-citrate) to 7–8, D-penicillamine, tiopronin (*KI* 2006;69:1041)

ANEMIA

↓ *in RBC mass: Hct <41% or Hb <13.5 g/dL (men); Hct <36% or Hb <12 g/dL (women)*

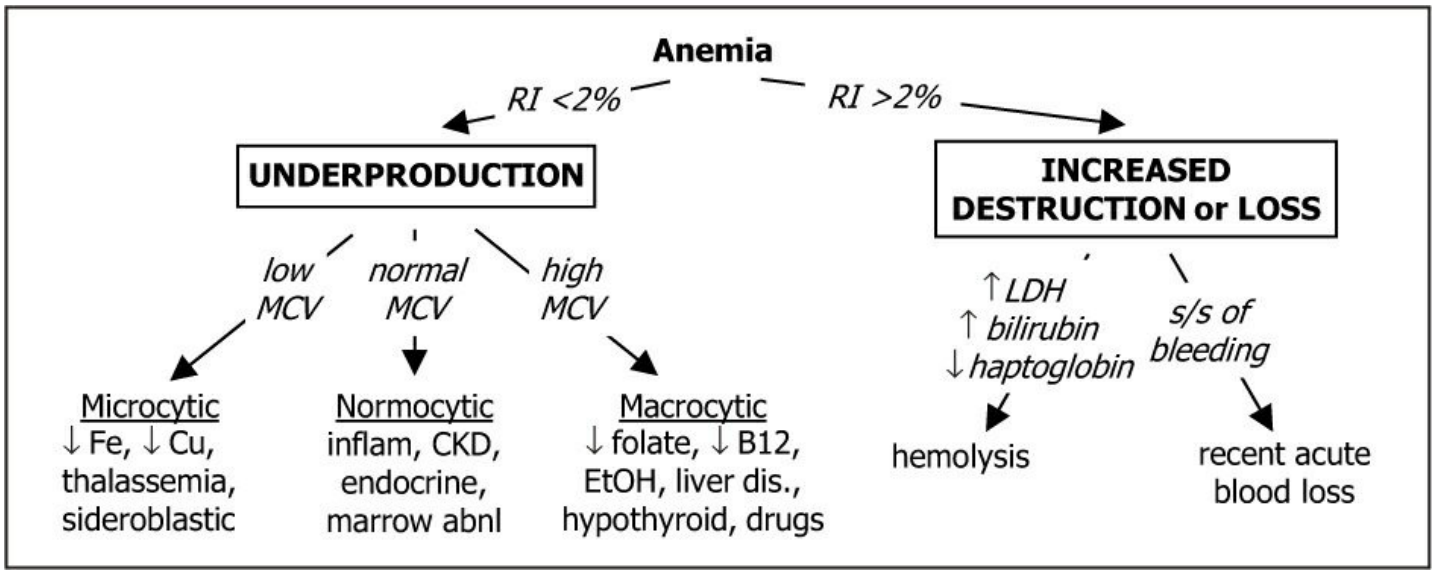
Clinical manifestations

- Symptoms: ↓ O_2 delivery → fatigue, exertional dyspnea, angina (if CAD)
- Signs: pallor (mucous membranes, palmar creases), tachycardia, orthostatic hypotension
- Other findings: jaundice (hemolysis), splenomegaly (thalassemia, neoplasm, chronic hemolysis), petechiae/purpura (bleeding disorder), glossitis (iron, folate, vitamin B_{12} defic.), koilonychia (iron defic.), neurologic abnormalities (B_{12} defic.)

Diagnostic evaluation

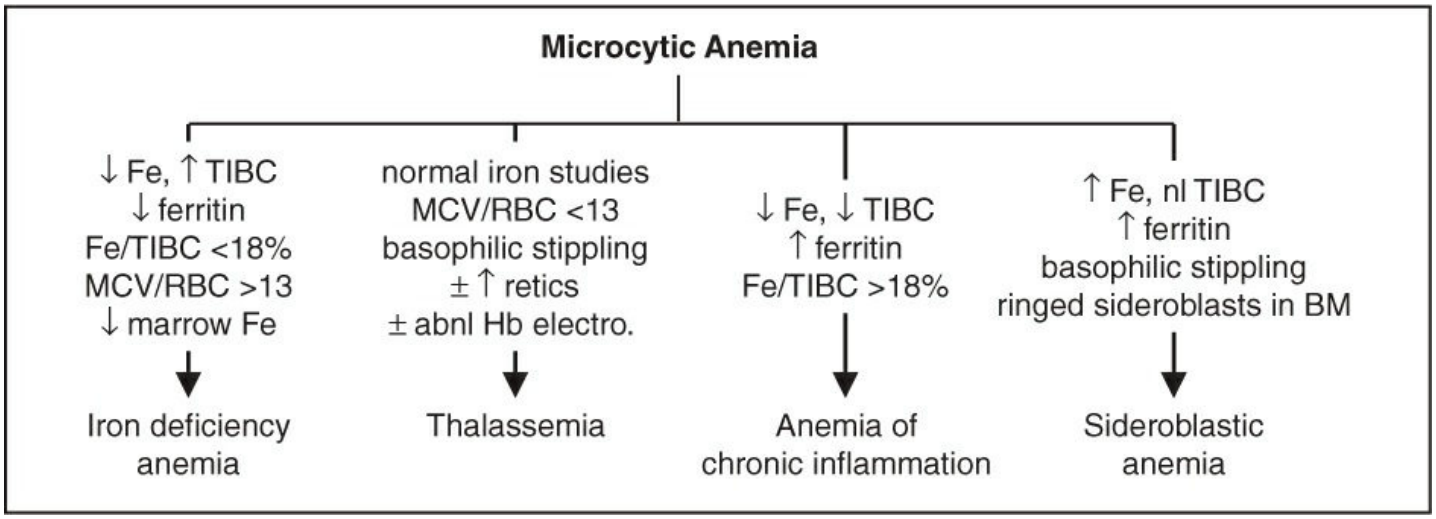
- History: bleeding, systemic illness, drugs, exposures, alcohol, diet (including pica), FHx
- CBC w/ diff.; RBC params incl. retics, MCV (nb, mixed disorder can → nl MCV), RDW
- Reticulocyte index (RI) = [reticulocyte count × (Pt's Hct/nl Hct)]/maturation factor
  maturation factors for a given Hct: 45% = 1, 35% = 1.5, 25% = 2, 20% = 2.5
  RI >2% → adequate marrow response; RI <2% → hypoproliferation
- Peripheral smear: select area where roughly ⅓ RBCs touch each other; ✔ RBC size, shape, inclusions (see "Appendix" & "Peripheral Smear"), WBC morphology, plt count
- Additional labs as indicated: hemolysis labs (if RI >2%, see below), iron/TIBC, ferritin, folate, B_{12}, LFTs, BUN & Cr, TFTs, Hb electrophoresis, enzyme/gene mutation screens
- Bone marrow (BM) aspirate and biopsy (bx) with cytogenetics as indicated

Figure 5-1 Approach to anemia and common causes



MICROCYTIC ANEMIAS

Figure 5-2 Approach to microcytic anemias (*NEJM* 2014;371:1324)



Iron deficiency (*NEJM* 2015;372:1832; *Lancet* 2016;387:907)

- ↓ marrow iron & depleted body iron stores → ↓ heme synthesis → microcytosis → anemia
- Special clinical manifestations: angular cheilosis, atrophic glossitis, pica (consumption of nonnutritive substances such as ice, clay), koilonychia (nail spooning)
  Plummer-Vinson syndrome (iron deficiency anemia, esophageal web & atrophic glossitis)
- Etiologies: chronic bleeding (GI—incl. cancer, menstrual, parasites, NSAIDs, etc.), ↓ supply (malnutrition; ↓ absorp. due to celiac sprue, Crohn's, ↑ gastric pH, subtotal gastrectomy), ↑ demand (preg; *Blood* 2017;129:940). Iron-refractory iron-defic. anemia (IRIDA; rare genetic disorder due to hepcidin dysregulation; *Nat Genet* 2008;40:569).
- Diagnosis (eval ideally before Rx): ↓ Fe, ↑ TIBC, ↓ ferritin (esp. <15), ↓ transferrin sat (Fe/TIBC; esp. <15%), ↑ soluble transferrin receptor; ↑ plt. Unless hx c/w other etiology, *initiate workup for GIB*, incl. *H. pylori* serology. ? Celiac labs (anti-TTG, antigliadin, anti-endomysial Abs). Cytogenetics & molecular testing as indicated.
- Treatment: oral Fe tid (~6 wks to correct anemia; ~6 mo to replete Fe stores; nb, oral Fe does not give ⊕ Hemoccult). In excessive/persistent GI losses or dialysis, cancer, CHF, or prior to Epo Rx, *IV iron* (Fe-sucrose, -gluconate, -dextran) should be considered.

Thalassemias (*Lancet* 2018;391:155)

- ↓ synthesis of α- or β-globin chains of Hb → ≠ subunits → destruction of RBCs and erythroid precursors; ∴ anemia from hemolysis *and* ineffective erythropoiesis
- α-thalassemia (*NEJM* 2014;371:1908): deletions in α-globin gene complex (nl 4 α genes), seen w/ Southeast Asian, Mediterranean, African, Middle East ancestry
  3 α → α-thal-2 trait = silent carrier; 2 α → α-thal-1 trait or α-thal minor = mild anemia
  1 α → HbH (β_4) disease = severe anemia, hemolysis, and splenomegaly
  0 α genes → Hb Barts (γ_4) = intrauterine hypoxia and hydrops fetalis
- β-thalassemia: mutations in β-globin gene → absent or ↓ gene product seen w/ Mediterranean (espec. Greek or Italian), African, or Asian ancestry
  1 mutated β gene → thal minor (or trait) = mild anemia (no transfusions)

2 mutated β genes → thal intermedia (occasional transfusions) or thal major (= Cooley's anemia; transfusion dependent) depending on severity of mutations

- Special clinical manifestations: chipmunk facies, pathologic fractures, hepatosplenomegaly (due to extramedullary hematopoiesis), high-output CHF, bilirubin gallstones, Fe overload
- Dx: MCV <70, normal Fe, ferritin, MCV/RBC count <13 [Mentzer Index, 60% Se, 98% Sp; (*Ann Hem* 2007;86:486)], ± ↑ retics, basophilic stippling; Hb electrophoresis: ↑ HbA_2 ($\alpha_2\delta_2$) in β-thal; *normal* pattern in α-thal trait, ∴ PCR or supravital stain for dx
- Treatment: folate; transfusions + Fe chelator [either deferoxamine (IV) or deferasirox (PO)]; ? splenectomy if ≥50% ↑ in transfusions; consider allo-HSCT in children w/ severe β-thal; gene therapy in development (*NEJM* 2018;378:1479)

Anemia of chronic inflammation (see below)

Sideroblastic anemia

- Defective heme biosynthesis within RBC precursors
- Etiologies: hereditary/X-linked (*ALAS2* mutations), idiopathic, MDS-RARS, reversible (alcohol, lead, isoniazid, chloramphenicol, copper deficiency, hypothermia)
- Special clinical manifestations: hepatosplenomegaly, iron overload syndromes
- Dx: social, work & TB hx; can be micro-, normo-, or macrocytic; variable populations of hypochromic RBCs; ↑ Fe, nl TIBC, ↑ ferritin, basophilic stippling, RBC Pappenheimer bodies (Fe-containing inclusions), ring sideroblasts (w/ iron-laden mitochondria) in BM
- Treatment: treat reversible causes; trial of pyridoxine, supportive transfusions for severe anemia with chelation therapy; high-dose pyridoxine for some hereditary cases

NORMOCYTIC ANEMIAS

Pancytopenia (see below)

Anemia of chronic inflammation (ACI; *NEJM* 2012;366:4)

- ↓ RBC production due to impaired iron utilization and functional iron deficiency from ↑ hepcidin; cytokines (IL-6, TNF-α) cause ↓ Epo responsiveness/production
- Etiologies: autoimmune disorders, chronic infection, inflammation, HIV, malignancy
- Dx: ↓ Fe, ↓ TIBC (usually normal or low transferrin sat), ± ↑ ferritin; usually normochromic, normocytic (~70% of cases) but can be microcytic if prolonged
- Coexisting iron deficiency common. Dx clues include ↓ serum ferritin levels, absence of iron staining on BM bx, ⊕ response to a trial of oral iron and/or ↑ soluble transferrin receptor/ferritin index (*Am J Clin Pathol* 2012;138:642).
- Treatment: treat underlying disease ± iron and/or erythropoiesis-stimulating agent (ESA; eg, Epo). Iron if ferritin <100 or Fe/TIBC <20%. Consider ESA if Epo <500. Avoid ESA in cancer if treatment goal is cure (*Lancet* 2009;373:1532). Transfuse PRBCs only if symptomatic & insufficient time to wait for response to Epo or underlying disease Rx.

Anemias of other chronic disorders

- Anemia of chronic kidney disease: ↓ Epo; treat w/ Epo (see "Chronic Kidney Disease")

- Endocrine deficiencies: hypometabolism and ↓ O_2 demand with thyroid, pituitary, adrenal, parathyroid disease → ↓ Epo; can be normocytic or macrocytic

Sideroblastic anemia (see above)

Pure red cell aplasia

- Destructive antibodies or lymphocytes → ineffective erythropoiesis
- Associated with thymoma, CLL and parvovirus infection, autoimmunity, drugs
- Diagnostic studies: lack of erythroid precursors on BM bx, other lines normal
- Treatment: thymectomy if thymus enlarged; IVIg if parvovirus and immunosuppressed (*Clin Infect Dis* 2013;56:968); immuno-suppression/chemoRx if CLL or idiopathic; supportive care w/ PRBC transfusions; ? erythropoietin receptor agonist if due to antierythropoietin Ab (*NEJM* 2009;361:1848) consider hematopoietic cell transplantation.

MACROCYTIC ANEMIAS

includes megaloblastic and nonmegaloblastic causes

Megaloblastic anemia

- Impaired DNA synthesis → cytoplasm matures faster than nucleus → ineffective erythropoiesis and macrocytosis; due to folate or B_{12} deficiency; also in MDS
- ✔ folate and vitamin B_{12}; ↑ LDH & indirect bilirubin (due to ineffective erythropoiesis)
- Smear: neutrophil hypersegmentation, macro-ovalocytes, anisocytosis, poikilocytosis

Folate deficiency

- Folate present in leafy green vegetables and fruit; total body stores sufficient for 2–3 mo
- Etiologies: malnutrition (alcoholics, anorectics, elderly), ↓ absorption (sprue), impaired metabolism (methotrexate, pyrimethamine, trimethoprim; *NEJM* 2015;373:1649), ↑ requirement (chronic hemolytic anemia, pregnancy, malignancy, dialysis)
- Diagnosis: ↓ folate; ↓ RBC folate, ↑ homocyst. but nl methylmalonic acid (unlike B_{12} defic.)
- Treatment: folate 1–5 mg PO qd for 1–4 mo or until complete hematologic recovery; *critical to r/o B_{12} deficiency first (see below)*

Vitamin B_{12} deficiency (*NEJM* 2013;368:149)

- B_{12} present only in foods of animal origin; total body stores sufficient for 2–3 y
- Binds to intrinsic factor (IF) secreted by gastric parietal cells; absorbed in terminal ileum
- Etiologies: malnutrition (alcoholics, vegans), pernicious anemia (PA, autoimmune disease against gastric parietal cells, a/w polyglandular endocrine insufficiency and ↑ risk of gastric carcinoma), other causes of ↓ absorption (gastrectomy, sprue, Crohn's disease), ↑ competition (intestinal bacterial overgrowth, fish tapeworm)
- Clinical manifestations: neurologic changes (subacute combined degeneration) affecting peripheral nerves, posterior and lateral columns of the spinal cord and cortex → numbness, paresthesias, ↓ vibratory and positional sense, ataxia, dementia
- Dx: ↓ B_{12}; ↑ homocysteine and methylmalonic acid; anti-IF Ab; Schilling test; ↑ gastrin in

PA

- Treatment: 1 mg B_{12} IM qd × 7 d → q wk × 4–8 wk → q month for life
  - neurologic abnormalities are reversible if treated w/in 6 mo
  - folate can reverse *hematologic* abnormalities of B_{12} deficiency but not *neurologic* changes (and can lead to "steal" of B_{12} stores → worsening of neuro complications)
  - oral supplementation (2 mg qd) appears feasible as well (*Cochrane Rev* CD004655) even w/o IF

Nonmegaloblastic macrocytic anemias

- Liver disease: often macrocytic, may see target cells, or spur cell anemia w/ hemolysis
- Alcoholism: BM suppression & macrocytosis independent of folate/B_{12} defic. or cirrhosis
- Reticulocytosis
- Other causes: hypothyroidism; MDS; meds that impair DNA synthesis (zidovudine, 5-FU, hydroxyurea, Ara-C); hereditary orotic aciduria; Lesch-Nyhan syndrome

---

PANCYTOPENIA

Etiologies

- Hypocellular bone marrow (nl cellularity ~100 – age): aplastic anemia, hypoplastic MDS
- Cellular bone marrow: MDS, aleukemic leukemia, PNH, severe megaloblastic anemia
- Marrow replacement (myelophthisis): myelofibrosis, metastatic solid tumors, granulomas
- Systemic diseases: hypersplenism, sepsis, alcohol, toxins

Clinical manifestations

- Anemia → fatigue
- Neutropenia → recurrent infections
- Thrombocytopenia → mucosal bleeding & easy bruisability

Aplastic anemia = stem cell failure (*NEJM* 2015;373:35)

- Epidemiology: 2–5 cases/10^6/y; biphasic (major peak in adolescents, 2nd peak in elderly)
- Diagnosis: pancytopenia w/ ↓ retics, BM bx w/ cytogenetics showing hypocellularity
- Etiologies: idiopathic ($^1/_2$ – $^2/_3$ of cases)
  - Stem cell destruction: radiation, chemotherapy, chemicals (eg, benzene)
  - Idiosyncratic med rxn (eg, chloramphenicol, NSAIDs, sulfa drugs, gold, carbamazepine, antithyroid)
  - Viruses (HHV-6, HIV, EBV, parvovirus B19); post-viral hepatic failure (not Hep A/B/C)
  - Immune disorders (SLE, GVHD post-HSCT, thymoma)
  - PNH (see below); Fanconi's anemia (congenital disorder w/ pancytopenia, macrocytic anemia, ↑ risk of MDS, AML, & SCC of head & neck, and multiple physical anomalies)
  - Shortened telomeres: seen w/ telomerase (*TERT, TERC*) mut. (10% of aplastic anemia), dyskeratosis congenita/DKC1 mut; a/w IPF, cirrhosis (*NEJM* 2009;361:2353)
  - Somatic mutations: PNH clones in ~50% of aplastic anemia (*Haematologica* 2010;95:1075)
- Treatment and prognosis

Allogeneic HSCT: for *young* Pts → ~80% long-term survival and significantly ↓ risk of malignant evolution, but has risk of transplant-related morbidity & mortality; if possible, avoid transfusions (and alloimmunization) pretransplant

Immunosuppression (CsA/tacrolimus, ATG): 70–80% respond, with 80–90% 5-y survival in responders (96% vs. 76% w/ horse vs. rabbit ATG; *NEJM* 2011;365:430); 15–20% 10-y incidence of clonal disorders (mostly MDS, AML, PNH)

TPO mimetics (eg, eltrombopag) use 1st-line w/ immunosuppression (*NEJM* 2017;376:1540)

Supportive care: transfusions, abx, possible utility of G-CSF & Epo (if Epo <500)

Myelodysplastic syndromes (MDS) (qv)

Paroxysmal nocturnal hemoglobinuria (PNH) (*Blood* 2009;113:6522)

- Acquired clonal stem cell disorder = inactivating somatic mutation of *PIG-A* gene → deficiency of GPI-anchor for CD55 & CD59 (inhib of complement) → complement-mediated RBC lysis, plt aggreg., & hypercoagulability
- Clinical: intravascular hemolytic anemia, hypercoagulability (venous > arterial; esp. intraabdominal, cerebral), smooth muscle dystonias, deficient hematopoiesis (cytopenias); a/w aplastic anemia, MDS and evolution to AML
- Dx: flow cytometry (↓ CD55 & CD59) on RBCs and granulocytes; urine hemosiderosis
- Treatment: supportive care (iron, folate, transfusions); consider anticoagulation

  allogeneic HSCT for hypoplasia or severe thrombosis

  eculizumab (Ab inactivates terminal complement C5s): ↓ hemolysis, improves QoL & stabilizes Hb levels (*NEJM* 2004;350:552 & 2006;355:1233; *Lancet* 2009;373:759); effective in pregnancy (*NEJM* 2015;373:1032); must have meningococcal vaccination

Myelophthisic anemia (see also "Primary Myelofibrosis")

- Infiltration of bone marrow by cancer, leukemia, infection, fibrosis (primary myelofibrosis), granulomas, lysosomal storage disorders

---

HEMOLYTIC ANEMIAS

Causes of Hemolytic Anemia by Mechanism (*Lancet* 2000;355:1169 & 1260)

Location	Mechanism	Examples	Mode
Intrinsic	Enzyme deficiency	*G6PD* deficiency	Hereditary
	Hemoglobinopathies	Sickle cell anemia, thalassemia	
	Membrane abnormalities	Hereditary spherocytosis	
		PNH, spur cell anemia in liver disease	Acquired
Extrinsic	Immune-mediated	Autoimmune; drug-induced, tx rxn	
	Traumatic	MAHA; prostheses (valves, TIPS)	
	Direct infections, toxins	Malaria, babesiosis; snake & spider venoms; Wilson's; hypotonic infusions	
	Entrapment	Hypersplenism	

Diagnostic evaluation

- ↑ reticulocyte count (RI >2%), ↑ LDH, ↓ haptoglobin (83% Se, 96% Sp), ↑ indirect bili
- Autoimmune hemolysis: Coombs' test = direct antiglobulin test (DAT) → ⊕ if agglutination occurs when antisera against Ig or C3 are applied to patient RBCs
- Intravascular: ↑↑ LDH, ↓↓ haptoglobin; hemoglobinemia, hemoglobinuria, hemosiderinuria
- Extravascular: splenomegaly
- Family h/o anemia; personal or family h/o cholelithiasis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (*Lancet* 2008;371:64)

- X-linked defect of metabolism (*G6PD* mutations) w/ ↑ susceptibility to oxidative damage
- Most common in ♂ of African or Mediterranean descent (malaria-endemic areas)
- Hemolysis precipitated by drugs (sulfonamides, dapsone, nitrofurantoin, rasburicase, primaquine, doxorubicin, methylene blue), infxn, DKA, foods (favism, *NEJM* 2018;378:60)
- Diagnosis: smear may show RBC Heinz bodies (oxidized Hb) that result in bite cells once removed by spleen; ↓ G6PD levels (*may be normal after acute hemolysis* because older RBCs have already lysed and young RBCs may still have near-normal levels)

Sickle cell anemia (*NEJM* 2017;376:1561 & *Lancet* 2017;390:311)

- Recessive β-globin mutation → structurally abnl hemoglobin (HbS). ~8% African Americans heterozygotes ("sickle trait"; usually w/o sx); ~1/400 homozygotes (sickle cell disease).
- ↓ O_2 → HbS polymerizes → RBC sickles, ↓ RBC deformability → hemolysis & microvascular occlusion due to endothelial activ. & PMN adhesion (*Blood* 2013;122:3892)
- Anemia: chronic hemolysis ± acute aplastic (parvo. B19) or splenic sequestration crises
- Vaso-occlusion & infarction: acute chest syndrome & stroke (high mortality), pulmonary HTN, painful crises, splenic sequestration, renal papillary necrosis, aseptic necrosis, dactylitis (hand-foot syndrome), priapism
- Infection: splenic infarction → overwhelming infection by encapsulated organisms; infarcted bone → osteomyelitis (*Salmonella*, *Staph. aureus*), can be life threatening
- Diagnosis: sickle-shaped RBCs and Howell-Jolly bodies on smear; Hb electrophoresis
- Treatment: hydroxyurea, folic acid; ? L-glutamine to prevent pain crises (*NEJM* 2018;379:226)
- Vaccines: pneumo, meningo, H flu, HBV
- Voxelotor (Hbs polymerization inhib) ↑ hemolysis to ↑ Hb (*NEJM* 2019;epub)
- Pain & vaso-occlusive crises: analgesia (consider PCA), IVF, transfusion if sx & Hgb < baseline; crizanlizumab (anti-P-selectin; *NEJM* 2017;376:429)
- Acute chest: O_2, abx, IVF, exchange transfusion
- TIA/stroke: often exchange transfusion (goal Hgb 10) ± thrombolytics
- Gene therapy in development (*NEJM* 2017;376:848)

Hereditary spherocytosis (HS) (*Lancet* 2008;372:1411)

- Defect in a cytoskeletal protein of RBC membrane → membrane loss mutations in ankyrin, α- and β-spectrin, band 3, and pallidin have been identified
- Most common in N. European populations (1/5000 births); ⊕ FHx (75% of Pts)

- Anemia, jaundice (mostly neonates), splenomegaly, pigmented gallstones
- Diagnosis: spherocytes on smear, ⊕ osmotic fragility test (~80% Se), ↓ eosin-5-maleimide (EMA) binding (93% Se; 99% Sp; *Haemat* 2012;97:516), acidified glycerol lysis test (Se 95%)
- Treatment: folate, transfusions, splenectomy for moderate and severe HS (balance w/ ↑ risk of future thrombosis and infection; *J Thromb Haemost* 2008;6:1289)

Paroxysmal nocturnal hemoglobinuria (see above)

Autoimmune hemolytic anemia (AIHA)

- Acquired, antibody-mediated RBC destruction
- Warm AIHA: IgG Abs opsonize RBCs *at body temp* → removal by spleen
  Etiologies: idiopathic, lymphoproliferative (CLL, NHL), autoimmune (SLE), drugs, HIV, Babesiosis (*NEJM* 2017;376:939)
- Cold AIHA: IgM Ab binds to RBCs *at temp <37°C* → complement fixation → intravascular hemolysis and acrocyanosis on exposure to cold
  Etiologies: idiopathic, lymphoprolif. disorders (eg, Waldenström's; monoclonal), *Mycoplasma pneumoniae* infxn and infectious mononucleosis (polyclonal)
- Diagnosis: spherocytes on smear, ⊕ Coombs'; ✔ cold agglutinin titer, splenomegaly
- Treatment (*Blood* 2017;129:2971): treat underlying disease
  Warm AIHA: corticosteroids ± splenectomy, IVIg, cytotoxic agents, rituximab
  Cold AIHA: avoid cold; steroids ineffective; rituximab (*Blood* 2004;103:2925)

Drug-induced hemolytic anemia

- Acquired, Ab-mediated, RBC destruction precipitated by a med. Abx: ceph., sulfa drugs, rifampin, ribavirin. CV: methyldopa, procainamide, quinidine, thiazides. TCAs, phenothiazines, NSAIDs, sulfonylureas, MTX, 5-FU, rasburicase (G6PD defic.)
- Diagnosis: Coombs' usually negative, ↑ LDH; Treatment: discontinue offending agent

Microangiopathic hemolytic anemia (*MAHA*; *NEJM* 2014;371:654)

- Intra-arteriolar fibrin damages RBCs → acquired intravascular hemolysis
- Etiologies: hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), malignancy, malignant HTN, eclampsia/HELLP, mech. cardiac valves, infected vascular prostheses
- Diagnosis: schistocytes ± thrombocytopenia ± abnormalities a/w specific disorders (eg, ↑ PT in DIC, ↑ Cr in HUS, ↑ LFTs in HELLP)
- Rx underlying dx; urgent plasma exchange w/ TTP (replace low ADAMTS13)

Hypersplenism

- Stasis/trapping in spleen → Mφ attack & remodeling of RBC → spherocytosis → hemolysis

Causes of Splenomegaly	
Etiology	Comments*
RES hyperplasia	Hemolytic anemia, sickle cell disease, thalassemia major
Immune hyperplasia	Infxn [HIV, EBV, CMV, TB, malaria, kala azar ("black water fever" from visceral leishmaniasis), *Mycobacterium avium* complex], autoimmune disorders (SLE, RA w/ Felty's

	syndrome), sarcoidosis, serum sickness
Congestion	Cirrhosis, CHF, portal/splenic vein thrombosis, schistosomiasis
Infiltration (nonmalignant)	Lysosomal storage disorders (Gaucher's, Niemann-Pick), glycogen storage diseases, histiocytosis X, splenic cysts
Neoplasm	MPN (CML, PMF, PV, ET), CMML, leukemia, lymphoma (NHL, HL, hairy cell leukemia, CLL, PLL, WM), T-LGL, myeloma, amyloid

RES = reticuloendothelial system; *boldface = causes of massive splenomegaly.

DISORDERS OF HEMOSTASIS

Clinical Characteristics of Bleeding Disorders		
Feature	Platelet/vascular Defect	Coagulation Defect
Site	Skin, mucous membranes	Deep in soft tissues (muscles, joints)
Lesions	Petechiae, ecchymoses	Hemarthroses, hematomas
Bleeding	After minor cuts: yes After surgery: immediate, mild	After minor cuts: unusual After surgery: delayed, severe

Figure 5-3 Approach to abnormal hemostasis (*NEJM* 2014;370:847)

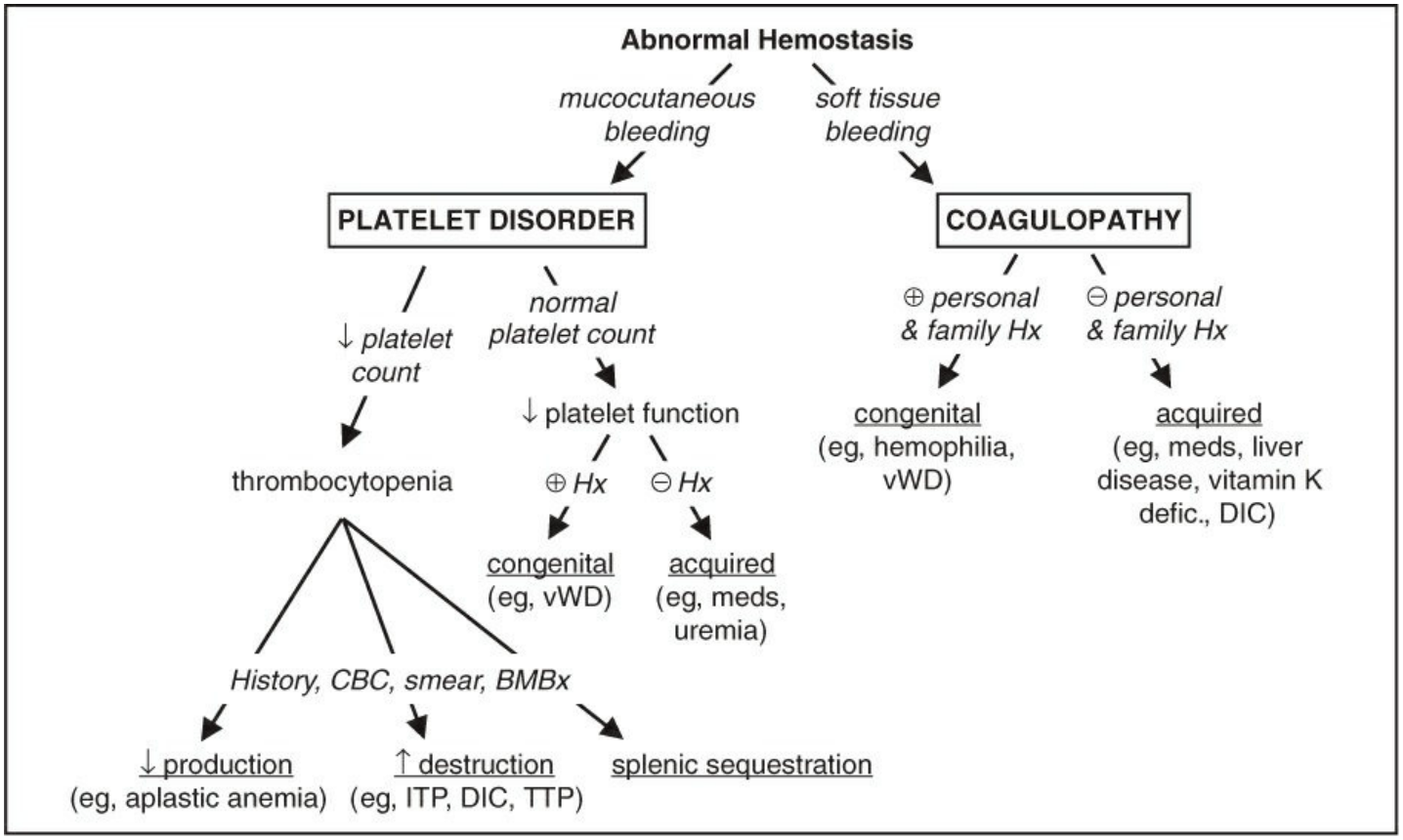
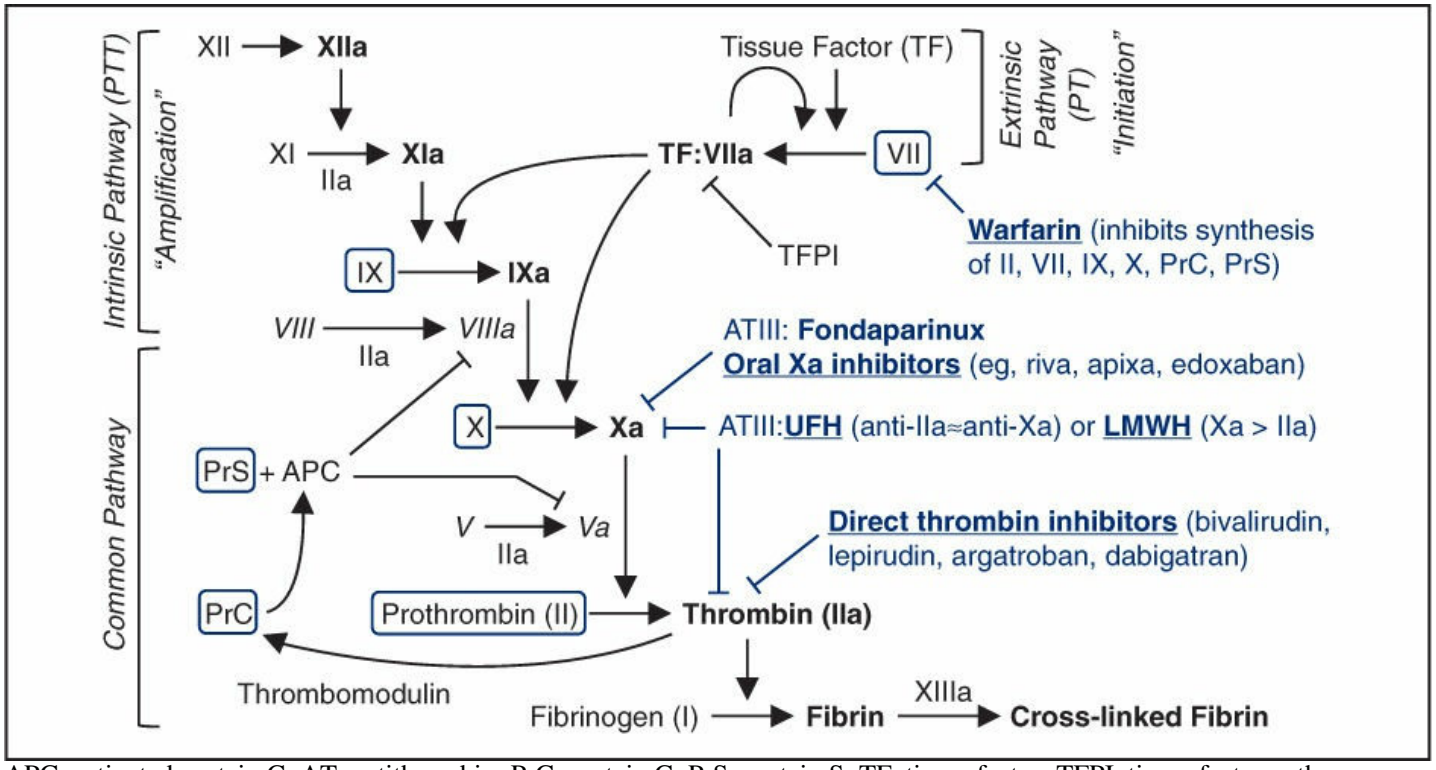


Figure 5-4 Coagulation cascade (*NEJM* 2008;359:938)



APC, activated protein C; AT, antithrombin; PrC, protein C; PrS, protein S; TF, tissue factor; TFPI, tissue factor pathway inhib.

Purpura (*nonblanching* purple/red lesions due to extravasation of RBCs into dermis)

- Nonpalpable (macular; ≤3 mm in diameter = petechiae; >3 mm = ecchymoses)
  platelet disorder: thrombocytopenia, defect in platelet fxn
  thromboemboli: DIC, TTP, cholesterol or fat emboli
  trauma or vascular fragility: amyloidosis, Ehlers-Danlos, scurvy
- Palpable (papular); vasculitis: leukocytoclastic, HSP, PAN, RMSF; infectious emboli: meningococcemia, bacterial endocarditis
- *Purpura fulminans* (aka retiform purpura): purpura + hypotension + DIC; typically due to infxn/sepsis, protein C or S deficiency or APS (see section on DIC)

PLATELET DISORDERS

THROMBOCYTOPENIA (PLT COUNT <150,000/μL)

Thrombocytopenia and Risk of Bleeding	
Platelet Count (cells/μL)	Risk
50,000–100,000	Risk with major trauma; can proceed with general surgery
20,000–50,000	Risk with minor trauma or surgery
<20,000	Risk of *spontaneous* bleeding (less so with ITP)
<10,000	Risk of severe, life-threatening bleeding

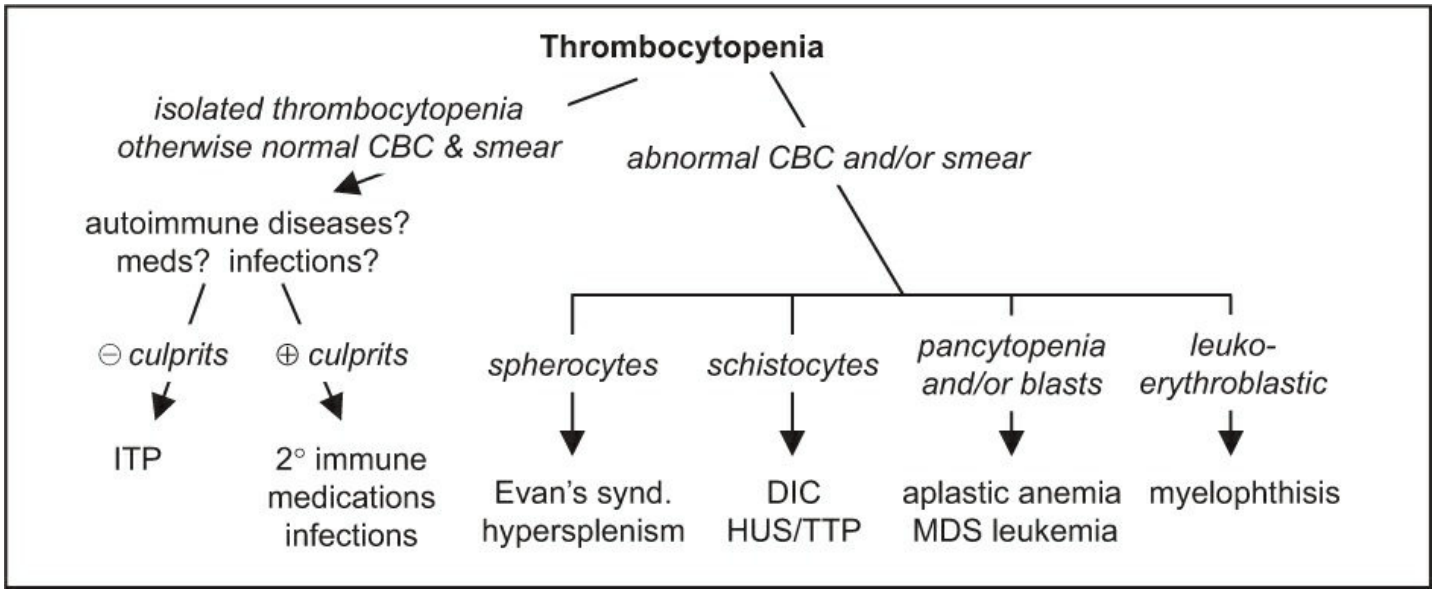
Etiologies

- ↓ production
  - Hypocellular bone marrow: aplastic anemia (qv), rarely MDS, drugs (eg, thiazides, antibiotics, chemotherapy), alcohol, cirrhosis
  - Hypercellular bone marrow: MDS, leukemia, severe megaloblastic anemia
  - Marrow replacement: myelofibrosis, hematologic and solid malignancies, granulomas
- ↑ destruction
  - Immune-mediated (distinguish primary from secondary; *Blood* 2009;113:2386)
    - Primary (idiopathic): immune thrombocytopenic purpura (ITP, see below)
    - Secondary: infxn (HIV, HCV, HSV), collagen vascular diseases (SLE), APS, lymphoproliferative (CLL, lymphoma), drugs (*many*, including heparin, abciximab, quinidine, sulfonamides, vancomycin), alloimmune (posttransfusion)
  - Non–immune-mediated: MAHA (DIC, HUS, TTP), ticlopidine/clopidogrel, vasculitis, preeclampsia/HELLP, cardiopulm bypass, CVVH, IABP, cavernous hemangioma, viral
- Abnormal distribution or pooling: splenic sequestration, dilutional, hypothermia
- Unknown: ehrlichiosis/anaplasmosis, babesiosis, RMSF

Diagnostic evaluation

- H&P: meds, infxns, underlying conditions, splenomegaly, lymph nodes, bleeding hx
- CBC with differential: isolated thrombocytopenia *vs.* multilineage involvement
- Peripheral smear (r/o pseudothrombocytopenia due to platelet clumping)
  - ↑ destruction → look for large plts, schistocytes (see "Peripheral Smear" inserts)
  - ↓ production → rarely limited to platelets → look for blasts, hypersegmented PMNs, leukoerythroblastic Δs; can see inclusion bodies (anaplasma), parasites (*Babesia*)

Figure 5-5 Approach to thrombocytopenia



- Additional laboratory evaluations as indicated (eg, viral titers, flow cytometry, ANA, APLA)
  if anemia: ✔ reticulocyte count, LDH, haptoglobin, bilirubin to detect hemolysis
  if hemolytic anemia: ✔ PT, PTT, fibrinogen, D-dimer, Coombs, ANA
  BM bx for unexplained thrombocytopenia, esp. if associated with splenomegaly

Primary immune thrombocytopenic purpura (ITP) (*Blood* 2010;115:168)

- Isolated thrombocytopenia due to immune plt *destruction* (auto-Ab to plts) & ↓ *production* (auto-Ab to megakaryocytes) without precipitant
- *Diagnosis of exclusion (r/o 2° ITP);* no robust clinical or lab parameters, but typically:
  CBC: isolated ↓ plt (<100,000/μL); 10% have ITP + AIHA = Evans syndrome
  Peripheral smear: large platelets (not specific), r/o pseudothrombocytopenia
  BM bx: ↑ megakaryocytes, nl cellularity. Consider if other CBC or smear abnl or diagnostic uncertainty (*Blood* 2011;117:4910).
  ✔ HBSAg & anti-HBc prior to rituximab (and before IVIg, which could alter results)
  Clinical manifestations: insidious onset of mucocutaneous bleeding; ♀:♂ = 3:1
- Treatment: rarely indicated if plt >50,000/μL unless bleeding, trauma/surgery, anticoag.

Treatment of Primary ITP in Adults		
Approach	Treatment	Notes
First-line or upfront therapy	Steroids: prednisone 0.5–2 mg/kg/d PO tapered ~4 wk, or dexamethasone 40 mg PO × 4 d	↓ Mφ FcR & ↓ anti-plt Ab 70–90% have initial response ~20% sustained remission
	IVIg (1 g/kg/d IV × 2–3 d) *Consider if need rapid ↑ in plt in 24–48 hrs; lasts 2–6 wks*	Blocks Mφ FcR, ↓ anti-plt Ab Interferes w/ Mφ uptake Ab-coated plts; 80% have initial response
	Anti-Rh(D) Ig: alternative to IVIg if RBC Rh(D) ⊕; 50–75 mcg/kg/d	Ab-coated RBCs overwhelm Mφ FcR Avoid if h/o hemolysis; *not often used*
Second-line or maint. therapy	Romiplostim or eltrombopag	TPO-R agonists → ↑ plt prod
	Rituximab (anti-CD20) ± dex	anti–B-cell Ab
	Splenectomy *(less common)*	~65% long-term remission
	AZA, CYC, MMF	Immunosuppressants

	Danazol: 600 mg/d	Androgen (hirsutism) ↓ plt clearance
Chronic/ refractory	Romiplostim or eltrombopag	Allows splenectomy to be deferred
	Fostamatinib: 75–150 mg BID	Spleen tyrosine kinase (SYK) inhibitor
Bleeding	Aminocaproic acid	Inhibits plasmin activation
	Methylprednisolone 1g/d IV × 3 d	See above
	IVIg	See above
	Platelet transfusion	Given w/ IVIg or anti-Rh(D)

(*Blood* 2017;129:2829 & 130:3624; *Lancet Haem* 2016;3:e489; *Eur J Haem* 2018;100:304; *Immunother* 2018;10:9)

Secondary immune thrombocytopenic purpura (2° ITP)

- Diagnosis: viral serologies (HIV, HCV, HBV, EBV), *H. pylori* Ab, ANA, pregnancy test, APLA, TSH, parvovirus, & CMV PCR. *Anti-plt Ab tests not useful.*
- Treat underlying etiology

Heparin-Induced Thrombocytopenias (*Chest* 2012;141:e495S; *NEJM* 2015;373:252)		
Feature	Type I (not clin. signif)	Type II (clinically significant HIT)
Mechanism	Direct effect of heparin (non-immune)	Immune (Ab)-mediated IgG against plt factor 4—heparin complex
Incidence	10–20%	1–3% with UFH, 0–0.8% LMWH
Onset	After 1–4 d of heparin therapy	After 4–10 d; but can occur in <24 h if prior exposure w/in 100 d (persistent Ab). Postop highest risk. Can occur after heparin d/c.
Platelet nadir	>100,000/μL	~60,000/μL, ↓ >50%
Sequelae	None	Thrombotic events (HITT) in 30–50% Rare hemorrhagic complications
Management	Can continue heparin and observe	Discontinue heparin Alternative anticoagulation

- Pathophysiology (type II): Ab binds heparin-PF4 → immune complex binds to plt → plt activation, further PF4 release → plt aggregates removed from circulation → thrombocytopenia; procoagulants released by plts and tissue factor released by endothelial cells damaged by HIT Abs → prothrombotic state
- Diagnosis *(need clinical + pathologic)*
  - Clinical: plt <100k *or* ↓ 50% from baseline; or venous (DVT/PE) or arterial (limb ischemia, CVA, MI) thrombosis (4:1 ratio); skin necrosis; ? ↑ heparin resistance
  - Pathologic: ⊕ HIT Ab using PF4-heparin ELISA (≥90% Se, IgG-specific ELISA Sp 94%), may confirm w/ functional plt aggregation (serotonin-release) assay (>95% Se/Sp)
  - Clinical context important: HIT Ab (esp. IgM ELISA) may be ⊕ in 10–20% of Pts on UFH/LMWH (*Am J Hem* 1996;52:90), up to 50% of cardiac bypass Pts (*Circ* 1997;95:1242)
  - Pretest prob w/ "4 T's" criteria (*Blood* 2012;120:4160): ≤3 points → 99% NPV, investigate other causes; 4–5 points 22% PPV & 6–8 points 64% PPV, ✔ lab test & replace UFH

Evaluation of Suspected HIT ("4T's")			
Factor	**2 points**	**1 point**	**0 points**
Thrombo-cytopenia	↓ >50% *and* nadir ≥20k	↓ 30–50% *or* nadir 10–19k	↓ <30% *or* nadir <10k
Timing	5–10 d *or* ≤1 d if heparin w/in 30 d	? 5–10 d (but not clear), >10 d *or* ≤1 d if hep w/in 30–100 d	≤4 d w/o recent hep
Thrombosis	New thromb, skin necrosis, acute rxn after IV UFH	Prog/recurrent thromb, suspect thromb or non-nec skin lesion	None
Other cause	None apparent	Possible	Definite

- Treatment of HIT (type II) (*Chest* 2012;141:e495S; *Blood* 2012;119:2209; *NEJM* 2013;368:737)
  - Discontinue heparin *(incl. flushes, LMWH Ppx, heparin lines).* Avoid plts (anecdotal link w/ thrombosis); if given warfarin, give vit K to reverse, prevent warfarin skin necrosis.
  - Nonheparin anticoag (argatroban, bivalirudin; *NEJM* 2013;368:737) *regardless of thrombosis;* start warfarin when plt >150k, overlap ≥5 d (✔ chromogenic Xa to titrate)
  - ⊕ thrombosis (HITT): anticoagulate for ≥3–6 mo
  - ⊖ thrombosis (HIT): screen for DVT; unclear duration of subsequent anticoag (until plt count recovers, often ~2–3 mo if no clot); *25–50% thrombosis rate w/in 30 d*
- H/o HIT: if PF4 Ab ⊖ or SRA ⊖ (typically >100 d after dx) → may consider re-exposure to UFH (eg, for surgery); HIT recurrence low but can be seen (*Blood* 2014;123:2485)

Thrombotic microangiopathies (*TMA; NEJM* 2014;371:654; *Lancet* 2017;390:681)

- Endothelial injury → plt aggreg. & microvasc. thrombosis → ↓ plt & RBC hemolysis (MAHA)
- Thrombotic thrombocytopenic purpura (TTP)
  - Pathophys: ↓↓ ADAMTS13 protease activity (hereditary or autoAb) → persistence of large vWF multimers on endothelial surface → adhesion & aggregation of plts → thrombosis
  - Clinical: pentad (all 5 in only ~5%) = ↓ plts + MAHA (100%) ± Δ MS (65%) ± renal failure (50%, late feature) ± fever (25%)
- Hemolytic-uremic syndrome (HUS)
  - Pathophys: (1) Shiga toxin damages renal endothelial cells → intrarenal thrombi; *or* (2) complement dysregulation (hereditary or acquired), so-called "atypical HUS"
  - Clinical: triad = thrombocytopenia + MAHA + renal failure; (bloody diarrhea if Shiga)
- Drug-induced TMA (*Blood* 2017;129:2857)
  - Immune-mediated (Ab reacts w/ plts & endothelial cells): eg, quinine, gemcitabine?
  - Direct toxicity mediated: eg, gemcitabine, mitomycin, tacrolimus, CsA, bevacizumab
  - Clinically similar to TTP
- Dx: unexplained thrombocytopenia (typically <20k) + MAHA → *sufficient for dx* ⊕ schistocytes (>2–3/hpf), ⊖ Coombs, normal PT/PTT & fibrinogen ↑↑ LDH (tissue ischemia + hemolysis), ↑ indirect bili., ↓↓ haptoglobin, ↑ Cr (esp. in HUS)

Biopsy: arterioles filled with platelet hyaline thrombi
Ddx: DIC, vasculitis, malignant hypertension, preeclampsia/HELLP syndrome

- Rx: urgent plasma exchange ± glucocorticoids if TTP; FFP if delay to plasma exchange? rituximab or caplacizumab (anti-vWF Ab) (*NEJM* 2019;380:335) for TTP eculizumab for atypical HUS (*J Nephrol* 2017;30:127) *plt transfusions contraindicated* → ↑ microvascular thromb (*NEJM* 2006;354:1927)

Disseminated intravascular coagulation (DIC): see "Coagulopathies"

DISORDERS OF PLATELET FUNCTION

Mechanisms and Etiologies of Platelet Function Abnormalities		
Function	Inherited	Acquired
Adhesion	Bernard-Soulier; vWD	Uremia; acquired vWD
Aggregation	Afibrinogenemia Glanzmann's thrombasthenia	Ticlopidine, clopidogrel, GP IIb/IIIa Dysproteinemias (myeloma)
Granule release	Chediak-Higashi syndrome Hermansky-Pudlak syndrome	Drugs (ASA, NSAIDs); liver disease; MPN; cardiopulmonary bypass

Tests of platelet function

- Platelet aggregation tests: measure aggregation in response to agonists (eg, ADP)

von Willebrand's disease (vWD) (*NEJM* 2016;375:2067)

- von Willebrand's factor (vWF) function = platelet glue & plasma carrier of factor VIII
- vWD most common inherited (usually auto dom) bleeding disorder; ~85% (type 1) have partial quantitative defic of vWF, ~15% (type 2) have qualitative defic in vWF
- Acquired vWD: a/w many disorders (malig, MPN w/ ↑ plt count; autoimmune; hypothyroidism; drugs) and caused by different mechanisms (anti-vWF Abs, ↑ clearance, ↓ synthesis); Heyde's syndrome = vWF destruction by severe AS, a/w GI AVMs/bleed
- Diagnosis: ↓ vWF:Ag, ↓ vWF activity (measured by ristocetin cofactor assay), ↓ factor VIII, ± ↑ PTT, ± ↓ platelets; confirm with vWF multimer analysis
- Clinical condition, factor VIII levels and ristocetin cofactor assay useful to guide Rx decision
- Rx: desmopressin (dDAVP, IV/IN) → ↑ endothelial cell release of vWF; efficacy depends on type (avoid in type 2), ∴ ✔ response before use w/ subseq. bleeding or procedures; vWF replacement: cryoprecipitate, factor VIII concentrates rich in vWF, recomb. vWF

Uremic bleeding

- Uremia → platelet dysfunction including ↓ aggregation, impaired adhesiveness
- Treatment: dDAVP, cryoprecipitate, correct anemia (improves plt aggregation and adhesion by increasing plt interactions with endothelium), consider holding anti-plt agents

COAGULOPATHIES

Screening Test Abnormalities in Inherited and Acquired Coagulopathies				
PT	**PTT**	**Factors**	**Inherited**	**Acquired**
↑	↔	VII	FVII defic.	**Vit. K defic.; liver dis.;** factor inhib.
↔	↑	VIII or IX	Hemophilias, vWD	**Antiphospholipid Ab;** factor inhib.
↑	↑	I, II, V or X	Fbgn, FII or FV defic.	**DIC; liver dis.;** factor inhib.

Further coagulation tests (*JAMA* 2016;316:2146)

- Mixing study: useful if ↑ PT or PTT; mix Pt's plasma 1:1 w/ normal plasma and retest
  PT/PTT normalizes → factor deficiency; PT/PTT remains elevated → factor inhibitor
- Coagulation factor levels: useful if mixing study suggests factor deficiency
  DIC → all factors consumed; ∴ ↓ factors V and VIII
  Liver disease → ↓ all factors *except* VIII; ∴↓ factor V, normal factor VIII
  Vitamin K deficiency → ↓ factors II, VII, IX, X (and protein C, S); ∴ normal V and VIII
- DIC screen: fibrinogen (consumed), fibrin degradation products (FDPs, ⊕ due to intense fibrinolysis), D-dimer (more specific FDP test that detects degradation of X-linked fibrin)

Hemophilias (*Lancet* 2016;388:187)

- X-linked recessive factor VIII (hemophilia A) or factor IX (hemophilia B) deficiency
- Classification: mild (5–25% normal factor activity), moderate (1–5%) or severe (<1%)
- Clinical manifestations: hematomas, hemarthroses, bruising, bleeding (mucosal, GI, GU)
- Diagnosis: ↑ PTT (normalizes w/mixing study), normal PT & vWF, ↓ factor VIII or IX
- Prophylaxis indicated if <1% activity of factor VIII or IX
- Rx: purified/recomb. factor VIII (*NEJM* 2016;374:2054) or IX; desmopressin (mild dis.); aminocaproic acid; cryo (FVIII); emicizumab (bridges factor IX and X), effective for hemophilia A w/ and w/o inhibitors (*NEJM* 2017;377:809 & 2018;379:811)

Coagulation factor inhibitors (most commonly anti–factor VIII)

- Etiologies: hemophilia; postpartum; lymphoproliferative & autoimmune disorders; cancers
- Diagnosis: ↑ PTT (does *not* normalize w/mixing study); Bethesda assay quantitates titer
- Treatment: if high titer → recomb. factor VIIa, porcine factor concentrates, activated prothrombin complex; for others → high-purity human factor, plasmapheresis, immunosupp. w/ steroids, CYC and/or RTX (*Curr Opin Hematol* 2008;15:451)

Disseminated intravascular coagulation (DIC) (*NEJM* 2014;370:847)

- Etiologies: trauma, shock, infection, malignancy (esp. APL), obstetric complications
- Pathogenesis: *massive* activation of coagulation that overwhelms control mechanisms

Thrombosis in microvasculature → ischemia + microangiopathic hemolytic anemia
Acute consumption of coagulation factors and platelets → bleeding
Chronic DIC → able to compensate by ↑ factors and platelets → thrombosis

- Diagnosis: ↑ PT, ↑ PTT, ↓ fibrinogen (may be *nl* b/c acute phase), ⊕ FDP/D-dimer, ↓ plts, ⊕ schistos, ↑ LDH, ↓ hapto; *chronic* DIC: ⊕ FDP/D-dimer, variable plts, other labs nl
- Treatment: Rx underlying process; support w/ FFP, cryo (goal fbgn >100 mg/dL) & plts

Vitamin K deficiency

- Etiologies: malnutrition, ↓ absorption (antibiotic suppression of vitamin K-producing intestinal flora or malabsorption), liver disease (↓ stores), warfarin

Properties and Antidotes for Anticoagulants & Fibrinolytics (*Circ* 2016;134:248)

Anticoag.	$t_{1/2}$	Labs	Rx for O/D w/ Serious Bleeding (+ d/c anticoag)
UFH	60–90′, RES	↑ PTT	**Protamine** IV 1 mg/100 U UFH (max 50 mg). For infusions, dose to reverse 2× UFH given per h.
LMWH	2–7°, K	anti-Xa*	Protamine reverses ~60%
Bivalirudin	25′, K	↑ PTT	Dialysis
Argatroban	45′, L	↑ PTT	? Dialysis
Warfarin	36°, L	↑ PT	*No bleeding:* consider vit K 2.5 mg PO if INR >9, o/w no e/o clinical benefit (*Blood Adv* 2019;3:789) *Bleeding:* **vit. K** 10 mg IV + **FFP** 2–4 U IV q6–8h; 4F-PCC (KCentra) faster, less volume, ↓ transfusion
Fibrinolytic	20′, LK	↓ fbgn	**Cryoprecipitate**, **FFP**, ± aminocaproic acid
Dabigatran	~12°, K	↑ PTT*	Idarucizumab: mAb binds drug (*NEJM* 2017;377:431)
Rivaroxaban Apixaban Edoxaban	8–12°, K > L	↑ PT* anti-Xa*	Andexanet alfa (factor Xa decoy receptor) (*NEJM* 2019;380:1326); consider 4F-PCC if andexanet not available (*Circ* 2017;135:e604; *JACC* 2017;70:3042)

*Routine monitoring not performed. Mode of excretion: K, kidney; L, liver; RES, reticuloendothelial system. 4F-PCC: prothrombin complex concentrate (FII, VII, IX, X; Protein C & S). Anti-fibrinolytics: tranexamic, aminocaproic acid.

HYPERCOAGULABLE STATES

Suspect in Pts with venous or arterial thrombosis at young age or unusual locations, recurrent thromboses or pregnancy loss, or ⊕ FHx

Inherited Hypercoagulable States			
Risk Factor	**Prevalence**	**VTE**	**Comments**
Factor V Leiden	3–7%	4.3×	Activated protein C (APC) resist.
Prothrombin mutation	2%	2.8×	G20210A → ↑ prothrombin level
Hyperhomocysteinemia	5–10%	2.5×	Inherited or acquired
Protein C deficiency	0.02–0.05%	11×	Warfarin-induced skin necrosis risk
Protein S deficiency	0.01–1%	32×	
Antithrombin III def.	0.04%	17.5×	May be heparin resistant

Vascular Beds Affected by Inherited and Acquired Hypercoagulable States		
	Venous	Venous and Arterial
Inher.	Factor V Leiden Prothrombin mutation ↓ protein C, S or AT III	Hyperhomocysteinemia (inherited or acquired) Dysfibrinogenemia
Acquired	Stasis: immobilization, surgery, CHF Malignancy Hormonal: OCPs, HRT, tamoxifen, pregnancy Nephrotic syndrome	Platelet defects: myeloproliferative disorders, HIT, PNH (although venous > arterial) Hyperviscosity: polycythemia vera, Waldenström's macroglobulinemia, sickle cell, acute leukemia Vessel wall defects: vasculitis, trauma, foreign bodies Others: antiphospholipid syndrome, IBD

Diagnostic evaluation (not routinely required for initial VTE; *NEJM* 2017;377:1177)

- APC resistance screen; prothrombin PCR test; functional assays for proteins C and S, ATIII; homocysteine level; factor VIII levels; anticardiolipin and lupus anticoagulant Ab. Also consider nephrotic syndrome, PNH (esp. if mesenteric thrombus).
- Consider *JAK2* mutation testing if suspect MPN or splanchnic thrombosis
- Proteins C & S and ATIII levels are affected by acute thrombosis and anticoagulation ∴ levels best assessed ≥2 wk after completing anticoagulation course
- Age-appropriate malignancy screening (occult cancer in ~4% of initial unprovoked VTE; no benefit of routine abd/pelvis CT; *NEJM* 2015;373:697)

Treatment

- Asx w/ inherited risk factor: consider prophylactic anticoag. if develops acquired risk factor
- Thrombosis w/ inherited risk factor: see "Venous Thromboembolism"

Antiphospholipid syndrome (APS) (*NEJM* 2018;398:2010)

- Definition: dx requires ≥1 clinical & ≥1 laboratory criteria
  - Clinical: thrombosis (any) or complication of pregnancy (≥3 spont. abortions before 10 wk or ≥1 fetal loss after 10 wk or premature birth before 34 wk)
  - Laboratory: ⊕ moderate–high titer anticardiolipin (ACL), ⊕ lupus anticoagulant (LA), or ⊕ β_2-glycoprotein-I (β_2-GP-I) Ab, on ≥2 occasions, at least 12 wk apart
- Clinical: DVT/PE/CVA, recurrent fetal loss, ↓ plts, hemolytic anemia, livedo reticularis; "catastrophic APS": ≥3 organ systems in <1 wk w/ ⊕ APLA & tissue microthrombi; 44% mortality (*Arth Rheum* 2006;54:2568); Rx w/ plasmapheresis, rituximab
- Antiphospholipid antibodies (APLA)
  - ✔ *if: SLE, age <40 y & arterial thromb, recurrent venous thromb, spontaneous abortion*
  - ACL: Ab against cardiolipin, a mitochondrial phospholipid; IgG more specific than IgM
  - LA: Ab that prolongs phospholipid-dependent coagulation reactions; ∴ ↑ PTT that does *not* correct with mixing study but does correct with excess phospholipids or platelets; PT not affected b/c the reaction contains much more phospholipid
  - β_2-GP-I: Ab against β_2-glycoprotein-I, IgG or IgM (uncertain role of Abs in pathogenesis)
  - False ⊕ VDRL: nontreponemal test for syphilis in which cardiolipin is part of Ag complex
  - Risk of thromboembolic phenomena may increase with titer of APLs
- Etiologies: primary (idiopathic) or secondary due to autoimmune syndromes (eg, SLE), malignancy, infections, drug reactions
- Treatment: UFH/LMWH → warfarin (lifelong for most Pts)
  - Rivaroxaban inferior to warfarin in triple positive (⊕ ACL, LA, & β_2-GP) (*Blood* 2018;132:1365)
  - Initial *venous thrombosis:* INR 2–3 (*NEJM* 2003;349:1133; *J Thromb Haemost* 2005;3:848)
  - Initial *arterial thrombosis:* typically INR 2–3 + ASA 81 mg/d
  - *Recurrent thrombosis* on warfarin: consider INR 3–4 vs. LMWH or fondaparinux (*Arth Rheum* 2007;57:1487)

DISORDERS OF LEUKOCYTES

Neutrophilia (>7500–10,000/μL)	
Infection	Usually bacterial; ± toxic granulations, Döhle bodies
Inflammation	Burn, tissue necrosis, MI, PE, collagen vascular disease
Drugs and toxins	Corticosteroids, β-agonists, lithium, G-CSF; cigarette smoking
Stress	Release of endogenous glucocorticoids and catecholamines
Marrow stimulation	Hemolytic anemia, immune thrombocytopenia
Asplenia	Surgical, acquired (sickle cell), congenital (dextrocardia)
Neoplasm	Can be 1° (MPN) or paraneoplastic (eg, carcinomas of lung, GI)
Leukemoid reaction	>50,000/μL + left shift, not due to leukemia; unlike CML, ↑ LAP

Neutropenia (ANC <1000/μL)	
Congenital	Myelokathexis, Shwachman-Diamond-Oski, Chédiak-Higashi, retic dysgen., WHIM syndrome, cyclic neutropenia, monoMAC syndrome (↓ monos, NKs)
Infection	Viral (CMV, EBV, HIV); bacterial (brucella, *Rickettsia*, TB); malaria
Nutritional	Vit B_{12} defic., copper defic.
Drugs and toxins	Chemotherapeutics, clozapine, methimazole, TMP-SMX, NSAIDs, sulfasalazine, phenytoin (*Am J Hem* 2009;84:428), alcohol
Neoplasm	MDS, leukemia (AML, ALL, hairy cell, LGL, others)

Lymphocytosis (>4000–5000/μL)	
Infection	Usually viral; "atypical lymphocytes" with mononucleosis syndromes Other: pertussis, toxoplasmosis
Hypersensitivity	Drug-induced, serum sickness
Stress	Cardiac emergencies, trauma, status epilepticus, postsplenectomy
Autoimmune	Rheumatoid arthritis (large granular lymphocytes), malignant thymoma
Neoplasm	Leukemia (eg, CLL, hairy cell, LGL), lymphoma (eg, mantle cell, folic.)

Monocytosis (>500/μL)	
Infection	Usually TB, SBE, *Listeria*, *Brucella*, *Rickettsia*, fungi, parasites
Inflammation	IBD, sarcoidosis, collagen vascular diseases
Neoplasm	Hodgkin lymphoma, leukemias, MPD, carcinomas

Eosinophilia (>500/μL)	
Infection	Usually parasitic (helminths)
Allergic	Drugs; asthma, hay fever, eczema; ABPA
Collagen vasc dis.	RA, Churg-Strauss syndrome, eosinophilic fasciitis, PAN
Endocrine	Adrenal insufficiency
Neoplasm	HL, CML, mycosis fungoides, carcinomas, systemic mastocytosis
Atheroembolic dis.	Cholesterol emboli syndrome

Hypereosinophilic syndrome	Multiorgan involvement incl. heart & CNS, a/w FIP1L1-PDGFRA fusion (*NEJM* 2003;348:1201)

Basophilia (>150/μL)	
Neoplasm	MPN, Hodgkin lymphoma
Alteration in BM or reticuloendothelial compartment	Hemolytic anemia, splenectomy
Inflammation or allergy	IBD, chronic airway inflammation

Lymphadenopathy	
Viral	HIV, EBV, CMV, HSV, VZV, hepatitis, measles, rubella
Bacterial	Generalized (brucellosis, leptospirosis, TB, atypical mycobacteria, syphilis) Localized (streptococci, staphylococci, cat-scratch disease, tularemia)
Fungal and parasitic	Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis Toxoplasmosis
Immunologic	Collagen vascular disease, drug hypersensitivity (eg, phenytoin), serum sickness, histiocytosis X, Castleman's and Kawasaki disease
Neoplasm	Lymphoma, leukemia, amyloidosis, metastatic carcinoma
Other	Sarcoidosis; lipid storage diseases
Factors that favor biopsy	Age (>40 y), size (>2 cm), location (supraclavicular is always abnormal), duration (>1 mo) Consistency (hard *vs.* rubbery *vs.* soft) & tenderness are not reliable

TRANSFUSION THERAPY

Blood Products and Indications (*Lancet* 2013;381:1845)	
Packed red blood cells (PRBCs) (*JAMA* 2016; 316:2025)	For acute blood loss or to ↑ O_2-carrying capacity if end organ ischemia. 1 U PRBC → ↑ Hb by ~1 g/dL. Hb goal >7 g/dL adequate for UGIB & critically ill (*NEJM* 2013;368:11 & 2014;371:1381); maybe >9 if cancer & septic shock (*Crit Care* 2017;45:766). Controversy re: coronary ischemia, although Hb 7–8 likely adequate (*AHJ* 2018;200:96), including peri-cardiac surg (*NEJM* 2018;379:1224).
Platelets (plts) (*Annals* 2014;162:205)	For plts <10k (*NEJM* 2010;362:600) *or* <20k w/ infxn *or* ↑ bleeding risk *or* <50k w/ active bleeding or preprocedure. 6 U pooled donor plts ≈ 1 single donor plt apheresis unit (↓ alloimmunization) → ↑ plt ~30–60k. *Contraindic:* TTP/HUS, HELLP, HIT. *Refractory* if ↑ <5k 30–60′ post-plts. Suggests consumption such as ITP, DIC, or alloimmunization → trial ABO-matched plts. If still refractory ✓ panel reactive Abs to assess utility of HLA-matched plts.
Fresh frozen plasma (FFP)	Contains all coagulation factors. For bleeding due to deficiency of multiple coagulation factors (eg, DIC, TTP/HUS, liver disease, warfarin excess, dilution) or INR >2 preprocedure (*Transfusion* 2006;46:1279).
Cryoprecipitate	Enriched for fibrinogen, vWF, VIII, and XIII. For bleeding in vWD, factor XIII deficiency or fibrinogen <100 mg/dL.
Irradiated	Prevents donor T-cell proliferation. Use if risk of transfusion-assoc. GVHD (HSCT, heme malignancy, congenital immunodeficiency).
CMV-negative	From CMV-negative donors. For CMV-seronegative pregnant women, transplant candidates/recipients, SCID, AIDS Pts.
Leuko-reduced	WBCs cause HLA alloimmunization & fever (cytokines) and carry CMV. For chronically transfused Pts, potential Tx recip., h/o febrile nonhemolytic transfusion rxn, cases in which CMV-neg products desired but unavailable.
Intravenous immune globulin (IVIg)	Polyvalent IgG from >1000 donors. For postexposure prophylaxis (eg, HAV), certain autoimmune disorders (eg, ITP, Guillain-Barré, MG, CIDP), congenital or acquired hypogammaglobulinemia (CVID, CLL).
Therapeutic apheresis	Removes large molec wt subst. (eg, cryoglobulinemia, Goodpasture's, Guillain-Barré, hyperviscosity syndrome, TTP) or cells (eg, leukemia w/ hyperleukocytosis, sx thrombocytosis, sickle cell) from plasma.
Massive transfusion	Large-vol. PRBC → ↓ Ca, ↑ K, ↓ plt, ↑ coags; initial ratio of 1 PRBC: 1 plt:1 FFP repletion generally accepted but controversial, follow labs (*JAMA* 2015;313:471; *JAMA Surg* 2017;152:574).

Transfusion Complications (*NEJM* 2017;377:1261)

Noninfectious	Risk (per unit)	Infectious	Risk (per unit)
Febrile	1:100	CMV	Common
Allergic	1:100	Hepatitis B	1:220,000
Delayed hemolytic	1:1000	Hepatitis C	1:1,600,000
Acute hemolytic	<1:250,000	HIV	1:1,800,000
Fatal hemolytic	<1:100,000	Bacteria (PRBCs)	1:500,000
TRALI	1:5000	Bacteria (platelets)	1:12,000

Transfusion reactions

- For all reactions (except minor allergic): stop transfusion; send remaining blood product and fresh blood sample to blood bank
- Acute hemolytic: fever, HoTN, flank pain, AKI w/in 24 h. Due to ABO incompatibility → preformed Abs vs. donor RBCs. Rx: IVF, ↑ UOP w/ diuretics, mannitol, or dopamine.
- Delayed hemolytic: generally less severe than acute hemolytic; 5–7 d after transfusion
  Due to undetected allo-Abs against minor antigens → anamnestic response.
  Rx: usually no specific therapy required; dx is important for future transfusion
- Febrile nonhemolytic: fever, rigors 0–6 h post transfusion. Due to Abs vs donor WBCs and cytokines in blood product. Rx: acetaminophen ± meperidine; r/o infection, hemolysis.
- Allergic: urticaria; rarely, anaphylaxis: bronchospasm, laryngeal edema, hypotension
  Reaction to transfused proteins; anaphylaxis seen in IgA-deficient Pts w/ anti-IgA Abs.
  Rx: urticaria → diphenhydramine; anaphylaxis → epinephrine ± glucocorticoids
- Transfusion-associated circulatory overload (TACO): ↑ volume → pulm edema, ↑ BP.
  Rx: slow transfusion rate, diuretics, O_2, ± nitrates, ± positive pressure ventilation
- Transfusion-related acute lung injury (TRALI): noncardiogenic pulmonary edema Due to donor allo-Abs that bind recipient WBCs, which then aggregate in pulmonary vasculature and release mediators causing ↑ capillary permeability. Rx: see “ARDS.”

MYELODYSPLASTIC SYNDROMES (MDS)

Myeloid neoplasm overview (*Blood* 2016;127:2391)

- Categories based on clinical features, morphology, immunophenotyping, and genetics

WHO 2016 Classification of Myeloid Neoplasms & Acute Leukemia	
Acute myeloid leukemia	Clonal myeloid stem cell (SC) disorder w/ ≥20% blasts
Myelodysplastic syndromes	Dysplastic clonal myeloid SC disorder → cytopenias; <20% blasts, risk of leukemic transformation
Myeloproliferative neoplasms	Nondysplastic multipotent myeloid SC clonal expansion
MDS/MPN neoplasms	Features of MDS & MPN (eg, CMML, atypical CML)
Myeloid/lymphoid malig. w/ eos & rearrangements of *PDGFR* or *FGFR1* or w/ *PCM1-JAK2*	May be responsive to TKI therapy (eg, imatinib) for *PDGFR* rearrangement
Mastocytosis	Systemic disease, assoc w/ *KIT* mutations
Myeloid neoplasms w/ germ line predisposition	MDS, MDS/MPN, acute leukemias in background of predisposing germline mutations

Myelodysplastic syndromes (MDS) overview (*Lancet* 2014;383:2239)

- Acquired clonal stem cell disorder → ineffective hematopoiesis → cytopenias, dysmorphic blood cells and precursors, variable risk of leukemic transformation
- Epidemiology: 20–30,000 cases/y; median age ~70 y; male predominance (1.8×)
- Idiopathic or 2° to chemo w/ alkylating agents; ↑ risk w/ radiation, benzene
- Clinical manifestations: anemia (85%), neutropenia (50%), thrombocytopenia (40–65%)
- Diagnosis: dysplasia (usually multilineage) in peripheral smear (oval macrocytes, pseudo-Pelger-Huët anomaly) and bone marrow (≥10% dysplasia with blasts ± RS)
- Both cytogenetic [eg, del(5q), mono 7, del(7q), trisomy 8, del(20q)] and molecular abnl (TP53, EZH2, ETV6, RUNX1, ASXL1, SF3B1, DNMT3A) may carry prognostic signif
- Prior to dx MDS: exclude AML (≥20% blasts) and CMML (monos >1 × 10^9/L); r/o 2° BM Δs (defic. of B_{12}, folate, copper); viral infx (eg, HIV); chemo; EtOH; lead, arsenic exposures

WHO 2016 Classification Systems for MDS (*Blood* 2016;127:2391)		
Classification	WHO 2008	Features
MDS w/ single lineage dysplasia (MDS-SLD)	RCUD (RA/RN/RT)	1 dysplastic lineage, 1–2 cytopenias, <15% RS*, <5% BM/<1% PB blasts, no Auer rods
MDS w/ multilineage dysplasia (MDS-MLD)	RCMD	2–3 dysplastic lineages, 1–3 cytopenias, <15% RS*, <5% BM/<1% PB blasts, no Auer rods
MDS w/ ring sideroblast (MDS-RS)	RARS	≥15% RS or ≥5% RS if *SF3B1* mut. is present, <5% BM/<1% PB blasts, no Auer rods
MDS w/ isolated del(5q)	Del(5q)	Del(5q) alone or w/ 1 abnl except –7 or del(7q)
MDS w/ excess blasts (MDS-EB)	RAEB-1	EB-1: 5–9% BM/2–4% PB blasts, no Auer rods

	RAEB-2	EB-2: 10–19% BM/5–19% PB blasts or Auer rods
MDS, unclassifiable (MDS-U)	MDS-U	w/ 1% PB blasts, single lineage dysplasia & pancytopenia, or defining cytogenetic alteration

Certain cytogenetics [eg, t(15;17), t(8;21), inv16, t(16;16), or MLL rearrangement] classified as AML, regardless of BM blast count. RS, ring sideroblast; BM, bone marrow; PB, peripheral blood. * <5% RS if *SF3B1* mutation.

- Rx (*Am J Hematol* 2012;87:692): intensity based on IPSS-R (qv), age, performance status (PS)
  - Poor PS, any risk → supportive care (transfusions, G-CSF, Epo, TPO-mimetic, abx prn)
  - Low/intermediate risk → Epo (if Epo level <500); lenalidomide (esp. for 5q syndrome; *Blood* 2011;118:3765); DNA hypomethylating agents (azacitidine or decitabine)
  - Intermediate/high risk (>4.5 on IPSS-4) → allogeneic HSCT if medically fit, otherwise DNA hypomethylating agents (decitabine or azacitidine; *Lancet Oncol* 2009;10:223)
  - Hypoplastic MDS (rare) → consider immunosuppression (CsA, ATG, pred), HSCT
- Prognosis: *TP53*, *RAS*, *JAK2* mutations (*NEJM* 2017; 376:536) & IPSS-R correlate w/ survival

Revised International Prognostic Scoring System (IPSS-R) (*Blood* 2012;120:2454)

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermed	Poor	Very poor
BM blasts (%)	≤2	-	>2 to <5	-	5–10	>10	-
Hb (g/dL)	≥10	-	8 to <10	<8	-	-	-
Plt (k)	≥100	50 to <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

Total score	≤1.5	>1.5 to 3	>3 to 4.5	>4.5 to 6	>6
Category	Very low	Low	Intermed	High	Very high
Median survival (y)	8.8	5.3	3.0	1.6	0.8

MYELOPROLIFERATIVE NEOPLASMS (MPN)

General (*NEJM* 2017;376:2168)

- Results from clonal expansion of multipotent hematopoietic stem cell
- Different from MDS in that the cells are not dysplastic (ie, normally developed)
- Categories of MPN: polycythemia vera (PV); essential thrombocythemia (ET); primary myelofibrosis (PMF); chronic myelogenous leukemia (CML), BCR-ABL1 ⊕; atypical CML (aCML); chronic neutrophilic leukemia (CNL); systemic mastocytosis; chronic eosinophilic leukemia, not otherwise specified; myeloproliferative neoplasms unclassifiable
- Mutations useful as clonal markers & dx tools:
  - Gain of fxn mutations in *JAK2* V617F (Janus kinase) frequently present (PV ~95%, ET ~50%, PMF ~50%; *NEJM* 2005;352:1779)
  - *BCR-ABL* fusion in all cases of CML; *SETBP1* in aCML
  - *CALR* exon 9 mutation (most MPNs w/o *JAK2* or *MPL* mutation, including ~25% of ET, ~35% of myelofibrosis Pts; *NEJM* 2013;369:2379 & 2391)
  - *MPL*, *TET2, & ASXL1* mutation w/ lower frequency
  - *CSF3R* mutation present in ~60% of CNL; *KIT* in 90% of systemic mastocytosis

---

POLYCYTHEMIA VERA (PV)

Definition

- ↑ in RBC mass ± ↑ granulocytes and platelets in the absence of physiologic stimulus

Etiologies of erythrocytosis

- Relative ↑ RBC (↓ plasma): dehydration; "stress" erythrocytosis (Gaisböck's syndrome)
- *Absolute* ↑ RBC: 1° (PV, other MPD) or 2° due to hypoxia; carboxyhemoglobinemia; inappropriate erythropoietin (renal, hepatic, cerebellar tumors); Cushing's syndrome

Clinical manifestations (common between PV and ET)

- Symptoms → often termed "vasomotor symptoms"
  - Hyperviscosity (erythrocytosis): headache, dizziness, tinnitus, blurred vision
  - Thrombosis (hyperviscosity, thrombocytosis): transient visual disturbances (amaurosis, ocular migraine); Budd-Chiari syndrome; erythromelalgia = intense burning, pain and erythema of extremities due to microvascular ischemia; ↑ risk of DVT, MI, stroke. Risk of thrombosis highly correlated with ↑ WBC in PV and ET (see below).
  - Bleeding (abnormal platelet function): easy bruising, epistaxis, GI bleeding
  - ↑ histamine from basophils → pruritus, peptic ulcers; ↑ uric acid (cell turnover) → gout
- Signs: plethora, splenomegaly, hypertension, engorged retinal veins
- Expression profiling beyond *JAK2* may define different phenotypes (*NEJM* 2014;371:808)

Diagnostic evaluation
- Men: Hb >16.5 g/dL or HCT >49%, women: Hb >16 g/dL or HCT >48%, or ↑ red cell mass
- BM bx → hypercellularity for age, trilineage growth, pleomorphic mature megakaryocytes
- *JAK2* V617F mutation in ~95% of PV; other Pts typically harbor *JAK2* exon 12 mutations
- ✔ Epo to rule out secondary causes of erythrocytosis; if Epo ↓, PV more likely
  If Epo ↑, then ✔ SaO_2 or PaO_2, carboxyhemoglobin, BM exam
- ± ↑ WBC, platelets, basophils; ↑ uric acid, leukocyte alkaline phosphatase, vit B_{12}
- Peripheral smear → no morphologic abnormalities

Treatment
- Phlebotomy to goal Hct <45% (*NEJM* 2013;368:22), consider <42% in women
- Low-dose ASA in all Pts (*NEJM* 2004;350:114)
- Hydroxyurea if high risk of thrombosis (age ≥60, prior thrombosis) or symptomatic thrombocytosis (plt >1.5 × 10^6/μL), or if inadequate Hct by phlebotomy alone
- PEG IFNα preferred in younger Pts and pregnancy (*Lancet Haematol* 2017;4:e165)
- Ruxolitinib (JAK1/2 inhibitor) if refractory to or intolerant of hydroxyurea (*NEJM* 2015;372:426)
- Supportive: allopurinol (gout), H_2-blockers/antihistamines (pruritus)

Prognosis
- Median survival w/ Rx ~13.5 y (*Blood* 2014;124:2507); ↑ age, WBC, additional acquired somatic mutations → worse prognosis (*Haematol* 2013;160:251)
- Post-PV myelofibrosis (spent phase) occurs in 10–20% of cases, usually after 10 y
- Risk of transformation into acute leukemia (<2–5%)

ESSENTIAL THROMBOCYTHEMIA (ET)

Definition
- Sustained ↑ in platelets (>450,000/μL) ± ↑ RBC and granulocytes

Etiologies of thrombocytosis
- 1° = ET or other MPN; myelodysplastic syndromes (5q-syndrome); RARS-T
- 2° = reactive thrombocytosis: inflammation (RA, IBD, vasculitis), infection, acute bleeding, iron deficiency, postsplenectomy, neoplasms (eg, Hodgkin lymphoma)
- Of patients with plt >10^6/μL, <1 in 6 will have ET

Clinical manifestations (also see "Polycythemia Vera")
- Thrombosis with erythromelalgia (risk of thrombosis highest in Pts with leukocytosis), bleeding, pruritus; mild splenomegaly; migraine, TIA; early fetal loss

Diagnostic evaluation
- Peripheral smear: large hypogranular platelets
- BM bx: megakaryocytic hyperplasia; absence of Philadelphia chromosome; rarely minor reticulin fibrosis; normal iron stores; if atypical megakaryoctyes, consider pre-PMF
- Mutations: *JAK2* V617F in 60-65%; *CALR* in 20-25%; *MPL* in 5%; triple negative 10-

15%

- Patients should not meet WHO criteria for diagnosis of CML, PV, PMF, or MDS

Treatment of ET			
Risk	**Features**	**ASA 81 mg qd**	**Cytoreduction**
Low	Age <60 *and* no h/o thrombosis *and* plt $<1.5\times10^6$/μL *and* no CV risk factors	Consider for vasomotor symptoms	No
Int.	Neither low nor high	±	Consider if plt $>1.5\times10^6$/μL
High	Age ≥60 *or* h/o thrombosis *or* plt $>1.5\times10^6$/μL	⊕ (consider holding if plt $>1\times10^6$/μL and lab evid. of acquired vWD)	**Hydroxyurea.** Goal plt $<0.4\times10^6$/μL or sx free. IFNα if young or pregnant.

Prognosis

- Low-risk Pts have overall survival ≈ control population
- Risk of transformation into acute leukemia <2%; risk of progression to MF similar

---

PRIMARY MYELOFIBROSIS (PMF)

Definition

- Clonal myeloproliferation with reactive marrow fibrosis & extramedullary hematopoiesis
- Prefibrotic stage (pre-PMF): megakaryocyte prolif, grade 1 reticulin fibrosis, ↑ BM cellularity. Important to distinguish from ET: ↑ thrombosis, ↑ progression, ↓ survival (*Blood* 2012;120:569)

Etiologies of myelofibrosis

- Myeloproliferative neoplasm = primary myelofibrosis; post-PV/ET myelofibrosis
- Other hematologic (CML, AML, ALL, MDS) and solid cancers (breast, prostate)
- Autoimmune (SLE and other collagen vascular disorders)
- Toxins (benzene); radiation; granulomas (TB, fungal, sarcoid); deposition dis. (Gaucher's)

Clinical manifestations (*BJH* 2012;158:453)

- Ineffective erythropoiesis → anemia; extramedullary hematopoiesis → massive splenomegaly (abdominal pain, early satiety) ± hepatomegaly
- Tumor bulk and ↑ cell turnover → fatigue, weight loss, fever, sweats

Diagnostic evaluation (*JAMA* 2010;303:2513; *Blood* 2016;127:2391)

- Anemia with variable WBC and platelet counts
- Peripheral smear → "leukoerythroblastic" (teardrop cells, nucleated RBCs, immature WBCs); large abnormal platelets
- BM aspirate → "dry" tap; BM bx → severe fibrosis, replacement by reticulin & collagen
- *JAK2* V617F in 45–50%; *CALR* mut in 45–50%, *MPL* mut in 7–10%, triple neg in 1–2%
- No BCR-ABL translocation; also does not meet criteria for PV or MDS

Treatment (*Blood* 2011;117:3494)

- In absence of adverse prognostic factors (eg, anemia or sx) → no treatment
- Allogeneic HSCT only potential cure → consider in young Pts with poor prognosis
- Supportive care: transfusions; ESA if Epo <500 but risk worsening splenomegaly; consider androgens vs immunomodulatory agents (eg, lenalidomide) + prednisone; ? splenectomy if refractory to transfusions, failed chemoRx, painful splenomegaly
- Hydroxyurea for significant leukocytosis or thrombocytosis
- Ruxolitinib (JAK1/JAK2 inhibitor) ↓ sx, ↓ splenomegaly, ↑ survival (*NEJM* 2012;366:787 & 799)
- JAK2 inh: pacritinib, momelotinib, & fedratinib are in phase 3 trials (*JAMA Oncology* 2018;4:652)
- Median survival ~6 y (*JCO* 2012;30:2981); transformation into AML occurs at a rate of ~8%/y

LEUKEMIA

ACUTE LEUKEMIA

Definition

- Clonal proliferation of hematopoietic progenitor with failed differentiation into mature elements → ↑ blasts in bone marrow and periphery → ↓ RBCs, platelets, and neutrophils

Epidemiology and risk factors

- Acute myelogenous (AML): ~20k cases/y in U.S.; median age 68 y
- Acute lymphocytic (ALL): ~6k cases/y in U.S.; median age 15 y but 2nd peak in older adults
- Risk factors: radiation, chemo (alkylating agents, topo II inhib), benzene, smoking, ? rising from acquired somatic mutations and clonal hematopoiesis (*NEJM* 2014;371:2477)
- Secondary to acquired hematopoietic dis.: MDS, MPN (esp. CML), aplastic anemia, PNH
- Inherited: Down's, Klinefelter's, Fanconi's anemia, Bloom syndrome, ataxia telangiectasia, Li-Fraumeni, germline mutations in *RUNX1*, *CEBPa*, & *GATA2*

Clinical manifestations

- Cytopenias → fatigue (anemia), infection (neutropenia), bleeding (thrombocytopenia)
- More common in AML
  - Leukostasis (more often when blast count >50,000/μL): dyspnea, hypoxemia, headache, blurred vision, confusion,TIA/CVA, interstitial infiltrates
  - DIC (esp. with APL); leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma: extramedullary tumor of leukemic cells, virtually any location
- More common in ALL
  - bony/lumbar pain, LAN, hepatosplenomegaly (also in monocytic AML), SVC syndrome
  - CNS involvement (up to 10%): cranial neuropathies, N/V, headache
  - anterior mediastinal mass (esp. in T-cell); tumor lysis syndrome (qv)

Diagnostic evaluation (*Blood* 2009;114:937)

- Peripheral smear: anemia, thrombocytopenia, variable WBC + circulating blasts (seen in >95%; ⊕ Auer Rods in AML), peripheral flow cytometry for blast origin (ALL vs. AML)
- Bone marrow: >20% blasts; mostly hypercellular; test for cytogenetics and flow cytometry
- Presence of certain cytogenetic anomalies, eg, t(15;17), t(8;21), inv(16) or t(16;16), are sufficient for dx of AML *regardless of the blast count*
- ✔ for tumor lysis syndrome (rapid cell turnover): ↑ UA, ↑ LDH, ↑ K, ↑ PO_4, ↓ Ca
- Coagulation studies to r/o DIC: PT, PTT, fibrinogen, D-dimer, haptoglobin, bilirubin

- LP (w/ co-admin of intrathecal chemotherapy to avoid seeding CSF w/ circulating blasts) for Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- TTE if prior cardiac history or before use of anthracyclines
- HLA typing of Pt, siblings > parents/children for potential allogeneic HSCT candidates

ACUTE MYELOGENOUS LEUKEMIA (AML; *LANCET* 2018;392:593)

Classification (WHO; *Blood* 2016;127:2391)

- Features used to confirm myeloid lineage and subclassify AML to guide treatment: morphology: blasts, ⊕ granules, ± Auer rods (eosinophilic needle-like inclusions)
- Immunophenotype: precursor: CD34, CD45, HLA-DR; myeloid: CD13, CD33, CD117; monocyte: CD11b, CD64, CD14, CD15
- Prognosis: *age*, prior *antecedent MPN/MDS* and *genetics* (cytogenetics + molecular mutation status) are key independent risk factors

ENL 2017 Genetic Risk Classification (*Blood* 2017;129:424)	
Risk Category	Genetic Abnormality
Favorable	APL: t(15;17); t(8;21): RUNX1-RUNX1T1; inv(16): CBFB-MYH1; mutated *NPM1 w/o FLT3-ITD or w/ FLT3-ITD^{low}*; biallelic mutation in *CEBPA*
Intermediate	FLT3-ITD^{low}; mutated NPM1 & FLT3-ITD^{high}; t(9;11): MLL-MLLT3; cytogenetic abnl not classified as favorable or adverse, including normal karyotype w/o mutations in FLT3-ITD & NPM1
Adverse	-5 or del(5q); -7; -17/abn(17p); complex or monosomal karyotype; t(6;9): DEK-NUP214 ; t(9;22) BCR-ABL1; inv(3): GATA2-MECOM; wildtype NPM1 & FLT-ITD^{high}; mutated TP53, RUNX1, ASXL1

Upfront treatment

- Induction chemo "7+3": 7 d cont. infusion cytarabine (Ara-C) + 3 d bolus anthracycline
- Ability to tolerate 7+3 regimen key determinant in subsequent Rx received (see below)
- Newer regimens if *fit* (generally age <75 y)
  - FLT3-ITD/TKD mutation: 7+3+midostaurin (early generation FLT3 inhib; *NEJM* 2017;377:454)
  - Cord-binding factor ⊕ → t(8;21) or inv(16): 7+3 ± gemtuzumab ozogamicin (mAb+cytotoxin)
  - 2° AML or w/ MDS-related changes: CPX-351 (liposomal Ara-C & daunorubicin)
  - Other: age <60 y: 7+3 (high-dose daunorubicin 90 mg/m^2); >60 y: dauno 60 mg/m^2
- Newer regimens if *unfit* (generally age ≥75 y or comorbidities; *Leukemia* 2013;27:997)
  - venetoclax (Bcl2 inhibitor) + *either* hypomethylating agents (azacytidine or decitabine) *or* low-dose cytarabine (*Blood* 2019;133:7)

Consolidation therapy

- If enters *complete remission* (CR) = ANC >1000, plts >100, off RBC Rx, <5% BM blasts
- CR does *not* equal cure

- Favorable risk: high-dose cytarabine (HiDAC); Intermediate/Poor risk: Allo-HSCT

Refractory/relapsed disease

- *Repeating mutation analysis* key b/c clonal evolution common and may affect Rx
- FLT3-ITD/TKD mutation: gilteritinib or quizartinib (both potent FLT3 inhibitors)
- *IDH1* mutation: ivosidenib; *IDH2* mutation: enasidenib (small-molecule inhib of IDH1 or 2)
- Chemo: MEC (mitoxantrone, etoposide, Ara-C); FLAG-Ida (fludarabine, Ara-C, G-CSF, & idarubicin); CLAM (clofarabine, Ara-C, mitoxantrone)

Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% for Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor-risk tumor genetics to >65% for younger Pts w/ favorable prognostic factors

Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare, ~8% of AML in U.S.; >90% cure rates
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: t(15;17); *PML-RARA* (>95% of cases)
- Medical emergency with DIC and bleeding common
- Remarkable responses to all-*trans*-retinoic acid (ATRA) & arsenic trioxide (ATO), which induce differentiation of leukemic blasts. ∴ early initiation as soon as APL *suspected*
- Non-high-risk APL: ATRA + ATO (induction + 4 cycles consolidation) → CR ~100%; event-free survival 97% and overall survival 99% at 2 y (*NEJM* 2013;362:111)
- High-risk APL: WBC >10k at diagnosis. No clear consensus. In general, chemo (anthracycline or gemtuzumab ozogamicin) added to ATRA + ATO induction and consolidation.
- Differentiation (ATRA) syndrome: ~25% of Pts; fever, pulm infiltrates, SOB, edema, HoTN, AKI; tx w/ dexamethasone 10 mg bid, supportive care (eg, diuresis) (*Blood* 2008;113:775)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Classification

- Lymphoblastic neoplasms may present as acute leukemia (ALL) with >20% BM blasts or as lymphoblastic lymphoma (LBL) w/ mass lesion w/ <20% BM blast
- Morphology: no granules (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- Immunophenotype

  Precursor: CD34, TdT

  B: CD19; variable CD10, CD22, CD79a

  T: CD1a, CD2, cytoplasmic CD3, CD5, CD7

Treatment

- Induction chemo

Ph ⊕ t(9;22) (seen in ~25% of B-ALL): tyrosine kinase inhibitor + chemo/steroids Adolescents & young adults (<40 y): pedi-like regimen typically w/ PEG-asparaginase Adults (40–75 y): multiagent chemo incl. anthracycline, vincristine, steroids, CYC Older (>75 y): reduced-intensity chemo

- CNS prophylaxis: intrathecal MTX/cytarabine ± cranial irradiation *or* systemic MTX
- Postremission therapy (choice depends on risk of recurrence)
  1) Average risk: consolidation/intensification chemo (~7 mo) → maintenance (~2–3 y)
  2) High risk: high-dose chemo w/ allo HSCT considered for Pts in CR1. High-risk disease includes: Ph ⊕; Ph-like (based on gene expression); MLL translocation t(4;11); complex karyotype; hypodiploid (<44 chromosomes); early T-cell phenotype (ETP; lacks CD1a, CD8, $CD5^{weak}$, myeloid markers); minimal residual disease (MRD) = morphologic remission but flow cytometry or molec. markers of tumor still detectable.
- Relapse/refractory: salvage therapy (*below*), then allogeneic HSCT if able

  B cell: blinatumomab (CD19 BiTE-bispecific T-cell engager; *NEJM* 2017;376:836), inotuzumab (CD22 Ab drug conjugate; *NEJM* 2016;375:740); tisagenlecleucel (CD19 CAR-T cell, *NEJM* 2018;378:449), TKI+chemo/steroids (Ph ⊕ t(9;22) only)

  T cell: nelarabine

  Both B & T cell: chemo including high-dose cytarabine regimens; clofarabine

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Definition (*Blood* 2009;114:937)

- Myeloproliferative neoplasm with clonal overproduction of hematopoietic myeloid stem cells that can differentiate
- Philadelphia chromosome (Ph) = t(9;22) → BCR-ABL fusion → ↑ Abl kinase activity

  BCR-ABL required for diagnosis (make via karyotyping or FISH; PCR)

Epidemiology and risk factors

- ~6600 new cases/y in U.S.; median age ~64 at presentation; ~15% of adult leukemias
- ↑ risk with irradiation; no clear relation to cytotoxic drugs

Disease classification & manifestations

- Chronic phase (CP): <10% blasts (peripheral or bone marrow)
- Accelerated phase (AP): 10–19% blasts, ≥20% basos, plts <100k, clonal evolution (karyotype changes) not seen at dx, megakaryocyte proliferation & fibrosis
- Blastic phase (BP): ≥20% blasts (2/3 w/ myeloid, 1/3 w/ lymphoid), may see extramedullary leukemia
- 85% present in the chronic phase, classic triphasic clinical course rarely seen in TKI era
- Most Pts asx or may have mild constitutional s/s related to splenomegaly.
- Worsening constitutional sx, bone pain, rapid ↑ in spleen size herald disease progression

Diagnostic evaluation

- Peripheral smear: leukocytosis, left-shifted with *all stages of myeloid maturation;* anemia, thrombocytosis, basophilia

- Bone marrow with karyotype: hypercellular, ↑ myeloid to erythroid ratio

Treatment (*Lancet* 2015;385:1447; *Hematol Oncol Clin North Am* 2017;31:577)

- Tyrosine kinase inhibitors (TKI) inhibit abl kinase activity
  - First line: imatinib, 1st TKI against BCR-ABL, remains gold standard (*NEJM* 2017;376:917). 2nd gen TKI: nilotinib, dasatinib, bosutinib; ↑ potency abl inhibitors, but ↑ toxicity.
  - Resistance: due to ↑ in BCR-ABL transcript level on TKI, often result of *BCR-ABL* mutation or amplification. Nilotinib, dasatinib, bosutinib & ponatinib approved for resistant disease, w/ only ponatinib effective on T315I resistance mutation (*NEJM* 2012;367:2075).
  - Side effects: nausea, diarrhea, muscle cramps, cytopenias, ↓ PO_4, ↑ QT, rarely CHF; dasatinib: pericardial & pleural effusions and pulm HTN; nilotinib: ↑ bili & lipase, CV toxicity; ponatinib: pancreatitis and arterial vascular events (cerebral, cardiac, & PAD)
- TKI discontinuation: consider if complete molecular response (>4.5 log reduction in bcr-abl transcript) for >2 y. Up to 50% of Pts remain off TKI at 2 y (ie, no molec. recurrence). Likelihood of success proportional to duration of CMR and risk score at presentation.
- Consider upfront allogeneic HSCT for AP and BP.
- CML in pregnancy: hydroxyurea & all TKIs contraindicated. If Rx needed IFN an option.

Milestones of Therapy	
Definition	Optimal Time
BCR-ABL ratio <10% IS = 1-log reduction by quantitative PCR	3 mo
BCR-ABL ratio <1% IS or <35% Ph chr in metaphase cells	6 mo
Absence of the Ph chromosome in metaphase cells	12 mo
BCR-ABL ratio <0.1% IS = 3-log reduction by quantitative PCR	12 mo
BCR-ABL ratio determined using RT-PCR & compares expression of BCR-ABL fusion in Pt to averaged expression in unRx'd Pts. Reported on International Scale (IS), which standardizes reporting across labs.	

Prognosis (*NEJM* 2017;376:917)

- Chronic phase CML Rx'd w/ imatinib: 89% 5-y overall survival, 95% survival free of CML-related deaths, 7% progression to blast phase at 5 y (*NEJM* 2006;355:2408). Pts with 4 log ↓ in bcr-abl transcript have normal life expectancy.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

see "Small Lymphocytic Lymphoma"

LYMPHOMA

Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Generally characterized as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL)

Clinical manifestations

- Lymphadenopathy (nontender)
  - HL: Reed-Sternberg (RS) cells; superficial (usually cervical/supraclavicular) ± mediastinal LAN; nodal disease with orderly, anatomic spread to adjacent nodes
  - NHL: diffuse; nodal and/or extranodal disease with noncontiguous spread; symptoms reflect involved sites (abdominal fullness, bone pain)
- Constitutional ("B") symptoms: fever (>38°), drenching sweats, ↓ weight (>10% in 6 mo)
  - HL: periodic, recurrent "Pel-Ebstein" fever; 10–15% have pruritus; ~35% "B" symptoms
  - NHL: "B" symptoms vary between subtypes, ~15–50%

Diagnostic and staging evaluation

- Physical exam: lymph nodes, liver/spleen size, Waldeyer's ring, testes (~1% of NHL), skin
- Pathology: excisional lymph node bx (not FNA b/c need surrounding architecture) with immunophenotyping and cytogenetics; BM bx or PET (except in HL clinical stage IA/IIA w/ favorable features or CLL by flow); LP if CNS involvement clinically suspected
- Lab tests: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; ✔ HBV & HCV (and must ✔ HBsAg & anti-HBc if planning rituximab Rx, b/c can lead to HBV reactivation); consider HIV, HTLV, & EBV serologies and connective tissue diseases autoAbs
- Imaging: PET-CT scans b/c CT alone does not reliably detect spleen/liver involvement (espec. in HL, DLBCL). PET response to Rx can be prognostic & possibly guide Rx (*NEJM* 2015;372:1598 & 2016;374:2419). Head CT/MRI *only* if neurologic symptoms.

Ann Arbor Staging System with Cotswolds Modifications	
Stage	Features
I	Single lymph node (LN) region
II	≥2 LN regions on the same side of the diaphragm
III	LN regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs
Modifiers: A = no symptoms; B = fever, night sweats or weight loss; X = bulky disease = greatest transverse diam. of mediastinal mass/max diam. of chest wall >1/3 on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic	

HODGKIN LYMPHOMA (HL) (*Am J Hematol* 2018;93:704)

Epidemiology and risk factors

- ~9,000 cases/y; bimodal distribution (15–35 & >50 y); ↑ ♂; role of EBV in subsets of HL, esp. immunocompromised patients (eg, HIV)

Pathology

- Affected nodes show RS cells (<1%) in background of non-neoplastic inflammatory cells
- Classic RS cells: bilobed nucleus & prominent nucleoli with surrounding clear space ("owl's eyes"). RS cells are clonal B-cells: CD15+, CD30+, CD20– (rarely +).

WHO Histologic Classification of Classical HL		
Nodular sclerosis	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I or II at dx
Mixed cellularity	15–30%	Pleomorphic; older age; male predominance; ≥50% stage III or IV at presentation; intermediate prognosis
Lymphocyte rich	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
Lymphocyte depleted	<1%	Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis

- Nonclassical (5%): nodular lymphocyte predominant (NLP); involves peripheral LN
  - 80% present in stages I–II and Rx can be RT alone or combination chemo + RT w/ 4-yr progression-free survival 88% and overall survival 96% (*JCO* 2008;26:434)
  - Consider rituximab because most NLP RS cells are CD20+
  - Stages III–IV treated with combination chemo (see below)

Treatment (*Lancet* 2012;380:836)

- Stages I–II: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) ± RT if favorable disease
- Stages III–IV: ABVD × 6 cycles (can omit B if PET ⊖ after 2 cycles *NEJM* 2016;374:2419; brentuximab (anti-CD30) may replace bleo but more toxic (*NEJM* 2018;378:331); or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); add RT for select Pts as consolidation
- Refractory/relapsed disease: salvage chemo + auto HSCT ± RT
  - brentuximab vedotin post-ASCT yields some long-term remissions (*Blood* 2016;128:1562)
  - PD1/PDL1 blockade (eg, pembrolizumab or nivolumab) (*NEJM* 2015;372:311)
- Late effects include ↑ risk for:
  - Second cancers: ~4.6× risk for up to 40 y (*NEJM* 2015;373:2499)
    - *breast* (if RT), ∴ annual screening at age 40 or 8–10 y post RT
    - *lung*, efficacy of screening chest CT remains a topic of research
    - *acute leukemia/MDS; NHL*
  - Cardiac disease (if RT or anthracycline), ? role of echo/stress at 10 y (controversial)
  - Pulmonary toxicity (if bleomycin)
  - Hypothyroidism (if RT), ∴ annual TSH (if neck RT)

International Prognostic Score (IPS) (*JCO* 2012;30:3383)		
Negative Prognostic Indicators	Total # of Indicators	5-y PFS
Albumin <4 g/dL; Hb <10.5 g/dL	0	88%
Male; Age >45 y	1	84%
Stage IV	2	80%
WBC ≥15k/μL	3	74%
Lymphocytes <600/μL or <8% of differential	4	67%
	≥5	62%

NON-HODGKIN LYMPHOMA (NHL)

Epidemiology and risk factors

- ~70,000 new cases/y; median age at dx ~65 y; ♂ predominance; 85% B-cell origin
- Associated conditions: immunodeficiency (eg, HIV, posttransplant); autoimmune disorders (eg, Sjögren's, RA, SLE); infection (eg, EBV, HTLV-I, *H. pylori*)
- Burkitt lymphoma: (1) endemic or African (jaw mass, 80–90% EBV-related); (2) sporadic or American (20% EBV-related); (3) HIV-related

WHO Classification of Lymphoid Malignancies (*Blood* 2016;127:2375)		
Type	**Examples**	**Associated Abnormalities**
Mature B cell ↑ *increasing aggressiveness*	Burkitt's lymphoma	*8q24, c-MYC*
	Diffuse large B-cell lymphoma (DLBCL)	*BCL2, MYC, MLL2, CREBBP, etc.*
	Mantle cell	*t(11; 14) BCL1-IgH* → cyclin D1
	Marginal zone lymphoma (nodal, extranodal [MALT ✓ *H. pylori*], splenic)	*AP12-MALT1 & BCL-10-Ig enh*
	Hairy cell leukemia (⊕ TRAP)	*BRAF V600E*
	Follicular lymphoma	*IGH-BCL2, MLL2*
	CLL/small lymphocytic lymphoma	*IGVH, ZAP70, TP53, SF3B1, etc.*
Mature T cell & NK cell	Peripheral T-cell lymphoma	*TET2 and DNMT3A*
	Mycosis fungoides (cutaneous lymphoma)/ Sézary syndrome (+ LAN)	
	Anaplastic large-cell lymphoma	Some *ALK1* ⊕
	Angioimmunoblastic T-cell lymphoma	

Treatment (*Lancet* 2017;390:298)

- Treatment and prognosis determined by histopathologic classification rather than stage
- Rituximab (anti-CD20; *NEJM* 2012;366:2008) if CD20+
- Indolent: generally no cure (except allo HSCT), goal sx mgmt (bulky dis, cytopenia, "B" sx)

  Initial: RT if localized, rituximab + chemo (bendamustine, CVP, fludarabine), ibrutinib. Obinutuzumab (anti-CD20) + chemo w/ obinutuzumab maintenance ↑ PFS but ↑ toxicity (*NEJM* 2017;377:1331)

  Maintenance: rituximab in indolent, aggressive, and relapsed disease (*Lancet* 2011;377:42)

Hairy cell: cladribine; oral BRAF inhibitor if relapsed/refractory (*NEJM* 2015;373:1733)
Gastric MALT: can cure by treating *H. pylori* if ⊕, RT for relapsed/refractory

- Aggressive: goal is cure (*Am J Hematol* 2019;94:604), treatment depends on subtype
  R-CHOP (rituximab, cyclophosphamide, doxorubicin = hydroxydaunorubicin, vincristine = Oncovin, prednisone) (*NEJM* 2002;346:235 & 2008;359:613) DLBCL 10-y PFS = 45%; overall survival = 55% (*Blood* 2010;116:2040)
  + Radiation for localized or bulky disease
  Consider CNS prophylaxis w/ intrathecal or systemic high-dose methotrexate if paranasal sinus, testicular, breast, periorbital, paravertebral, or bone marrow involved; ≥2 extranodal sites + ↑ LDH may also warrant
  Refractory/relapsed disease: salvage chemo; high-dose chemo + auto-HSCT (*JCO* 2001;19:406); allo-HSCT if beyond 2nd relapse (*JCO* 2011;29:1342)
  CAR-T (qv): axicabtagene or tisagenlecleucel (*NEJM* 2017;377:2531 & 2545)
  Mantle cell: ibrutinib for relapsed/refractory disease (*Lancet* 2016;387:770)
- Highly aggressive
  Burkitt: dose-adjusted EPOCH-R (*NEJM* 2013;369:1915) or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, high-dose cytarabine rituximab) (*Blood* 2008;112:2248)
  All Pts receive CNS prophylaxis & tumor lysis syndrome prophylaxis
  Addition of rituximab improves EFS (*Lancet* 2016;387:2402)
  Lymphoblastic lymphoma (B or T cell): treated like ALL (see "Acute Leukemia")
  High-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6: previously "double-/triple-hit" lymphoma, assoc. w/ poor prognosis

Prognosis

- Indolent: typically incurable, but long median survival
- Aggressive: ↑ chance of cure, but overall worse prognosis

Follicular Lymphoma International Prognostic Index (FLIPI) (*Blood* 2004;104:1258)		
Factors: age >60, stages III/IV, Hb <12 g/dL, >4 nodal areas, LDH >nl		
# Factors	5-y Overall Survival	10-y Overall Survival
0–1	90%	71%
2	78%	51%
≥3	52%	35%

International Prognostic Index (IPI) for Aggressive NHL (*Blood* 2007;109:1857)		
Factors: age >60, stage III/IV, ≥2 extranodal sites, performance status ≥2, LDH > nl		
# Factors	Complete Response	5-y Overall Survival
0–1	87%	73%
2	67%	51%
3	55%	43%
4–5	44%	26%
Revised IPI Prognosis in Patients Rx'd with CHOP-R		
Factors	% at Dx	4-y Overall Survival

0	10%	94%
1–2	45%	79%
3–5	45%	55%

HIV-associated NHL (*Blood* 2006;107:13)

- HIV ⊕ imparts 60–100× relative risk
- NHL is an AIDS-defining malignancy along with Kaposi's, cervical CA, anal CA
- Concurrent HAART & chemotherapy likely provide survival benefit
- DLBCL & immunoblastic lymphoma (67%): CD4 <100, EBV-associated Treat as immunocompetent (CHOP-R), but avoid rituximab if CD4 <100 Alternative regimens include R-EPOCH (etop, pred, vincristine, cyclophos, doxorubicin)
- Burkitt lymphoma (20%): can occur with CD4 >200 Treat as immunocompetent; prognosis is not significantly worse
- Primary CNS lymphoma (16%): CD4 <50, EBV-associated (also seen in Pts w/o HIV). Rx w/ high-dose MTX-based regimen + steroids ± temozolomide ± RT, consider auto HSCT.
- Primary effusion lymphoma (<5%): HHV8 driven; also can be seen in other immuno-supp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20–) or consider EPOCH, overall poor prognosis.

SMALL LYMPHOCYTIC LYMPHOMA (SLL) OR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Definition (*NEJM* 2005;352:804; *Blood* 2008;111:5446)

- Monoclonal accumulation of functionally incompetent mature B lymphocytes
- CLL (>5000/μL malignant cells) & small lymphocytic lymphoma (SLL; <5000/μL malignant cells, with + LAN ± splenomegaly) classified as same disease
- Monoclonal B lymphocytosis: resembles but does not meet CLL criteria, observe

Epidemiology and risk factors

- ~15,000 new cases/y; median age at dx is 71 y; most common adult leukemia
- ↑ incidence in 1st-degree relatives; no known association with radiation, chemicals, drugs

Clinical manifestations

- Symptoms: often asx & identified when CBC reveals lymphocytosis; 10–20% p/w fatigue, malaise, night sweats, weight loss (ie, lymphoma "B" sx)
- Signs: lymphadenopathy (80%) and hepatosplenomegaly (50%)
- Autoimmune hemolytic anemia (AIHA) (~10%) or thrombocytopenia (ITP) (~1–2%)
- Hypogammaglobulinemia ± neutropenia → ↑ susceptibility to infections
- Bone marrow failure in ~13%; monoclonal gammopathy in ~5%
- Aggressive transformation: ~5% develop Richter's syndrome = transformation into high-grade lymphoma (usually DLBCL) and sudden clinical deterioration

Diagnostic evaluation (see "Lymphoma" for general approach)

- Peripheral smear: lymphocytosis (>5000/μL, mature-appearing small cells) "smudge" cells from damage to abnl lymphs from shear stress of making blood smear

- Flow cytometry: clonality with dim surface Ig (sIg); CD5+, CD19+, CD20(dim), CD23+. CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prognosis.
- Bone marrow: normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (≥30%)
- Lymph nodes: infiltrated w/ small lymphocytic or diffuse small cleaved cells = SLL
- Genetics: del 11q22-23 & 17p13 unfavorable; trisomy 12 neutral; del 13q14 and mut *IgVH* favorable. Nine significantly mutated genes, including *TP53, NOTCH1*, *MYD88*, and *SF3B1*. Key role for spliceosome mutations (*NEJM* 2011;365:2497; *JCI* 2012;122:3432).

CLL Staging

Rai System		Median Survival	Binet System	
Stage	Description		Description	Stage
0	Lymphocytosis *only*	>10 y	<3 node areas	A
I	⊕ lymphadenopathy	7–10 y	>3 node areas	B
II	⊕ hepatosplenomegaly			
III	⊕ anemia (not AIHA)	1–2 y	Anemia or thrombocytopenia	C
IV	⊕ thrombocytopenia (not ITP)			

Treatment (*Lancet* 2018;391:1524)

- No treatment unless: Rai stage III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- First-line: ibrutinib (inhibits Bruton's tyrosine kinase [BTK], which is found in B cells; *NEJM* 2015;375:25 & 2018;379:2517), risk of AF, HTN & bleeding (avoid if on warfarin), PNA, ILD
- Other options: purine analogues: fludarabine ("F"), pentostatin ("P");
  alkylating agents: cyclophosphamide ("C"), bendamustine ("B");
  ± anti CD20 (rituximab, "R"; ofatumumab; obinutuzumab) or CD52 (alemtuzumab)
  ibrutinib + obinutuzumab ↑ PFS vs. chlorambucil + obinutuzumab (*Lancet Oncol* 2019;20:43)
  venetoclax + obinutuzumab ↑ PFS vs. chlorambucil + obinutuzumab (*NEJM* 2019;380:2225)
  ibrutinib + venetoclax under study as 1st-line Rx: 88% with CR (*NEJM* 2019;380:2095)
- Refractory: venetoclax (α-BCL2; *NEJM* 2018;378:1107), acalabrutinib (BTK inhibitor; *NEJM* 2016;374:323), idelalisib (PI3K inhibitor; *NEJM* 2014;370:997)
- 17p- or *TP53* mutation: venetoclax, idelalisib, or ibrutinib ± rituximab (*Lancet Oncol* 2014;10:1090), consider allo-HSCT with reduced intensity conditioning
- Supportive care & managing complications: PCP, HSV, VZV prophylaxis; CMV monitoring for Pts receiving anti-CD52; AIHA/ITP → steroids; recurrent infections → IVIg

Prognosis (*NEJM* 2004;351:893; *JCO* 2006;24:4634)

- Survival varies substantially. Median overall survival ~10 y (*Am J Hematol* 2011;12:985)
- Favorable prognosis: 13q14 deletion (~50% of CLL cases)
- Poor prognosis:
  unfavorable cytogenetics: eg, 17p- or *TP*53 mutation (*JCO* 2010;28:4473), IgH

translocations
unmutated (<2% c/w germline) *IgVH* gene (<8–10 y vs. >20–25 y if mutated)
high (>20–30%) Zap-70 expression (part of T cell receptor; correlated w/ unmutated *IgVH*)
CD38 >30% or CD49d <30%: correlated with unmutated *IgVH* (*Blood* 2008;111:865)
higher β_2-microglobulin levels (correlate with disease stage and tumor burden)

PLASMA CELL DYSCRASIAS

MULTIPLE MYELOMA (MM)

Definition and epidemiology (*NEJM* 2011;364:1046)

- Malignant neoplasm of plasma cells producing a monoclonal Ig = "M protein"
- ~27,000 new cases/y; median age at diagnosis 69 y; more common in African Americans

Clinical manifestations (CRAB criteria and other less common features)

- HyperCalcemia due to ↑ osteoclast activity
- Renal disease: multiple mechanisms include toxic effect of filtered light chains → *renal failure* (cast nephropathy) or *type II RTA;* amyloidosis or light chain deposition disease → *nephrotic syndrome;* hypercalcemia, urate nephropathy, type I cryoglobulinemia
- Anemia (normocytic) due to bone marrow involvement; rarely, may see AIHA
- Lytic Bone lesions due to ↑ osteoclast activity → pathologic fx
- Recurrent infxns due to relative hypogammaglob. (clonal plasma cells suppress nl Ig)
- Neurologic: cord compression; POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome
- Hyperviscosity: usually when IgM >4 g/dL, IgG >5 g/dL, or IgA >7 g/dL
- Coagulopathy: seen in amyloid due to binding & depletion of Factor X
- AL amyloidosis (see "Amyloidosis")

Diagnostic and staging evaluation (*Lancet Onc* 2014;15:e538)

- MM criteria: clonal BM plasma cells ≥10% or bx-proven plasmacytoma and ≥1 myeloma-defining event:
  (a) myeloma-related organ or tissue impairment (ROTI) = lytic bone lesions, Ca >11 mg/dL, Cr >2 mg/dL, or Hb <10 g/dL
  (b) any of the following biomarkers: BM plasma cells ≥60%, serum free light chain (FLC) ratio ≥100:1, >1 focal lesion on MRI studies
- Variants
  Smoldering MM: M protein >3 g/dL or plasmacytosis >10%, but no myeloma-defining event or amyloidosis; see below under MGUS for approach
  Solitary bone plasmacytoma: 1 lytic lesion w/o plasmacytosis or other ROTI
  Extramedullary (nonosseous) plasmacytoma: usually upper respiratory tract
  Plasma cell leukemia: plasma cell count >2000/μL in peripheral blood
  Nonsecretory MM (~2% of MM Pts): no M protein, but marrow plasmacytosis & ROTI
- Ddx of M component: MM, MGUS (see below), CLL, lymphoma, sarcoidosis, RA. Polyclonal hypergam can be seen in inflammatory states: HIV, rheumatic dis., cirrhosis.
- Peripheral smear → rouleaux (see insert); ✔ Ca, alb, Cr; ↓ anion gap, ↑ globulin, ↑ ESR
- Protein electrophoresis and immunofixation

serum protein electrophoresis (SPEP): quantitates M component; ⊕ in >80% of Pts
urine protein electrophoresis (UPEP): detects Pts who secrete only light chains (= Bence Jones proteins), which are filtered rapidly from the blood
immunofixation: shows component is monoclonal and identifies Ig type → IgG (50%), IgA (20%), IgD (2%), IgM (0.5%), light chain only (20%), nonsecretors (<5%)
serum FLC assay: important for dx (esp. light chain–only Pts) and f/up response to Rx

- β_2-microglobulin and LDH levels reflect tumor burden
- BM bx cytogenetics: normal karyotype better than abnl. Standard risk = hyperdiploidy or t(11;14); high risk = hypodiploidy, del. 17p13 (~10% of Pts), t(4;14) & t(4;16)
- Skeletal survey (plain radiographs) to identify lytic bone lesions and areas at risk for pathologic fracture; *bone scan is not useful for detecting lytic lesions.* Increasingly, whole-body PET-CT (scalp to toe) or MRI is being used to detect bone lesions.

Multiple Myeloma Staging Systems (OS does not account for cytogenetics)

Stage	ISS Criteria*	Durie-Salmon (DS) Criteria	ISS Median OS
I	**β_2-microglobulin** <3.5 mg/L *and* **albumin** >3.5 g/dL	*All of the following:* Hb >10 g/dL; Ca ≤12 mg/dL; 0–1 lytic bone lesions; IgG <5 g/dL or IgA <3 g/dL or urine light chain <4 g/24 h	62 mo
II	Fulfilling criteria for neither I nor III		44 mo
III	**β_2-microglobulin** >5.5 mg/L	*Any of the following:* Hb <8.5 g/dL; Ca >12 mg/dL; >5 lytic bone lesions; IgG >7 g/dL or IgA >5 g/dL or urine light chain >12 g/24 h	29 mo (30 mo if Cr <2 mg/dL; 15 mo if Cr ≥2 mg/dL)

*Consider R-ISS incl chrom abnl & LDH (*JCO* 2005;23:3412 & 2015;61:2267).

Treatment (*NEJM* 2016;375:754 & 1319; 2018;378:518 & 379:1811)

- Decisions generally dictated by *risk stratification* and *transplant eligibility*
- Rx incl. proteasome inhibitors: bortezomib (V), carfilzomib (K), ixazomib (I); immunomodulators: lenalidomide (R), thalidomide (T), pomalidomide (P); immunotherapy: daratumumab (anti-CD38, Dara), elotuzumab (Elo)
  Other active drugs incl. dexamethasone (D), melphalan (M), panobinostat, cyclophosphamide (CYC);
  CAR-T cells (anti-BCMA) promising (*NEJM* 2015;373:621 & 1207; 380:1726; *Lancet* 2016;387:1551)
- Induction Rx w/ best response rate: proteasome inhib (V or K) + immunomod (eg, R). Triplet Rx ↑ OS vs. double (*Lancet* 2017;389:519). RVD most common regimen in US; KRD if high-risk (*NEJM* 2014;371:906 & 2016;374:1621). Dara-RD an option (*NEJM* 2019;380:2104).
- If *not* transplant eligible: induction chemo ↑ survival, not curative; consider maint chemo
- If transplant *eligible:* after induction chemo then high-dose melphalan + auto-HSCT. Not curative, but ↑ progression-free survival (PFS) vs. chemo alone (*NEJM* 2014;371:895, *Lancet Onc* 2015;16:1617). Offer if good perf. status & no prohibitive comorbid. Maint Rx w/ R

improves PFS/OS (*NEJM* 2014;371:10). Timing of HSCT (upfront vs. relapse) debatable.
- Relapsed/refractory: based on prior response & HSCT eligibility: HSCT (if good prior response, no prior HSCT), Elo-PD, Dara-PD; rarely use Allo-SCT.
- Local radiation for solitary or extramedullary plasmacytoma
- Adjunctive Rx: *bone:* bisphosphonates (*JCO* 2007;25:2464), XRT for sx bony lesions
  renal: avoid NSAIDs & IV contrast; consider plasmapheresis for acute renal failure
  hyperviscosity syndrome: plasmapheresis; *infxns:* consider IVIg for recurrent infections
- Common toxicities of Rx: melphalan → myelosuppression; lenalidomide → low plts & thromboembolism; bortezomib → periph. neuropathy; steroids → hyperglycemia, infxn

MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (MGUS)

Definition and epidemiology (*NEJM* 2006;354:1362 & 355:2765)
- M prot. <3 g/dL, marrow plasmacytosis <10%, neither myeloma ROTI nor amyloidosis
- Prevalence ~3% in population >50 y of age, ~5% in >70 y of age, 7.5% in >85 y of age

Management
- ✔ CBC, Ca, Cr, SPEP, serum free light chains, UPEP w/ immunofixation (to exclude MM)
- Close observation: repeat SPEP in 6 mo, then yearly thereafter if stable

Prognosis (*NEJM* 2018;378:241)
- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum free light chain ratio & M protein ≥1.5 g/dL: ↑ risk of progression to MM

Smoldering MM (not MGUS, but variant of MM that req no Rx)
- Need whole-body MRI or PET-CT to rule out occult bone lesions
- Risk of prog. 10%/y, depends on [M protein], subtype, FLC ratio. No defined role for Rx yet.

WALDENSTRÖM'S MACROGLOBULINEMIA (WM)

Definition (*Blood* 2009;114:2375; *NEJM* 2012;367:826)
- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- 91% w/ *MYD88* (NF-κB pathway) L265P mut., may distinguish from MM
- *No evidence of bone lesions* (IgM M component + lytic bone lesions = "IgM myeloma")

Clinical manifestations
- Fatigue from anemia is most common sx
- Tumor infiltration: BM (cytopenias), hepatomegaly, splenomegaly, lymphadenopathy
- Circulating monoclonal IgM
  Hyperviscosity syndrome (~15%): *Neurologic:* blurred vision ("sausage" retinal veins), HA, dizziness, Δ MS. *Cardiopulmonary:* congestive heart failure, pulm.

infiltrates.
Type I cryoglobulinemia → Raynaud's phenomenon
Platelet dysfxn → mucosal bleeding

- IgM deposition (skin, intestine, kidney); amyloidosis and glomerulopathy
- Autoantibody activity of IgM: *Chronic AIHA* (prominent rouleaux; 10% Coombs' ⊕ = AIHA). *Peripheral neuropathy:* may be due to IgM against myelin-associated glycoprotein.

Diagnostic evaluation

- SPEP + immunofixation with IgM >3 g/dL; 24-h urine for UPEP (only 20% have ⊕ UPEP)
- Bone marrow biopsy: ↑ plasmacytoid lymphocytes; β_2-microglobulin for prognostic eval
- Relative serum viscosity: ratio serum viscosity to H_2O (nl 1.8); hyperviscosity when >5–6

Treatment

- Hyperviscosity: plasmapheresis
- Sx (eg, prog. anemia): rituximab ± chemo (eg, bendamustine, Cy, etc.); data for rituximab + ibrutinib (*NEJM* 2018;378:2399). Everolimus or HSCT in salvage.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

Categories of Stem Cell Transplantation		
Feature	Allogeneic (Allo)	Autologous (Auto)
Donor-recipient relationship	Immunologically distinct	Donor is also recipient
Graft-vs.-host disease	*Yes*	*No*
Graft-vs.-tumor effect	*Yes*	*No*
Risk of graft contam. w/ tumor	No	Yes
Relapse risk (leukemia)	Lower	Higher
Transplant-related mortality	*Higher*	*Lower*

- Types of Allo HSCT: *based on donor/recipient matching of major HLA antigens on Chr. 6* (4 principal genes for serotyping: *HLA-A*, *-B*, *-C*, & *-DR;* each w/ 2 alleles ∴ 8 major Ag)
  Matched related (MRD, sibling 8/8 major Ag match): lowest GVHD; preferred donor
  Matched unrelated (MUD): ↑ risk of GVHD; ∴ matching of 10 HLA alleles (*DQ* also) to ↓ risk; chance of match correlates w/ ethnicity (*NEJM* 2014;371:339)
  Mismatched related (eg, 1/8 Ag mismatch): ↑ available donor pool, but ↑ GVHD, rejection; ∴ need additional immunosuppression
  Haploidentical: typically, between parents and children ("half" match); early post-tx cyclophosphamide reduces GVH by destroying proliferating alloreactive T-cells
  Umbilical cord blood: HSC processed at birth & stored. Low cell number, need 2 cords in adults. Neonatal immune cells: HLA-mismatch tolerated better, ↓ GVHD, slow immune reconstitution → ↑ late viral infections (*Blood* 2010;116:4693)
- Graft-vs.-host disease (GVHD): *undesirable* side effect of allo HSCT allogeneic T cells view host cells as foreign; ↑ incid. w/ mismatch or unrelated donors
- Graft-vs.-tumor (GVT): *desired* effect in allo-SCT; graft T cells attack host tumor cells

Indications (*BBMT* 2015;21:1863; *BMT* 2015;50:1037)

- Malignant disease:
  Auto HSCT allows *high-dose myeloablative chemo* and then rescue what would be otherwise lethal cytopenias with autologous stem cells. Used in chemosensitive diseases such as relapsed/refractory DLBCL, MM, testicular germ cell tumor.
  Allo HSCT produces graft-vs.-tumor (GVT) effect, in addition to hematopoietic rescue (used for AML, ALL, MDS, CML-blast crisis, CLL, lymphoma)
- Nonmalignant disease: allo HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodeficiencies, aplastic anemia, hemoglobinopathies)

Transplantation procedure (for Allo HSCT)

- Pre-tx preparative regimen goal: immunosuppression to allow donor cell engraftment & anti-tumor efficacy to ↓ relapse risk. Type and dose of agents determine this balance.
  Myeloablative conditioning: high-dose chemo and/or total body irradiation. Low relapse rates, high immunosuppression, high transplant–related morbidity.
  Reduced-intensity conditioning ("RIC"): lower dose of chemo → ↓ transplant-related morbidity/mortality, but ↑ relapse b/c it relies more on GVT effect (*Blood* 2015;126:23). Allows allo HSCT for older adults (>60) or Pts w/ comorbidities.
- Sources of stem cells (*NEJM* 2012;367:1487)
  Bone marrow (BM): original source of HSCT, now less commonly used than PBSC
  Peripheral blood stem cells (PBSC): easier to collect, more commonly used. BM vs. PBSC ≈ survival; BM ↓ chronic GVHD, PBSC ↓ graft failure, faster engraftment.
  Umbilical cord blood stem cells (UCB): see above in Types of Allo HSCT
- Engraftment: absolute neutrophil count (ANC) recovers to 500/μL w/in ~2 wk w/ PBSC, ~2.5 wk w/ BM, ~4 wk w/ UCB. G-CSF accelerates recovery by 3–5 d in all scenarios.
  Engraftment syndrome: fever, rash, noncardiogenic pulm edema, abnl LFTs, AKI, wt gain. Dx of exclusion: r/o infection, GVHD; Rx w/ 1 mg/kg steroids, rapid taper over 3–4 d.

Complications

- Either direct chemoradiotoxicities associated with preparative regimen or consequences of interaction between donor and recipient immune systems
- Sinusoidal obstruction syndrome (SOS): incidence ~10%, mortality ~30%
  Previously known as veno-occlusive disease (VOD) (*BBMT* 2016;22:400). Mechanism: direct cytotoxic injury to hepatic venules → *in situ* thrombosis.
  Symptoms: tender hepatomegaly, ascites, jaundice, fluid retention with severe disease → liver failure, encephalopathy, hepatorenal syndrome
  Diagnosis: ↑ ALT/AST, ↑ bilirubin; ↑ PT with severe disease; Doppler U/S *may* show reversal of portal vein flow; ↑ hepatic wedge pressure; abnl liver bx
  Treatment: supportive; prophylaxis with ursodiol; treat w/ defibrotide (*Blood* 2016;127:1656)
- Idiopathic pneumonia syndrome (IPS): 5–25% of Pts, >50% mortality (*Blood* 2003;102:2777)
  Alveolar injury 2/2 direct toxicity → fever, hypoxia, diffuse infiltrates; occult infxn frequent
- Diffuse alveolar hemorrhage (DAH): Diagnosis: bronchoscopy to exclude infection; ↑ bloody lavage fluid seen with DAH. Treatment: pulse 500–1000 mg Solu-Medrol × 3 d ± etanercept (*BBMT* 2015;1:67).
- Acute GVHD (usually within 6 mo of transplant; *NEJM* 2017;377:2167)
  Clinical grades I–IV based on scores for skin (severity of maculopapular rash), liver (bilirubin level) and GI (volume of diarrhea); bx supports diagnosis
  Prevention: immunosuppression (MTX + CsA or tacrolimus) or T-cell depletion of graft
  Treatment: grade I → topical Rx; grades II–IV → associated with ↓ survival and ∴ treated with immunosuppressants (corticosteroids, CsA, tacrolimus, rapamycin, MMF)

- Chronic GVHD (developing or persisting >3 mo posttransplant; *NEJM* 2017;377:2565)
  Clinical: malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, bile duct degeneration, cholestasis and many others. More common w/ PBSC than BM.
  Treatment: immunosuppression; rituximab; photopheresis; ibrutinib (*Blood* 2017;130:21)
- Graft failure
  Primary = persistent neutropenia without evidence of engraftment
  Secondary = delayed pancytopenia after initial engraftment; either immune mediated via immunocompetent host cells (graft rejection) or non–immune mediated (eg, CMV)
- Infectious complications
  due to regimen-induced pancytopenia and immunosuppression
  auto HSCT recipients: no immunosuppression ∴ at ↑ risk only pre-/postengraftment
  both primary infections and reactivation events occur (eg, CMV, HSV, VZV)

Timing of Complications Following Allogeneic HSCT

	Time After Transplant and Associated Risk Factors		
	Days 0–30 Mucositis Organ dysfunction Neutropenia	**Days 30–90** Acute GVHD ↓ cellular immunity	**>90 Days** Chronic GVHD ↓ cellular & humoral immunity
Viral infection	Respiratory and enteral viruses, BK virus		
	HSV*	CMV*, HHV 6 & 7	
		EBV-related lymphoma	
			VZV*, JC
Bacterial infection	Gram ⊕ cocci (coagulase-negative *Staph.*, *S. aureus*, *S. viridans*) GNRs (Enterobacteriaceae, *Pseudomonas*, *Legionella*, *S. maltophilia*)		Encapsulated bacteria
Fungal infection	*Candida* spp.		
	Aspergillus spp.		
Parasitic infection		*T. gondii* *P. carinii* *S. stercoralis*	*T. gondii* *P. carinii*
Regimen-related	Pancytopenia		Growth failure
	Mucositis, rash, alopecia		Hypogonadism/infertility
	Nausea, vomiting, diarrhea		Hypothyroidism
	Peripheral neuropathies		Cataracts
	Hemorrhagic cystitis		Avascular necrosis of bone
	Veno-occlusive disease		2nd malignancy
	IPS/Interstitial pneumonitis		Chronic GVHD
Immune-mediated	Acute GVHD		
	Primary graft failure	Secondary graft failure	

*Primarily among persons who are seropositive before transplant.

Prophylaxis/Supportive Medications During HSCT		
Medication	Prophylaxis Against	Duration
Fluconazole or posaconazole	*Candida*	75 d
Acyclovir	HSV/VZV	365 d
Valganciclovir or ganciclovir if CMV ⊕	CMV	100 d or when no longer immunosuppressed
Antibiotics (eg, fluoroquinolone)	Bacterial infxn	While neutropenic
TMP-SMX	PCP	365 d or when off immunosupp.
Allopurinol	Hyperuricemia	Until d –1
Ursodiol	SOS/VOD	60 d

LUNG CANCER

Pathology and Genetics				
	Pathology	**%**	**Typ locat.**	**Genetic Mutations in**
Non-small Cell	Adeno-carcinoma	40	Peripheral	*KRAS* (20–30%), *EGFR* (15–20%, esp. ♀, Asian, never smokers), *HER2* (6%) or rearrang. in *ALK* (~4%), *ROS1* (~2%) and *RET* (~1%)
	Squamous	20	Central	*FGFR1*, *SOX*, *PIK3CA*, *PTEN*, *TP53*, *SOX2*, *DDR2*, *BRAF*
	Large cell	5	Peripheral	
	Other/not classif.	20		
Small cell		15	Central	Complex; most have inactiv. of *TP53* and *RB1*

(*NEJM* 2008;359:1367; *JCO* 2012;30:863; *J Thorac Oncol* 2012;7:924; *Nature* 2011;489:519; *Cell* 2012;150:1107)

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in the U.S.
- Cigarette smoking: 85% of lung cancers occur in smokers; risk ∝ total pack-yrs, ↓ risk after quitting/reducing but not to baseline (*Int J Cancer* 2012;131:1210)
  squamous & small cell almost exclusively in smokers
  adenocarcinoma most common type in nonsmokers
- Asbestos: when combined with smoking, synergistic ↑ in risk of lung cancer
- Other: RT (for other cancer); HIV; environ. toxins (radon, 2nd-hand smoke); pulm. fibrosis

Clinical manifestations

- ~10% asymptomatic at dx, detected incidentally (only 16% w/ localized dis. at presentation)
- Endobronchial growth of 1° tumor: cough, hemoptysis, dyspnea, pain, wheezing, post-obstructive pneumonia; more common with squamous or small cell (central location)
- Regional spread
  Pleural effusion, pericardial effusion, hoarseness (recurrent laryngeal nerve palsy), dysphagia (esophageal compression), stridor (tracheal obstruction)
  Pancoast's syndrome: apical tumor → brachial plexus involvement (C8, T1, T2) → Horner's syndrome, shoulder pain, rib destruction, atrophy of hand muscles
  SVC syndrome (*NEJM* 2007;356:1862): central tumor → SVC compression → face/arm swelling (>80%), neck/chest vein distention (~60%), SOB/cough (~50%), HA (~10%); Rx = steroids, diuretics, RT ± chemo, SVC stent if severe sx, anticoag if clot
- Extrathoracic metastases: brain, bone, liver, adrenal, weight loss
- Paraneoplastic syndromes
  Endocrine:

ACTH (SCLC) → Cushing's syndrome; ADH (SCLC) → SIADH
PTH-rP (squamous cell) → hypercalcemia

Skeletal: digital clubbing (non-small cell), hypertrophic pulm. osteoarthropathy (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones

Neurologic (SCLC): Eaton-Lambert (anti-P/Q-type voltage-gated Ca^{2+} channel Abs), peripheral neuropathy (anti-Hu, anti-PCA-2, anti-CRMP5), cerebellar degeneration (anti-Hu, anti-Yo, anti-Ri, anti-Tr), encephalomyelitis (anti-Hu, anti-Ma1/2, anti-CRMP5)

Cutaneous: acanthosis nigricans, dermatomyositis

Hematologic: hypercoagulable state (adenocarcinoma), DIC, marantic endocarditis

Screening (*Lancet* 2014;382:732)

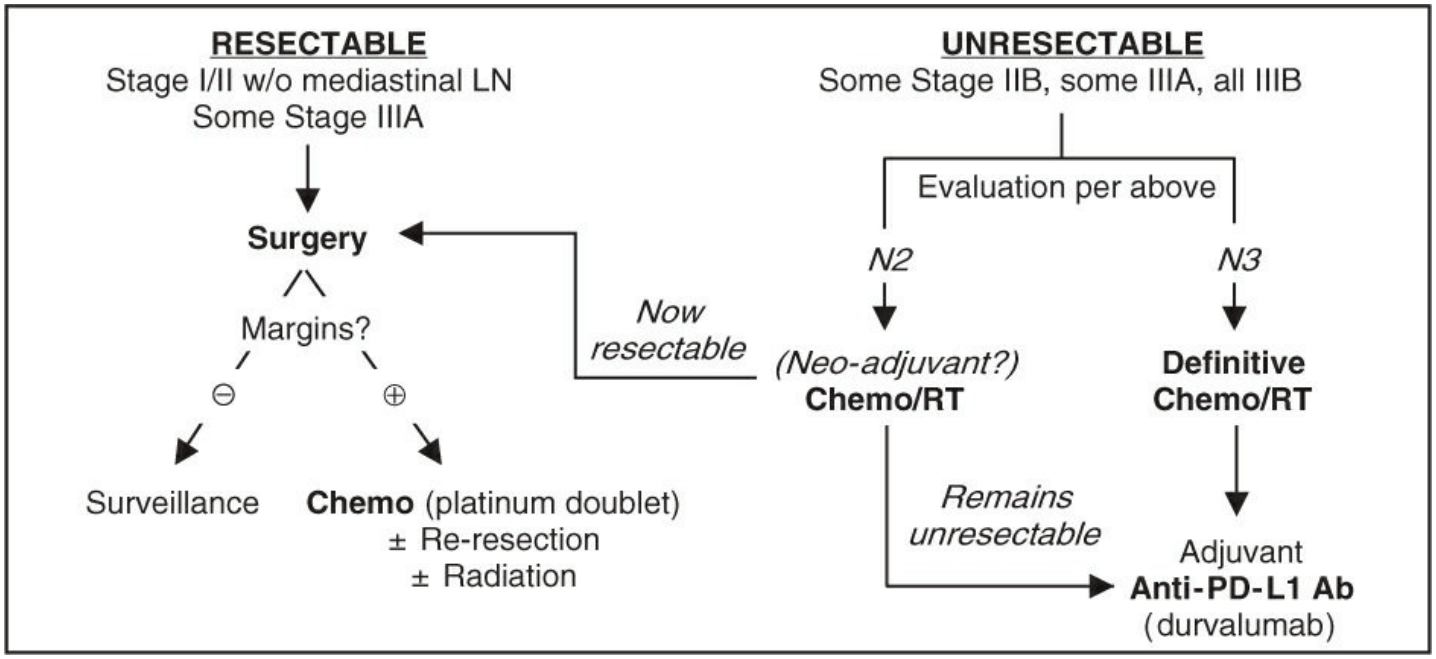
- No benefit to CXR or sputum cytology, even in high-risk Pts
- Annual low-dose chest CT in ≥30 pack-y current or former (quit w/in 15 y) smokers, age 55–74 y → 20% ↓ lung cancer-related mortality (*NEJM* 2011;365:395; 2013;368:1980; USPSTF)
  number needed to screen = 320; high false ⊕ rate
  consider risk scores to target screening (*NEJM* 2013;369:245 & 910; *JAMA* 2016;315:2300)

Diagnostic and staging evaluation (*NCCN Guidelines* v.1.2019)

- Initial imaging: contrast chest CT including liver and adrenals
- Pathology: via bronchoscopy (central lesions) or CT-guided needle bx (peripheral lesions or accessible sites of suspected metastasis); mediastinoscopy (LN bx), VATS (eval. of pleura peripheral lesions), thoracentesis (cell block for cytology)
- TNM staging: based on tumor size and extent of invasion (T), regional LN involvement [N: N0 (none), N1 (ipsilat. hilar), N2 (ipsilat. mediast.), N3 (contralat., supraclav.)] and presence of metastases (M) (*Chest 2017*;151:193). 5-y survival: ~70-90% for stage I, 50-60% stage II, 15–35% stage III, 0–10% stage IV (*J Thorac Oncol* 2016;11:39).
- Pretreatment evaluation
  Intrathoracic: mediastinoscopy (± preceded by U/S-guided transesoph. or transbronch. needle aspiration; *JAMA* 2010;304:2245) or VATS; thoracentesis if pleural effusion
  Extrathoracic: PET-CT more Se than CT alone for detecting mediastinal and distant mets as well as bone mets (*NEJM* 2009;361:32); brain MRI for all Pts (except stage IA)
- Genetics: ✔ *EGFR* mut., *ALK, ROS1, RET, BRAF, NTRK* fusion for adv/metastatic non-squamous dis. (note incidence lower in squamous; only test if nonsmoker, mixed histo)
- PFTs w/ quantitative V/Q if planned treatment includes surgical resection; need to have 30% of normal, predicted lung fxn *after* resection

NSCLC treatment (*Lancet* 2017;389:299; *NEJM* 2017;377:849; *NCCN Guidelines* v.1.2019)

Figure 5-6 NSCLC treatment algorithm



NEJM 2018;379:2342. Encouraging data on PD-1 blockade as *neoadjuvant* therapy (*NEJM* 2018;378:1976).

Stage IV Treatment			
Type	**Genetics**	**%**	**Treatment**
Adeno or Other	EGFR	~15	EGFR TKI ("3rd gen" osimertinib pref.; *NEJM* 2018;378:113)
	ALK	~4	ALK TKI (alectinib pref.: CNS activity; *NEJM* 2017;377:829)
	ROS1	1–2	ROS1 TKI (crizotinib pref.; JCO 2017;35:2613)
	BRAF V600E	1–3	B-Raf inhib. (dabrafenib) + MEK inhib. (trametinib) (*Lancet* Onc 2016;17:984)
	NTRK fusion	<1	Larotrectinib after progression on chemotherapy and immunotherapy (*NEJM*:2018;378:731)
	PD-L1≥50%	30	Anti-PD-1 Ab w/ pembrolizumab; *NEJM* 2016;375:1823)
	No targets		Chemo (carboplatin/pemetrexed) + pembro (*NEJM* 2018;378:2078), *or* Chemo (carbo/paclitaxel) + anti-VEGF Ab (bevacizumab) + anti-PD-L1 Ab w/ atezolizumab (*NEJM* 2018;378:2288)
Squam	PD-L1 ≥50%		Pembrolizumab (*NEJM* 2016;375:1823)
	PD-L1 <50%		Chemo [carbo + (nab-)paclitaxel] + pembro (*NEJM* 2018;379:2040)
Palliative radiation: to control local sx caused by tumor or metastasis			
Solitary brain metastasis: surgical resection + brain radiation may ↑ survival			
Palliative care ↑ survival (*NEJM* 2010;363:733)			

TKI toxicities: rash & diarrhea (common); lung & liver injury (rare but potentially serious)

SCLC staging and treatment (NCCN Guidelines v.1.2019)

- SCLC usually disseminated at presentation but can be very responsive to chemoradiation
- Chemotherapy (platinum + etoposide) is primary treatment modality

- Addition of anti-PD-L1 Ab (eg, atezolizumab) ↑ survival (*NEJM* 2018;379:2220)
- Thoracic radiation added to chemotherapy improves survival in limited-stage disease
- Prophylactic cranial irradiation (PCI) ↑ survival for limited disease in complete remission (*NEJM* 1999;341:476) & ↓ symptomatic brain mets in extensive disease (*NEJM* 2007;357:664)

SCLC Staging Schema and Treatment

Stage	% at dx	Definition	Treatment	Median Survival
Limited	30–40	Confined to ipsilat. hemithorax w/in 1 radiation port	Radiation + chemotherapy ± PCI	1–2 y
Extensive	60–70	Beyond 1 radiation port	Chemotherapy ± PCI	~1 y

BREAST CANCER

Epidemiology

- In U.S., most common cancer in women; 2nd leading cause of cancer death in women
- Genetic risk: 15–20% ⊕ FHx → 2× ↑ risk; ~45% familial cases a/w germline mutation
  BRCA1/2: 35–85% lifetime risk of breast ca & ↑ risk of ovarian & prostate ca; ? ↑ colon ca; BRCA2: ↑ *male* breast, prostate & pancreatic ca. Germline loss-of-function mutations in *PALB2* a/w 35% ↑ risk breast cancer by age 70 (*NEJM* 2014;371:497).
- Estrogen: ↑ risk with early menarche, late menopause, late parity or nulliparity (*NEJM* 2006;354:270); ↑ risk with prolonged HRT (RR = 1.24 after 5.6 y; *JAMA* 2003;289:3243); OCP use a/w extremely low to no ↑ risk (*NEJM* 2017:317:2228; *JAMA Oncol* 2018;4:516)
- Benign breast conditions: ↑ risk if atypia (atypical ductal or lobular hyperplasia; *NEJM* 2015;372:78) or proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; *no* ↑ risk w/ cysts, simple fibroadenoma, or columnar changes
- ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin lymphoma

Prevention (if high-risk: eg, FHx, LCIS, atypical hyperplasia)

- Tamoxifen (contraindic. in preg): ↓ risk contralat. breast ca as adjuvant Rx. Approved for 1° prevent. if ↑ risk: ↓ invasive breast cancer, but ↑ DVT & uterine ca.
- Raloxifene (only if post-menopausal): ↓ risk of invasive breast ca & vertebral fx, ↑ risk of stroke & DVT/PE (*NEJM* 2006;355:125); less effective than tamoxifen in prevention of breast ca but lower risk of VTE, cataracts, & uterine ca (*Ann Int Med* 2013;158:604)
- Aromatase inhib. (post-menopausal): ↓ risk >50% (*Lancet* 2014;383:1041), ↑ osteoporosis
- *BRCA1/2* ⊕: intensified surveillance vs. prophylactic bilat. mastectomy which ↓ risk ~90%; bilat. salpingo-oophorectomy ↓ risk of ovarian *and* breast cancer (*NEJM* 2016;374:454)

Clinical manifestations

- Breast mass (hard, irregular, fixed, nontender), nipple discharge (higher risk if unilateral, limited to 1 duct, bloody, associated with mass)
- Special types: Paget disease → unilateral nipple eczema + nipple discharge; inflammatory breast cancer → skin erythema and edema *(peau d'orange)*
- Metastases: lymph nodes, bone, liver, lung, brain

Screening (*JAMA* 2015;314:1599; *Annals* 2019;170:547)

- Mammography: ~20–30% ↓ in breast cancer mortality, smaller abs. benefit in women <50 y (*JAMA* 2018;319:1814); digital breast tomosynthesis (3-D) ↑ specificity (*JAMA Oncol* 2019;5:635); suspicious findings: clustered microcalcifications, spiculated, enlarging
- ACS recommends annual mammo beginning at age 45 (consider biennial after age 54)
- USPSTF recommends beginning at 50 and biennially (some may want to begin at age 40)
- ↑ risk: screen earlier w/ exam and mammo (age 25 in *BRCA1/2* carrier, 5–10 y before

earliest FHx case, 8–10 y after thoracic RT, upon dx of ↑ risk benign disease)
- MRI: superior to mammo in high-risk and young Pts; consider annually if >20% lifetime risk (eg, ⊕ FHx, *BRCA1/2*, prior chest RT) (*Lancet* 2011;378:1804)
- Genetic testing: recommended in women with strong FHx (*NCCN* v2.2019)

Diagnostic evaluation

- Palpable breast mass: age <30 y → observe for resolution over 1–2 menstrual cycles; age <30 y, unchanging mass → U/S → aspiration if mass not simple cyst;
  age >30 y *or* solid mass on U/S *or* bloody aspirate *or* recurrence after aspiration → mammo (detect other lesions) *and* either fine-needle asp. or core-needle bx
  clearly cancerous on exam or indeterminate read or atypia on bx → excisional bx
- Suspicious mammogram with normal exam: stereotactically guided bx
- MRI: detects contralateral cancer in 3% of Pts w/ recently dx breast cancer & contralateral mammo (but PPV only 21%) (*NEJM* 2007;356:1295); utility remains unclear

Staging

- Anatomic: tumor size, chest wall invasion, axillary LN mets (*strongest prognostic factor*)
- Histopathologic: type (little prognostic relevance) & grade; lymphatic/vascular invasion
  In situ carcinoma: no invasion of surrounding stroma
    Ductal (DCIS): ↑ risk of invasive cancer in *ipsilateral* breast (~30%/10 y)
    Lobular (LCIS): marker of ↑ risk of invasive cancer in *either* breast (~1%/y)
  Invasive carcinoma: infiltrating ductal (70–80%); invasive lobular (5–10%); tubular, medullary and mucinous (10%, better prognosis); papillary (1–2%); other (1–2%)
  Inflammatory breast cancer (see above): not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics; very poor prognosis
  Paget disease (see above): ductal cancer invading nipple epidermis ± associated mass
- Biomarkers: estrogen, progesterone receptor (ER/PR) and HER2/*neu* amplification
- Oncotype DX 21-gene expression recurrence score is predictive & prognostic in ER ⊕, HER2 ⊖, node ⊖ cancers (*NEJM* 2018;379:111); also 70-gene profile (*NEJM* 2016;375:717)

Simplified Staging & 5-y Dis. Specific Survival (*CA Cancer J Clin* 2017;67:290; *SEER* 2017)

Stage	Characteristics	Description	5-y DSS
I	Tumor ≤2 cm	Operable locoregional	99%
IIA	Tumor >2 cm or *mobile* axillary nodes		98%
IIB	Tumor >5 cm		96%
IIIA	Internal mammary or *fixed* axillary nodes	Locally advanced	95%
IIIB/C	Chest wall, skin, infra or supraclavic. nodes	Inoperable	80-85%
IV	Distant metastases	Metastatic	27%

General Approach to Treatment (*JAMA* 2019;321:288 & 1716)	
LCIS	Close surveillance ± chemoprevention (often tamoxifen) (*JCO* 2015;33:3945)
DCIS	Mastectomy or lumpectomy ± RT ± chemoprevention (*Lancet* 2016;387:849 & 866)
I	Surgery + RT

II	+ adjuvant chemo if ↑ risk: tumor >2 cm *or* ⊕ LN *or* ER/PR ⊖ *or* Oncotype DX ≥31 + hormonal Rx for ER/PR ⊕: add ovarian suppression if ↑ risk (*NEJM* 2018; 379:122) + anti-*HER2* Rx and chemo if *HER2* ⊕ and tumor ≥1 cm or ⊕ LN
III	Neoadjuvant chemo → surgery + RT ± adjuvant chemotherapy + hormonal Rx for ER/PR ⊕: add ovarian suppression if premenopausal + anti-*HER2* Rx for *HER2* ⊕: usually trastuzumab + pertuzumab
IV	ER/PR ⊕: combined aromatase & CDK4/6 inhibitors (*NEJM* 2016; 375:1925) ER/PR ⊖: *HER2* ⊕ → chemo + anti-*HER2* therapy; *HER2* ⊖ → chemotherapy Bony mets: bisphosphonates & denosumab ↓ fractures (*Cochrane* 2017;CD003474)

Surgery and Radiation for Local Control	
Intervention	Indication
Breast conserving	Stage I-II, lumpectomy + sentinel lymph node biopsy* + RT
Modified radical mastectomy	Large tumor relative to breast, multicentric dis., prior chest RT, diffuse microcalcifications, ⊕ margins after lumpectomy
Post mastectomy radiation	≥4 ⊕ LN, tumor >5 cm, ⊕ surgical margins, chest wall or skin involvement (*Lancet* 2014;384:1848)

*Axillary lymph node dissection indicated for palpable axillary LNs

Systemic Therapy		
Indic.	Class	Examples
ER/PR ⊕ (*Lancet* 2017;389: 2403)	Endo (*NEJM* 2019;380: 1226)	Tamoxifen: adjuvant Rx for low risk pre-meno; ↓ recurrence & ↓ mortality; 10 y superior to 5 y (*Lancet* 2011;378:771 & 2013;381:805) Aromatase inhibitor (AI; anastrozole, letrozole, exemestane): adjuvant Rx for post-meno; ↑ OS vs. tam. (*Lancet* 2015;386:1341); 10 y of Rx ↑ DFS vs. 5 y of Rx (*NEJM* 2016;375:209) Adding selective ER degrader (fulvestrant) to AI ↑ OS if mets
	Ovarian suppress.	LHRH agonists (eg, leuprolide) or oophorectomy: adjuvant Rx for high risk pre-meno combined with tam. or AI (*NEJM* 2018;379:122)
	Cell prolif. (*NEJM* 2012;366: 520)	CDK 4/6 inhib (eg, palbociclib, abemaciclib, ribociclib): + AI (preferred 1st-line Rx for metastatic dis.) or fulvestrant ↑ PFS in stage IV vs. AI alone (*NEJM* 2018;379:1926; *JCO* 2017;35:3638) mTOR inhib (everolimus): + AI (exemestane) ↑ OS in stage IV
PIK3CA ⊕	PI3K inhib	Alpelisib added to fulvestrant ↑ PFS in metastatic ER/PR ⊕ (*NEJM* 2019;380:1929)
HER2 ⊕ (*Lancet* 2017;389: 2415)	HER2-targeted	Trastuzumab (anti-HER2): 1st-line Rx combined w/ chemo Pertuzumab (prevents HER2 dimerization): + trastuzumab ↑ PFS in adjuvant & metastatic settings (*NEJM* 2017;377:122) Trastuzumab emtansine (mAb linked to chemo): ↓ risk of recurrence/death if residual disease post neoadjuvant Rx (*NEJM* 2019;380:617); preferred 2nd line Rx for metastatic disease
Stage I–IV (above)	Chemo	Neoadjuvant: conserve breast & evaluate Rx efficacy, equivalent OS as adjuvant (*JCO* 2008;26:778) Adjuvant: calc Oncotype DX score for benefit after surgery in ER/PR⊕ (*NEJM* 2018;379:111); use anthracycline ± taxane
PDL-1 ⊕ triple ⊖	Immune	PDL-1 Ab (atezolizumab) added to nab-paclitaxel (microtubule inhibitor): ↑ PFS & OS in stage IV (*NEJM* 2018;379:2108)
BRCA ⊕	PARP inh	Olaparib & talazoparib (*NEJM* 2017;377:523 & 2018;379:753)
Triple ⊖	Ab-drug conjugate	Sacituzumab govitecan: anti-trop-2 linked to chemo ↑ PFS & OS in heavily pre-Rx'd metastatic disease (*NEJM* 2019;380:741)

DFS, disease-free survival; OS, overall survival; PFS, progression-free survival

PROSTATE CANCER

Epidemiology and risk factors (*NEJM* 2003;349:366)

- Most common cancer in U.S. men; 2nd most common cause of cancer death in men
- Lifetime risk of prostate cancer dx ~16%; lifetime risk of dying of prostate cancer ~3%
- ↑ risk with ↑ age (rare if <45 y), in African Americans, ⊕ FHx, BRCA mutations

Clinical manifestations

- Most prostate cancers (78%) are asymptomatic and localized at diagnosis
- Metastatic dis. sx primarily from bone mets: bone pain, spinal cord compression, cytopenias

Screening (*JAMA* 2014;311:1143; *Lancet* 2014;384:2027)

- PSA: 4 ng/mL cut point neither Se nor Sp; can ↑ with BPH, prostatitis, acute retention, after bx or TURP, and ejaculation (*no significant ↑ after DRE, cystoscopy*); 15% of men >62 y w/ PSA <4 & nl DRE have bx-proven T1 cancer (*NEJM* 2004;350:2239)
- Digital rectal exam no longer recommended due to limitations, no mortality benefit
- ACS rec: ≥50 y (or ≥45 y AA or ⊕ FHx) discuss PSA screening, informed decision making
- USPSTF (*JAMA* 2018;319:1901) rec *against* screening if asx (no ↓ in prostate ca-related mort.)

Diagnostic evaluation, staging, and treatment (*NCCN Guidelines* v4.2018)

- Transrectal ultrasound (TRUS) guided biopsy (6–12 cores)
- Multiparametric MRI (± endorectal coil): improves detection (*NEJM* 2018;378:1767)
- Gleason grade and grouping (histology*): Gleason score* = sum of Gleason grades (1 = best, 5 = worst) of 2 most prevalent patterns in bx; correlates w/ prognosis

Risk Stratification & Treatment of Localized Prostate Cancer (*JAMA* 2017;317:2532)

Risk	T stage	Gleason Score & Path	Imaging	Treatment
Very low*	T1c	Gleason ≤6, <3 cores ⊕, <50% ⊕ in any core, *and* PSA <10 ng/mL & density <0.15 ng/mL/g	Not Indic.	Active surveillance strongly considered if very low risk, *or* EBRT (external beam RT), *or* Radical prostatectomy (RP) RP vs. EBRT based on Pt, tumor, long-term tox of Rx
Low*	T1-2a	Gleason score ≤6, *and* PSA <10 ng/mL		
Intermed*	T2b-T2c	Gleason score 7, *or* PSA 10-20 ng/mL	Bone scan & CT A/P	RP *or* EBRT+ADT (4-6 mo)
High Very high	T3a-T4	Gleason score 8–10, *or* PSA >20 ng/mL		EBRT+ADT (18-36 mo) *or* RP

*In asx Pts w/ life expectancy ≤5 y & very low-to-intermediate risk disease, no workup or Rx indicated until sx. *NEJM* 2016;375:1415 & 2017;376:417 & 2018;378:2465 & 2018;379:2319; *JCO* 2016;34:2182.

Treatment of Metastatic Prostate Cancer (*NEJM* 2018;378:645)	
Androgen deprivation therapy (ADT)	Prostate ca requires androgen signaling for growth. ADT backbone of Rx. Med: 1. Luteinizing hormone-releasing hormone (LHRH) agonist (eg, goserelin) ± 1st-gen anti-androgen (nilutamide, bicalutamide), *or* 2. LHRH antagonist (degarelix) Surg: Bilateral orchiectomy
Hormone- sensitive prostate cancer (HSPC)	Def: ADT sensitive (ie, PSA ↓ w/ Rx): all prostate ca initially sensitive Workup/testing: PEx & PSA q 3-6 mos; sx-guided imaging Rx: 1. ADT; *or* 2. Docetaxel + ADT (↑ OS vs. ADT alone, espec. in high-volume dis.); *or* 3. ADT + abiraterone/pred (↑ OS vs. ADT alone)
Castration-resistant prostate cancer (CRPC) *Always continue ADT*	Def: All met. HSPC eventually becomes CRPC (ie, progression despite castration level of androgens on ADT), due to re-estab. of androgen signaling via other mech. ∴ more potent anti-androgens are active Rx. Rx: New-gen. anti-androgens: abiraterone (biosynth inhib.), enzalutamide (receptor blocker), & apalutamide (receptor blocker) ↑ PFS & OS Chemo: docetaxel & cabazitaxel +pred/dex Bone-active agents: 1. denosumab or zoledronic acid ↓ skeletal-related events (SREs); 2. radium-223 used in bone-only dis, ↓ SREs & ↑ OS Misc: *Homologous recombination-defic. tumors (BRCA1/2, ATM)*: olaparib; *MSI-H/Lynch synd.*: pembrolizumab; *Cancer vaccine*: Sipuleucel-T

NEJM 2010;363:411 & 2013;368:138 & 2013;369:213 & 2014;371:424 & 2015;373:737 & 2015;373:1697 & 2017;377:338 & 352; 2018;378:1408; 2019;381:13; *Lancet* 2016;387:1163; *JCO* 2017; 35:2189.

Prognosis

- PSA level, Gleason grade and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- Metastatic disease: median survival ~44–57 mo (*NEJM* 2015;373:737)

COLORECTAL CANCER (CRC)

Epidemiology and risk factors (*CA Cancer J Clin* 2018;68:7)

- 4th most common cancer in U.S. men & women; 2nd leading cause of all cancer death
- 90% of cases occur after age 50. ~75% are sporadic.

Genetic Risk Factors

Disorder	*CRC risk*	*Pathophysiology*	*Assoc Cancers*
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch)	~80% lifetime	Most common hered. CRC (~3%). Mismatch repair mut (eg *MSH2*, *MLH1*). Dx: ≥3 family HNPCC cancer, 1 dx before 50 y, involves 2 gen. Typically **right-sided**.	**Endometrial**, ovarian, stomach, urothelial, small bowel & pancreas
Familial adeno polyposis (FAP)	100% lifetime	Mutation in *APC* gene → 1000s of polyps at young age	Thyroid, stomach, small bowel
Inflammatory bowel disease	0.3%/y	↑ risk with ↑ extent and duration of disease	Small bowel, lymphoma, cholan.
MYH-associated polyposis (MAP)	40–100%	Autosomal *recessive*; consider if mult. polyps but ⊖ for FAP	Duodenal, ovarian, bladder, skin

- COX-2 plays a role. ASA rec for 1° prevention if 50–59 y & ≥10% 10-y CRC risk

Screening (*NEJM* 2017;376:149)

- Colonoscopy: preferred; 90% Se for lesions >1 cm. If polyp, re ✔ in 3–5 y. Removal of adenomatous polyps a/w lower CRC mortality (*NEJM* 2012;366:687)
  Average-risk Pts: start at age 50 & repeat q10y preferred
  ↑ *risk Pts*: ⊕ FHx: screen age 40 or 10 y before index dx, then q5y. IBD: 8–10 y after dx, then q1–2y. Suspect familial syndrome: gene counsel, screen 20–25 yo yearly.
- Sigmoidoscopy: benefit w/ 1-time flex-sig (*Lancet* 2017;389:1299); less Se than colo or CTC
- CT colonography (CTC): ~90% Se for lesions ≥1 cm but less if smaller (*NEJM* 2008;359:1207). If high-risk, Se only 85% for neoplasia ≥6 mm (*JAMA* 2009;301:2453).
- Occult blood (FOBT): use 3-card home testing (Se 24%) yearly
- DNA: ↑ Se, ≈ Sp c/w FOBT but less Se than colonoscopy (*NEJM* 2004;351:2704)
- Combo DNA + Hb immunoassay w/ ~90% Se & Sp (*NEJM* 2014;370:1287)

Pathology and genetics (*Cell* 1990;61:759; *Nature* 2014;513:382)

- Adenoma: ↑ risk of malig. if polyps >2.5 cm, villous, or sessile. Adenomas typically observed ~10 y prior to onset of cancer (both sporadic & familial).
- Microsatellite stable (MSS) vs. high instability (MSI-H): latter sign of mismatch repair gene failure, accounts for 15% CRC, presents more often as early stage, ~5% of met

dis.

- Mutations: *APC* (~80%); *KRAS* (~40%); *TP53* (50–70%); *DCC*, *SMAD4*, *BRAF* (~15%)

Clinical manifestations

- Distal colon: Δ bowel habits, obstruction, colicky abdominal pain, hematochezia
- Proximal colon: iron defic. anemia, dull vague abd pain, liquid stool
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Staging and treatment (*NCCN Clin Pract Guidelines*; version 1.2019)

- TNM staging: colonoscopy + biopsy/polypectomy + intraoperative + pathologic
- CT scans of chest and abdomen/pelvis for mets
- Baseline CEA: monitor post resection or follow response; *not* for screening
- Chemo options (*Lancet* 2014;383:1490): 5FU/ & leucovorin (LV) foundation. 5FU/LV + oxaliplatin &/or irinotecan (FOLFOX, FOLFIRI, FOLFOXIRI, resp). Capecitabine oral 5FU prodrug. TAS102 (trifluridine + tipiracil) in progressive disease (*NEJM* 2015;372:1909).
- Biologics: *anti-VEGF* (bevacizumab) added to chemo ↑ OS in all subsets of mCRC; *anti-EGFR mAb* (cetuximab or panitumumab) only in unmutated KRAS/NRAS/BRAF (*NEJM* 2013;369:1023); *multikinase inhibitor* (regorafenib) generally in chemo (& biologic) refractory setting (*Lancet* 2013;381:303); anti PD-1 & PD-1 + CTLA-4 in MSI-H met CRC.

TNM	Path. Criteria	5-y Surv.	Treatment
I	Submucosa/muscularis	94–97%	Surgery alone (resect & analyze ≥12 LN)
IIA	Serosa	83%	Surgery. Consider adjuvant chemo for high-risk Stage II: obstruction, perf, adherence, inadequate LN sampling (<12 LNs).
IIB	Peritoneum	74%	
IIC	Direct invasion	56%	
IIIA	≤6 ⊕ LNs	86%	Surgery + FOLFOX (6 mo) or CAPOX (3-6 mo) (*NEJM* 2018;378:13) Pre RT ± chemo if rectal (*NEJM* 2006;355:1114)
IIIB	Varying # ⊕ LNs & local invasion	51–77%	
IIIC		15–47%	
IV	Distant metastases (*NEJM* 2014;371:1609)	5%	Chemo (FOLFOXIRI if high-risk) ± anti-PD-1 (MSI-H only) ± resect isolated mets

PANCREATIC TUMORS

Genetics and path (*Nat Rev Dis Primers* 2016;2:16022)

- Histologic types: adenocarcinoma (~85%), acinar cell carcinoma, endocrine tumors, cystic neoplasms (<10%); rarely, mets to pancreas (eg, lung, breast, renal cell)
- Location: ~60% in head, 15% in body, 5% in tail; in 20% diffuse infiltration of pancreas
- Mutations in adenoca.: *KRAS* (>90%), *p16* (80–95%), *p53* (50–75%), *SMAD4* (~55%)

Epidemiology and risk factors (*Lancet* 2016;388:73)

- 4th leading cause of cancer death in U.S.; 80% panc adeno in ages 60–80 y; M>F (1.3:1)
- Acquired risk factors: smoking (RR ~1.5; 25% cases), obesity, chronic pancreatitis, T2DM
- Hereditary (5–10%): familial breast/ovarian CA (*BRCA2*); *hereditary chronic pancreatitis* (mutation in cationic trypsinogen gene (*PRSS1*, *SPINK1*); *familial cancer syndromes:* atypical multiple mole melanoma (*CDKN2A/p16*), Peutz-Jeghers (*LKB1*), ataxia-telang.

Clinical manifestations

- Painless jaundice (w/ pancreatic head mass), pain radiating to back, ↓ weight & appetite
- New-onset atypical DM (25%); migratory thrombophlebitis (Trousseau's syndrome)
- Exam: RUQ/epigastric nontender mass, palpable gallbladder (Courvoisier's sign); hepatomegaly; ascites; L supraclav. node (Virchow's) & palpable rectal shelf (non-spec.)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation (*NCCN Guidelines* v.1.2019)

- Pancreatic protocol CT scan (I^+ w/ arterial & venous phase imaging) or MRI w/ contrast
- *If no lesion seen* → EUS, ERCP, or MRCP
- Biopsy pancreatic lesion via EUS-guided FNA (preferred in potential surgical candidates) or CT-guided (potential risk of seeding) or biopsy of possible metastasis
- ✔ CA19-9 preop (nb, can be ↑ in benign liver/biliary dis.); may be useful to trend postop

Clinical (Radiologic) Staging Non-Metastatic Panc Adenoca (~40% of cases)	
Resectable	No extrapanc dis. or bulky LAN; no arterial tumor contact [celiac axis (CA), SMA, common hepatic (CHA)]; and no venous contact [SMV, portal vein (PV)] or ≤180° + patent veins (ie, no tumor thrombus)
Borderline resectable	No extrapanc dis. or bulky LAN. Head/uncinate: contact w/ CHA (no extension to CA or HA bifurcation), SMA contact ≤180°, variant anatomy. Body/tail: contact CA ≤180° or >180° but w/o gastro-duodenal art. or aortic. Venous: SMV & PV contact ≤180° w/ contour irreg; contact w/ IVC.
Unresect.	Distant mets; or head/uncinate: contact >180° SMA, CA; or Body/tail: contact >180° SMA or CA; CA & aortic involvement; or Venous: SMV/PV involvement/not reconstructible

Treatment of pancreatic adenocarcinoma (*Lancet* 2016;388:73)

- Resectable: pancreaticoduodenectomy (Whipple procedure) + adjuvant chemo:
  modified FOLFIRINOX (5-FU + leucovorin, irinotecan, oxaliplatin) if ECOG 0-1 (*NEJM* 2018;379:2395), o/w gemcitabine + capecitabine (*Lancet* 2017;389:1011). Gemcitabine monoRx used to be recent standard, but now w/ ↓ role. Role of RT is controversial.
- Borderline: goal to ↓ tumor to allow complete resection (R0 – neg margin at histology) using neoadjuvant Rx (various approaches tested). General schema: chemo ± RT → restage & potential resection depending on response. May need vasc. reconstruction during resection. Regimens include: FOLFIRINOX; gemcitabine + nab-paclitaxel.
- Locally advanced (ie, unresectable): Rx is typically palliative. However, in highly select Pts recent trend toward Rx w/ FOLFIRINOX plus XRT followed by laparotomy for response assessment (imaging can be unreliable) and potential resection.
- Metastatic: *clinical trials preferred;* Rx based on performance status (PS)
  Good PS: FOLFIRINOX (± olaparib); gemcita. + nab-paclitaxel (*NEJM* 2013;369:1691)
  Poor PS: gemcitabine; capecitabine; continuous infusion 5-FU
- Palliative and supportive care
  obstructive jaundice or gastric outlet obstruction: endoscopic stenting or surgical bypass
  pain: opiates, celiac plexus neurolysis, XRT; wt loss: enzyme replacement, nutrition c/s

Prognosis

- Resectable: if Rx'd w/ adjuvant FOLFIRINOX, 50+ mos, o/w ~30 mos
- Unresectable: if locally advanced ~1–2 y; if metastatic, ~1 y

Cystic lesions of the pancreas (*NEJM* 2004;351:1218; *Oncologist* 2009;14:125)

- Serous cystadenoma: usually benign; central scar or honeycomb appearance on imaging
- Mucinous cystic neoplasm (MCN): predominantly young females; multiloculated tumors in body or tail w/ ovarian-type stroma and mucin-rich fluid w/ ↑ CEA levels; precancerous
- Intraductal papillary mucinous neoplasm (IPMN): arises in main panc duct or branch → ductal dilation; ? prog to CA (5–20 y); surgery based on age, size, location, dysplasia

HEPATOCELLULAR CARCINOMA (HCC)

Risk factors (globally, 3rd leading cause of cancer death, espec. in Africa & Asia)

- Cirrhosis: present in 70–90% HCC cases
- Infectious: HCV & HBV (~75%), HBV/HDV coinfection; HBV can cause HCC w/o cirrhosis
- Toxic: EtOH (⅓ cases in U.S.), tobacco, aflatoxin from Aspergillus
- Metabolic disorders: NASH, DM, autoimmune hepatitis, hemochromatosis

Screening (screen Pts w/ cirrhosis, chronic HBV or HCV infection)

- Ultrasonography (U/S) + AFP q 6 mos; if high-risk may alternate U/S w/ MRI
- If lesion found or increasing AFP, perform 3-phase contrast CT or MRI

Diagnosis

- At least 3-phase contrast-enhanced CT or MRI; no biopsy or PET required for HCC dx
- Of note, only 15% of liver masses are HCC; metastatic dis. from other 1° more common

Clinical manifestations

- Exam: nonspecific, c/w liver dysfxn (eg, hepatomegaly, ascites, jaundice, encephalopathy)
- Labs: as above, c/w liver dysfunction (eg, coagulopathy, low albumin, elevated LFTs)

Treatment (*NEJM* 2019;380:1450)

- If localized disease, goal is cure
  - Resection: typically ablation of HCC; surgery generally only considered for solitary lesions in Pts w/ preserved liver fxn & adequate postop liver volume
  - Liver transplant: 1 lesion ≤5 cm or 3 lesions ≤3 cm, no vasc invasion or mets
- Palliative
  - Transarterial embolization (TAE), ± chemo (TACE) or radioembolization
  - Systemic therapy: kinase inhibitors (lenvatinib, sorafenib), PD-1 inhib (nivolumab) ä OS in advanced HCC (*Lancet* 2017;389:2492 & 2018;391:1163)

ONCOLOGIC EMERGENCIES

FEVER AND NEUTROPENIA (FN) (*NCCN Guidelines* v.1.2019)

Definition

- Fever: single oral temp ≥38.3°C (101°F) or ≥38°C (100.4°F) for ≥1 h
- Neutropenia: ANC <500 cells/μL or <1000 cells/μL with predicted nadir <500 cells/μL

Pathophysiology and microbiology

- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect associated with malignancy
- Most episodes thought to result from seeding of bloodstream by GI flora
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- GNRs (esp. *P. aeruginosa*) were historically most common
- Gram ⊕ infections have recently become more common (60–70% of identified organisms)
- Fungal superinfection often results from prolonged neutropenia & antibiotic use

Prevention (only if intermediate or high-risk)

- Bacterial: consider fluoroquinolone if neutropenic; no mortality Δ (*NEJM* 2005;353:977 & 988)
- Fungal: consider during neutropenia in blood cancers (posa/fluconazole, micafungin)
- Viral: consider during active Rx in blood cancers (acyclovir, famciclovir, valacyclovir)

Diagnostic evaluation

- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; avoid DRE
- Labs: CBC with differential, electrolytes, BUN/Cr, LFTs, U/A
- Micro: blood (peripheral & through each indwelling catheter port), urine, & sputum cx; for localizing s/s → ✔ stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s → CNS, sinus, chest or abdomen/pelvis imaging
- Caveats: neutropenia → impaired inflammatory response → *exam and radiographic findings may be subtle;* absence of neutrophils by Gram stain does *not* r/o infection

Risk stratification (factors that predict lower risk)

- History: outPt, ECOG 0-1, age <60 y, solid tumor, no sx, no major comorbidities, no h/o fungal infection, MASCC Risk Index ≥21 (*Support Care Cancer* 2013;21:1487)
- Exam: temp <39 °C, no tachypnea, no HoTN, no Δ MS, no dehydration
- Labs: ANC >100 cells/μL, anticipated duration of neutropenia ≤100 cells/μL <7 d

Initial antibiotic therapy (*NCCN Guidelines* v.1.2019)

- Empiric regimens should include antipseudomonal activity; consider VRE coverage if ⊕
- Low risk: PO abx or home IV abx may be considered in select Pts;
  PO options: cipro+amoxicillin-clavulanate; levofloxacin; moxifloxacin (avoid if FQ ppx)

- High risk: hospital admission & IV abx; monotherapy preferred
  options: cefepime, imipenem, meropenem, piperacillin/tazobactam, ceftazidime
- Vancomycin if HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, gram ⊕ BCx, mucositis on quinolone ppx & ceftazidime for viridans strep; d/c when BCx ⊖ × 48 h

Modification to initial antibiotic regimen based on site-specific evaluation

- Mouth/esophageal (ulcer, thrush): consider anaerobic, anti-HSV and/or antifungal Rx
- Sinus/nasal: add vanc if periorbital cellulitis, ampho if concern for Aspergillus/Mucor
- Abd pain/diarrhea: PO vanc if concern for *C. diff*; ensure adequate anaerobic coverage
- Lung infiltrates: consider atypical coverage; vanc/linezolid if c/f MRSA; TMP/SMX if c/f PCP
- CNS: ID consult; empiric meningitis Rx (incl. *Listeria*), high-dose acyclovir for encephalitis
- Antifungal Rx added for neutropenic fever ≥5 d despite abx. Liposomal amphotericin B, caspofungin, micafungin, anidulafungin, voriconazole, & posaconazole are options.

Duration of therapy

- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile *and* ANC >500 cells/μL
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

Role of hematopoietic growth factors (*NCCN Guidelines* 2.2018)

- Granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors can be used as 1° prophylaxis when expected FN incidence >20% or as 2° prophylaxis after FN has occurred in a previous cycle (to maintain dose-intensity for curable tumors). CSFs ↓ rate of FN but have not been shown to affect mortality (*Cochrane* 2014 CD003039).
- Colony-stimulating factors can be considered as adjuvant therapy in high-risk FN Pts

SPINAL CORD COMPRESSION

Clinical manifestations (*Lancet Neuro* 2008;7:459)

- Metastases located in vertebral body extend and cause epidural spinal cord compression
- Prostate, breast, and lung cancers are most common, followed by RCC, NHL, myeloma
- Site of involvement: thoracic (60%), lumbar (25%), cervical (15%)
- Signs and symptoms: pain (>95%, *precedes neuro* Δ*s*), weakness, autonomic dysfunction (urinary retention, ↓ anal sphincter tone), sensory loss

Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- Do *not* wait for neurologic signs to develop before initiating evaluation b/c duration & severity of neuro dysfunction before treatment are best predictors of neurologic outcome
- Urgent whole-spine MRI (Se 93%, Sp 97%); CT if unable to get MRI

Treatment (*NEJM* 2017;376:1358)

- Dexamethasone (10 mg IV × 1 stat, then 4 mg IV or PO q6h)
  initiate immediately while awaiting imaging if back pain + neurologic deficits
- Emergent RT or surgical decompression if confirmed compression/neuro deficits
- Surgery + RT superior to RT alone for neuro recovery in solid tumors (*Lancet* 2005;366:643)
- If pathologic fracture causing compression → surgery; if not surgical candidate → RT

TUMOR LYSIS SYNDROME

Clinical manifestations (*NEJM* 2011;364:1844)

- Large tumor burden or a rapidly proliferating tumor → spontaneous or chemotherapy-induced release of intracellular electrolytes and nucleic acids
- Most common w/ treatment of high-grade lymphomas (Burkitt's) and leukemias (ALL, AML, CML in blast crisis); rare with solid tumors; rarely due to spontaneous necrosis
- Electrolyte abnormalities: ↑ K, ↑ uric acid, ↑ PO_4 → ↓ Ca; renal failure (urate nephropathy)

Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m^2 IV (adjusted for renal fxn) & aggressive hydration prior to beginning chemotherapy or RT
- Rasburicase (recombinant urate oxidase) 0.15 mg/kg or 6-mg fixed dose (except in obese Pts) & aggressive hydration prior to beginning chemotherapy or RT (see below)

Treatment

- *Avoid* IV contrast and NSAIDs; treat hyperK, hyperphos, and symptomatic hypocalcemia
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP for goal 80–100 cc/h
- Consider alkalinization of urine w/ isotonic $NaHCO_3$ to ↑ UA solubility, ↓ urate nephropathy risk (controversial: avoid w/ rasburicase; may cause met. alkalosis or $Ca_3(PO4)_2$ precip.)
- Rasburicase (0.1–0.2 mg/kg) for ↑↑ uric acid esp. in aggressive malig (*JCO* 2003;21:4402; *Acta Haematol* 2006;115:35). *Avoid in G6PD deficiency* b/c causes hemolytic anemia. Consider G6PD testing in Jehovah's witnesses espec. if African American (12% prevalence).
- Hemodialysis may be necessary; early renal consultation for renal insufficiency or ARF

CHEMO AND IMMUNORX SIDE EFFECTS

Nausea & vomiting common (*NEJM* 2016;374:1356; 375:134 & 177)

Select Adverse Effects from Chemotherapy		
Toxicity	Common Agents	Comments
Cardiotoxicity (*NEJM* 2016;375;1457)	Anthracyclines	Dose-dependent CMP; ✔ EF pre-Rx
	5-FU	Spasm → ischemia; CCB may prevent
	Trastuzumab	CMP, esp w/ anthracycline, ✔ EF pre-Rx
	Tyrosine kinase inhib (TKI)	QTc prolongation, CMP, angina
	Cyclophosphamide	Myopericarditis (esp. in BMT)
	Cisplatin	HypoMg → arrhythmia, ischemia
Pulmonary (*Sem Oncol* 2006;33:98)	Busulfan	~8% fibrosis or DAH; if severe → steroids
	Bleomycin	~10% IPF; d/c drug, Rx: steroids
	TKI (esp. dasatinib)	Pleural effusion
	Cyclophosphamide	Pneumonitis, progressive fibrosis; Rx: d/c
	Bevacizumab	Pulm hemorrhage (esp. NSCLC)
Nephrotoxicity/ urologic toxicity	Platinum Rx (cisplatin)	Esp. proximal tubule; pretreat w/ IV saline
	Methotrexate	Via deposition; Rx: alkalinize urine, IVF
	Cyclophosphamide	Hemorrhagic cystitis; Rx: Mesna
Neurotoxicity (*Sem Oncol* 2006;33:324)	Platinum Rx (cisplatin)	"Stocking-glove;" Ppx: vit E (*JCO* 2003;21:927)
	Cytarabine	Cerebellar toxicity (irreversible 5–10%)
	Methotrexate (esp. intrathecal)	Late leukoenceph, meningitis; reverse w/ intrathecal glucarpidase, leucovorin
	Ifosfamide	Enceph; Rx: methylene blue, thiamine
	Taxanes, vincristine	Sensorimotor long fiber neuropathy
Hepatotoxicity (*Sem Oncol* 2006;33:50)	TKI (eg, imatinib, nilotinib)	↑ LFTs, rarely necrosis; Rx: d/c ± steroids
	Gemcitabine	Common ↑ ALT/AST; ↓ dose if ↑ bili
	Methotrexate	↑ ALT/AST, rarely fibrosis
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg SJS)

Immune checkpoint inhibitors (*ICI; Science* 2018;359:1350)

- mAb against co-inhibitory signaling molecules, which cancers can use to prevent antitumor immunity
- Targets & drugs include
  - Programmed cell death protein 1 (PD-1; T & pro-B cells): nivolumab, pembrolizumab
  - Prog. death-ligand 1 (PD-L1; tumor & immune cells): atezolizumab, avelumab, durvalumab
  - Cytotoxic T-lymphocyte-assoc. protein 4 (CTLA-4; T cells): ipilimumab
- Toxicity (*NEJM* 2018; 378:158): increased w/ combination of CTLA-4 + PD-1/PD-L1

Most commonly colitis (CTLA-4), pneumonitis (PD-1/PD-L1), hepatitis (CTLA-4), dermatitis, hypothyroidism (PD-1) / hypophysitis (CTLA-4)
Rarely: myocarditis (can be fulminant), myositis, myelitis, uveitis, diabetes

- Treatment: *multidisciplinary care*; hold ICI; give steroids, r/o infection. If severe, consider TNF-α inhibitor for colitis, mycophenolic acid for hepatitis, hormones for endocrinopathy

Chimeric antigen receptor (CAR)-T cells (*Science* 2018;359:1350)

- Autologous T cells w/ modified/chimeric receptor for Ag recognition and T cell activation w/o MHC or 2nd co-stim signal.
- CD19 CAR-T cells targeting B-cell malig. most developed: tisagenlecleucel, axicabtagene ciloleucel

CAR- T Toxicity		
Syndrome	Mechanism & Manifestations	Treatment
Cytokine release syndrome (CRS)	Due to proliferating CAR-T. Fevers to shock.	Anti-IL-6 (tocilizumab or siltuximab) + steroids if severe
CAR-T-cell-related encephalopathy syndrome (CRES)	Cerebral edema due to CAR-T in CNS. Delirium, aphasia, seizures, or death.	Steroids, ativan/keppra for seizures.
Hemophagocytic lymphohistiocytosis (HLH)	Rare hyper-inflammation. Ferritin >10k & liver/kidney/lung toxicity.	CRS Rx, etoposide ± intrathecal cytarabine if not improving (*Nat Rev Clin Onc* 2018;15:47)

NOTES

PNEUMONIA

Microbiology of Pneumonia	
Clinical Setting	Etiologies
Community-acquired (CAP) (*NEJM* 2014;371:1619 & 373:415; *Lancet* 2015;386:1097)	*No pathogen identified in 50–60%*, virus alone in ~25%, bacteria alone in ~10%, virus-bacteria coinfection in <5% Viruses: influenza, RSV, hMPV, rhinovirus (unknown significance), parainfluenza virus, coronavirus *S. pneumoniae* (most common bacterial cause) *S. aureus* (esp. postinfluenza) *Mycoplasma*, *Chlamydia* (esp. in young & healthy) *H. influenzae*, *M. catarrhalis* (esp. in COPD) *Legionella* (esp. in elderly, smokers, ↓ immunity, TNF inhibitors) *Klebsiella* & other GNR (esp. in alcoholics & aspiration)
Hospital-acquired or ventilator-assoc. (HAP/VAP)	*S. aureus*, *Pseudo.*, *Klebsiella*, *E. coli, Enterobacter*, *Acinetobacter, Stenotrophomonas.* IV abx w/in 90 d RF for MDR. Viral~ 20% cases (*Chest* 2017; 154:1)
Immunosuppressed	*Above* + PCP, fungi, *Nocardia*, non-TB mycobacteria (NTM), CMV
Aspiration (*NEJM* 2019;380:651)	*Chemical pneumonitis* due to aspiration of gastric contents *Bacterial pneumonia* ≥24–72 h after aspiration event outPt: oral flora (strep, *S. aureus*, anaerobes) inPt or chronically ill: GNR (*Pseudomonas*) and *S. aureus*

Clinical manifestations

- Presenting features are variable and depend upon several host factors (esp. age)
- Classically: fever, cough w/ purulent sputum, consolidation on CXR
- Atypical pathogens (*Legionella, Mycoplasma, Chlamydia*, virus): historically classified as "atypical" b/c they failed to grow on routine cx. Presentation varies from insidious to acute; imaging features vary from interstitial infiltrates to tree-in-bud opacities, to dense consolid.
- Clinical and imaging features do NOT distinguish "typical" from "atypical"
- Aspiration pneumonitis/PNA: can be infectious or non-infectious; may p/w acute inflammatory syndrome (fever, ↑ WBC, etc.) or insidious course
- HAP/VAP: develops w/in 48 h after admission or mechanical ventilation, respectively

Diagnostic studies

- Sputum Gram stain/Cx: reliable if high quality (ie, sputum not spit; <10 squamous cells/lpf) & if PNA should be purulent (>25 PMNs/lpf). Yield ↓ >10 h after abx (*CID* 2014;58:1782).
- Blood cultures (*before antibiotics!*): ⊕ in ~10% of inPts, depending on pathogen
- Procalcitonin: ↑ in acute bacterial (not viral) PNA. Consider stopping abx if levels <0.25 ng/ml (<0.5 ng/ml in ICU Pts) or ↓ ≥80% from peak. ↓ abx exposure by 2–3 d (*Lancet ID* 2016;16:819 & 2018;18:95). Not validated in immunocompromised hosts. Levels harder to interpret in CKD. False ⊕ in cardiac arrest, shock, surgery.
- CXR (PA & lateral; see Radiology inserts) → tap effusions if >5 cm or severe PNA

- Other: S_aO_2 or P_aO_2, arterial pH (if severe), CBC w/ diff, Chem-20; HIV test (if unknown)
- Other micro based on clinical suspicion (paired serologies available for most atypicals):
  Mycoplasma: PCR of throat or sputum/BAL *before* first dose abx
  Legionella urinary Ag (detects *L. pneumophila* L1 serotype, 60–70% of clinical disease)
  S. pneumoniae urinary Ag (Se 70%, Sp >90%)
  MTb: (induced) sputum AFB stain ×3 q ≥8h (w/ ≥1 early morning specimen). Mycobacterial cx (*empiric respiratory isolation while pending*); MTb DNA PCR if smear ⊕.
- Viral testing (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: consider if immunosupp., critically ill, failing to respond, VAP, suspected TB or PCP, or inadequate or ⊖ sputum cx. Some pathogens need specific cx media (eg, *Legionella* on BCYE).
- Reasons for failure to improve on initial Rx:
  Insufficient time: may take ≥72 h to see improvement (fever persists >4 d in ~20%)
  Insufficient drug levels for lung penetration (eg, vanco trough <15–20 µg/mL)
  Resistant organisms (or superinfxn): eg, MRSA, *Pseudo.;* consider bronchoscopy
  Wrong dx: fungal/viral, chemical pneumonitis, PE, CHF, ARDS, DAH, ILD; consider CT
  Parapneumonic effusion/empyema/abscess: if CXR ⊖, consider CT (dx tap ± chest tube if effusion present, esp. if loculated)
  Metastatic infection (eg, endocarditis, meningitis, septic arthritis)

Triage

- qSOFA predicts poor outcomes, prolonged ICU stay, and in-hospital mortality if >2 of 3: RR>22, AMS, SBP<100 (*JAMA* 2016; 315:801)
- CURB-65: confusion, BUN >20, RR >30, BP <90/60, age >65 If score 0–1: Rx as outpt; 2: Rx as inpt; >3 consider ICU (*Thorax* 2013; 58:377)

Treatment (*CID* 2007;44 Suppl:S27; *JAMA* 2016;315:593; *NEJM* 2019;380:651)		
Scenario	Regimen	Special Considerations
CAP (outPt)	Azithro *or* doxy	*Avoid* azithro/doxycycline if >25% resist- ance locally. Use FQ OR B-lactam + azithro/doxy.
CAP (ward)	Resp FQ *or* [3rd-gen ceph + azithro]	Doxycycline can replace azithro Omadacycline ≈ FQ (*NEJM* 2019;380:517)
CAP (ICU)	Resp FQ + [3rd-gen ceph *or* amp-sulbactam]	Only cover MRSA or Pseudomonas if risk factors. If resp FQ contraindic., use azithro
HCAP (incl. VAP)	[Pip-tazo *or* cefepime *or* carbapen.] + [vanco or linezolid]	May add resp FQ (or azithro) when concerned re: atypicals
Aspiration	Treat if abnl CXR (or if need to be intubated or develops septic shock) Amox-clav, amp-sulbactam, FQ, carbapenem If hosp-acquired and concern for multidrug-resistant pathogens: [pip-tazo, cefepime, or carbapenem] + [AG or colistin]	

- Avoid quinolones if suspect TB
- Steroids: not standard practice, but appear to ↓ mortality, mech vent, & ARDS (*Cochrane*

2017;12:CD007720). Consider in severe CAP (F_iO_2 >0.5 + ≥1 of: pH<7.3; lactate >4; CRP >150). *Avoid* in suspected or known influenza. Dosing: pred 50 mg PO ×7 d or methylpred 0.5 mg/kg IV BID ×5 d.

- Duration: for CAP, 5 d if stable & afebrile for 48–72 h; for HAP/VAP, 8 d (*CID* 2017; 65:8)
- When possible, de-escalate abx based on sensitivities

Prognosis

- For low-risk Pts, can discharge immediately after switching to PO abx (*CID* 2007;44:S27)
- CXR resolves in most by 6 wk; consider f/u to r/o underlying malig (esp. if >50 y or smoker)

Prevention

- All persons >65: give PCV13 vaccine followed by PPSV23 vaccine 1 y later. If PPSV23 already received, give PCV13.
- Age 19–64 w/ CHF/CMP, lung disease (including asthma), cirrhosis, DM, EtOH, or smoker: give PPSV23.
- Any age w/ immunocomp., CSF leak, cochlear implant, asplenia: give PCV13 followed by PPSV23 8 wks later.
- Smoking cessation counseling
- VAP precautions: HOB >30°, chlorhexidine rinse; aspiration precautions in high-risk Pts

---

VIRAL RESPIRATORY INFECTIONS

URI, bronchitis, bronchiolitis, pneumonia (*Lancet* 2011;377:1264)

Microbiology & epidemiology (http://www.cdc.gov/flu/weekly)

- Typical pathogens
  short, mild = rhinovirus, coronavirus
  longer, more severe or complicated = influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, metapneumovirus. Can be esp. severe in immunosupp.

Diagnosis

- Sx: fever, cough, myalgias, SOB, wheezing, sore throat, rhinorrhea, malaise, confusion
- Respiratory viral panel on nasal washing or sputum/BAL
- Rapid influenza *nasopharyngeal swab* preferred to nasal swab (Se 50–70%, Sp >90%)
- RT-PCR for influenza A/B (>95% Se & Sp)

Treatment (*NEJM* 2017;390:697)

- Influenza: neuraminidase inhib. (oseltamivir, zanamivir), which are effective vs. A & B (↓ sx by ~1 d), but resistance emerging.
- Oseltamivir dosed 75 mg PO bid × 5 d. Must start w/in 48 h of sx for low-risk; for critically ill or immunosupp., start ASAP even if >48 h.
- Baloxavir superior to oseltamivir in ↓ sx & viral load on 1st day of Rx, but risk of resistance emerges w/in Pts (*NEJM* 2018; 379:913)
- RSV: Can consider inhaled ribavirin in immunosupp. (eg, BMT, lung tx); limited adult data

Prevention

- Inactivated influenza vaccine: incl. H1N1. Rec for *all* >6 mo of age and esp. if pregnant, >50 y, immunosupp., or HCW (*MMWR* 2012;61:613)
- Isolation, droplet precautions for inPts strongly recommended
- Prophylaxis for high-risk contacts of confirmed influenza: oseltamivir 75 mg PO daily × 10 d

FUNGAL INFECTIONS

Fungal diagnostics

- Antigen detection
  - 1,3-β-D glucan (Se 77%, Sp 86%): Candida, Aspergillus, Histo, Coccidio, PCP. *Cannot* detect Mucor, Rhizopus, Blasto, Crypto. False ⊕ w/ IVIG, albumin, HD, gauze.
  - Galactomannan (Se 40%, but *improved to 85% w/ BAL*; Sp 89%) detects Aspergillus. Test *serum* if heme malig or HSCT. Do not use for screening or Rx monitoring in solid organ Tx, chronic granulomatous dis., or Rx/ppx for Asperg. (false ⊕ w/ colonization).
  - Histo urine/serum Ag: Se of urine Ag 90% (serum 80%) if dissem; Sp limited by X-react
  - Crypto Ag (serum, CSF): serum Ag >90% Se & Sp in invasive infxn, less for pulm only
  - Blastomyces: urine > serum Ag, high Se but modest Sp given X-react w/ other fungi
- Culture: *Candida* grows in blood/urine Cx, but ↓ Se of BCx in deep tissue infection; others (eg, *Crypto*, *Histo*) ↓↓ Se of BCx; if suspect *Coccidio* alert lab *(biohazard)*
- Antibody detection: only useful for *Coccidio*
- Biopsy (histopathology): no grinding of tissue if Zygomycetes suspected

Candida species

- Microbiology: normal GI flora; *C. albicans* & nonalbicans spp.
- Risk factors: neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure, age >65
- Clinical manifestations
  - Mucocutaneous: cutaneous (eg, red, macerated lesions in intertriginous zones); oral thrush (exudative, erythematous or atrophic; if unexplained, r/o HIV); esophageal (odynophagia; ± oral thrush); vulvovaginal, balanitis
  - Candiduria: typically *colonization* due to broad-spectrum abx and/or indwelling catheter
  - Candidemia: *never a contaminant!* R/o retinal involvement (ophtho consult in all cases as req ↑ Rx duration); endocarditis rare but serious (esp. w/ nonalbicans & prosthetic valve). May present with erythematous papules or pustules in immunocompromised.
  - Hepatosplenic: occurs w/ neutrophil recovery

Treatment (*CID* 2016;62:409)	
Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria *(if pyuria or sx of infxn)*	Fluconazole or intravesical ampho if sx, severely immunosupp. or will undergo GU procedure
Candidemia w/o	Echinocandin (mica 1st line) *or* fluc *or* ampho; *remove intravascular catheters if possible*.

neutropenia	*Test for azole resist.*
Febrile neutropenia	Echinocandin *or* ampho

Cryptococcus (*CID* 2010;50:291)

- Epidemiology: immunosupp. (esp. AIDS) most susceptible; can occur in healthy host, esp. elderly, EtOH, DM. Consider *C. gattii* (typically in healthy host).
- Clinical manifestations
  - CNS (meningitis): HA, fever, meningismus, ↑ ICP, CN abnl, ± stupor, often subacute. Dx: CSF CrAg, India ink stain, fungal cx. Cell counts vary; serum CrAg >1:8 Se/Sp in AIDS.
  - Other sites: pulm, GU, cutaneous, CNS cryptococcoma. *With any crypto dx, LP all Pts.*
- Treatment
  - CNS: if ↑ ICP, repeat large-volume LPs or temp. lumbar drain; few require VP shunt
  - CNS Rx has induction (ampho ± flucytosine x2 wks), consolidation and maintenance (fluconazole) phases (*NEJM* 2013;368:1291). If r/o CNS disease, then fluconazole. Dosing and duration vary by host.
  - Non-CNS disease (pulm, skin, bone, blood) in HIV ⊖ Pts: consider fluconazole

Histoplasmosis (*CID* 2007;45:807)

- Endemic to central & SE US, but sporadic cases throughout U.S.
- Clinical manifestations
  - Acute: often subclinical, but may see mild to severe PNA ± cavitary & hilar LAN
  - Chronic pulm: ↑ productive cough, wt loss, night sweats, apical infiltrates, cavitation
  - Disseminated (typically in immunosupp.): fever, wt loss, HSM, LAN, oral ulcers, skin lesion, fibrosing mediastinitis, reactive arthritis, pericarditis
- Treatment: itraconazole (monitor levels); ampho ± steroids if severe or immunosupp

Coccidioidomycosis (*CID* 2016;63:112)

- Endemic to SW U.S. (San Joaquin or "Valley" fever)
- Clinical manifestations
  - Acute: 50–67% subclinical; PNA w/ cough, chest pain, fever, arthralgias, *fatigue*
  - Chronic pulm: nodule(s), cavity or progressive fibrocavitary PNA (can be asx or sx)
  - Disseminated (typically in immunosupp.): fever, malaise, diffuse pulmonary process, bone, skin, & meningeal involvement
- Treatment: monitor mild disease closely q3–6mo; for severe disease: fluconazole, itraconazole or amphotericin

Blastomycosis (*CID* 2008;46:1801)

- Endemic to south central, SE, and Midwest U.S.
- Clinical manifestations
  - Acute: 50% subclinical; cough, multilobar PNA; can progress to ARDS
  - Chronic pulm: cough, wt loss, malaise, CT w/ masses & fibronodular infiltrates
  - Disseminated: (25–40% of all but ↑ in immunosupp.): verrucous & ulcerated skin lesions, bone, & GU involvement; CNS rare unless immunosupp.
- Treatment: itraconazole (monitor levels); ampho if severe, disseminated or immunosupp.

Aspergillosis (*CID* 2008;46:327; *NEJM* 2009;360:1870)

- ABPA; hypersensitivity pneumonitis
- Aspergilloma: usually in pre-existing cavity (from TB, etc.); most asx, but can lead to hemoptysis; sputum cx ⊕ in <50%; CT → mobile intracavitary mass with air crescent
  Rx: antifungals w/o benefit; embolization or surgery for persistent hemoptysis
- Necrotizing tracheitis: white necrotic pseudomembranes in Pts w/ AIDS or lung Tx
- Chronic necrotizing: mild immunosupp.; sputum production, fever, wt loss; CT: infiltrate ± nodule ± thick pleura; lung bx → invasion
- Invasive: seen if immunosupp. (neutropenia for >10 d, transplant, high-dose corticosteroids, AIDS); s/s PNA w/ *chest pain & hemoptysis;* CT: nodules, halo sign (cavitates w/ Rx → air crescent sign); dx w/ galactomannan >0.5 (serum or BAL)
- Rx (necrotizing/invasive): voriconazole (or isavuconazole) superior to ampho; ✔ drug levels

Zygomycetes (eg, *Mucor, Rhizopus*)

- Epidemiology: diabetes (70%, esp. DKA), heme malignancy, s/p transplant, chronic steroids, deferoxamine or iron overload, trauma, h/o voriconazole Rx or Ppx
- Clinical: rhinocerebral = periorbital/forehead pain (more extensive than orbital cellulitis), ± fever (may appear nontoxic at first), exophthalmos, ↓ EOM, CNs (V > VII); nasal turbinates ± black eschar but exam can be quite nl. Also, pulm (PNA w/ infarct & necrosis); cutaneous (indurated painful cellulitis ± eschar); GI (necrotic ulcers).
- Treatment: debridement + Rx (ampho, posaconazole, or isavuconazole); high mortality

INFXNS IN IMMUNOSUPPRESSED HOSTS

Overview

- Many Pts have ≥1 risk (eg, DM, ESRD, transplant, extremes of age)
- The following is not an exhaustive list, but a delineation of common or classic etiologies

Predisposition	Classic Infectious Etiologies
Humoral immune dysfunction (eg, CVID, myeloma) and asplenia	Encapsulated bacteria: *S. pneumo*, *H. flu*, *N. meningitidis* (vaccinate against these 3, ideally prior to splenectomy) Other bacteria: *E. coli* and other GNRs, *Capnocytophaga* Parasites: *Babesia, Giardia;* Viruses: VZV, echovirus, enterovirus
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	Bacteria: Gram positive: coag ⊖ staph, *S. aureus*, viridans strep, *S. pneumo*, other strep; *Corynebacterium* spp., *Bacillus* spp. Gram negative: *E. coli*, *Klebsiella*, *Pseudomonas* Fungi: Yeast: *Candida albicans* and other *Candida* spp. Molds: *Aspergillus, Mucor* spp., endemic fungi and others Viruses: VZV, HSV1 and 2, CMV
Impaired cell-mediated immunity (CMI) (eg, HIV, chronic steroids, posttransplant, DM, ESRD)	Bacteria: *Salmonella* spp., *Campylobacter*, *Listeria*, *Yersinia*, *Legionella* (*Lancet* 2016;387:376), *Rhodococcus*, *Nocardia*, TB, non-TB mycobacteria Fungi: *Candida*, *Crypto*, *Histo*, *Coccidio*, *Aspergillus*, *Pneumocystis, Zygomycetes* spp. and other molds Viruses: HSV, VZV, CMV, EBV, JC virus, BK virus Parasites: *Toxoplasma*, *Cryptosporidium*, *Isospora*, *Microsporidia Babesia; Strongyloides*
Organ dysfunction	Liver (esp. cirrhosis): *Vibrio* spp., encapsulated bacteria ESRD: impaired granulocyte fxn and CMI as above Iron overload (or deferoxamine Rx): *Yersinia*, *Zygomycetes*
Biologics (eg, TNF inhibitors, anti-B-cell Rx; ✔ for TB before starting)	Bacteria: sepsis, septic arthritis, TB, NTM, *Listeria*, *Legionella* Fungi: *Pneumocystis, Histo, Coccidio, Aspergillus*, endemic fungi Viruses: JC virus (PML), EBV, HSV, VZV, HBV Parasites: *Strongyloides* reactivation

(*NEJM* 2007;357:2601; *Am J Med* 2007;120:764; *CID* 2011;53:798)

URINARY TRACT INFECTIONS

Definitions

- Lower: urethritis, cystitis (superficial infection of bladder)
- Upper: pyelonephritis (inflam of renal parenchyma), renal/perinephric abscess, prostatitis
- Uncomplicated: confined to bladder. No upper tract or systemic infection signs.
- Complicated: extends beyond bladder (fever, rigors, malaise, flank pain, CVA tenderness, pelvic/perineal pain in male). Men, those w/ nephrolithiasis, strictures, stents, urinary diversions, immunocompromised, poor controlled DM, are not automatically complicated. Follow closely w/ low threshold to escalate Rx. Pregnant & renal Tx *are* complicated.

Microbiology

- Uncomplicated: *E. coli* (80%), *Proteus*, *Klebsiella*, *S. saprophyticus* (*CID* 2004;39:75). In healthy, nonpregnant women, lactobacilli, enterococci, Group B strep and coag-neg staph (except *S. saprophyticus*) are likely *contaminants* (*Annals* 2012;156:ITC3).
- Complicated: as above + PsA, enterococci, staph (uncommon 1° urinary pathogen w/o catheter or recent instrumentation; ? bacteremia w/ hematogenous spread). ↑ MDR.
- Catheter-associated: *E. coli* most prevalent, but high risk for yeast (24%), MDR PsA, *Klebs*, *Enterococcus*
- Urethritis: *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Trichomonas vaginalis, Mycoplasma genitalium*, HSV

Clinical manifestations

- Cystitis: dysuria, urgency, frequency, hematuria, suprapubic pain; fever *absent.* R/o vaginitis if symptoms of cystitis & urethritis. Neurogenic bladder Pts may have atypical sx (↑ spasticity, autonomic dysreflexia, malaise).
- Urethritis: similar to cystitis except *urethral discharge* can be present
- Prostatitis: chronic: similar to cystitis except *symptoms of obstruction* (hesitancy, weak stream); acute: perineal pain, fever, tenderness on prostate exam
- Pyelonephritis: fever, chills, flank or back pain, nausea, vomiting, diarrhea
- Renal abscess (intrarenal, perinephric): identical to pyelonephritis w/ *persistent fever despite appropriate antibiotics*

Diagnostic studies (*NEJM* 2016;374:562)

- Urinalysis: pyuria + bacteriuria ± hematuria ± nitrites
- Urine Cx (clean-catch midstream or straight-cath)
  - Obtain cx only if symptoms (although in ill Pts, can include ΔMS, autonomic instability)
  - ⊕ if: $\geq 10^5$ CFU/mL in women, $\geq 10^3$ CFU/mL in men. Counts may vary depending on dilution & stage of infxn; interpret in context of sx and host.
  - Pyuria & ⊖ UCx = sterile pyuria → urethritis, nephritis, renal tuberculosis, foreign body

- Catheter-associated: requires (1) s/s (incl atypical) + (2) urine Cx w/ 1 species ≥10^3 coloni from clean urine sample (after replacing Foley). Pyuria alone *not* sufficient to dx UTI in this setting (may be colonization, do not Rx or screen for asx bacteruria).
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- For all men w/ UTI, consider prostatitis: ✔ prostate exam; UCx including 1st void, midstream, and ideally prostatic expressage & postprostatic massage UCx
- Abdominal CT: r/o abscess in Pts with pyelo who fail to defervesce after 72 h
- Urologic w/u (renal U/S w/ PVR, abd CT, voiding cystography) if recurrent UTIs in men

Treatment of UTIs (*CID* 2010;50:625; *JAMA* 2014;312:1677)	
Scenario	Empiric Treatment Guidelines (choice can be individualized)
Cystitis *(JAMA* 2014;16:1677)	Uncomp: nitrofurantoin 100 mg × 5 d *or* TMP-SMX DS PO × 3 d *or* fosfomycin (3 g × 1). Refer to dosing guidelines for ↑ Cr. Complicated: FQ or TMP-SMX PO × 7–14 d FQ or TMP-SMX superior to β-lactams (*NEJM* 2012;366:1028) Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d
Catheterized	Await cultures if HD stable & remove (or exchange) catheter
Urethritis	Treat for both *Neisseria* and *Chlamydia* *Neisseria:* CTX 250 mg IM × 1 and 1 g azithro PO × 1 *Chlamydia:* doxy 100 mg PO bid × 7 d *or* azithro 1 g PO × 1 *M. genitalium:* 1 g azithro PO × 1
Prostatitis	FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wk (chronic)
Pyelonephritis	OutPt: FQ × 7 d *or* TMP-SMX PO × 14 d (*Lancet* 2012;380:452) InPt: CTX *or* aminoglycoside × 14 d; if at risk for MDR pathogen cefepime, pip-tazo, carbapenem, or plazomicin (*NEJM* 2019;380:729) (Δ IV → PO when clinically improved & afebrile 24–48 h, tailor to Cx)
Renal abscess	Drainage + antibiotics as for pyelonephritis

SOFT TISSUE AND BONE INFECTIONS

SKIN AND SOFT TISSUE INFECTIONS (SSTI; *CID* 2014;59:e10)

Clinical

- Cellulitis: infxn of dermis/sc fat, w/ erythema, edema, warmth, pain (rubor, tumor, calor, dolor)
- Erysipelas: infxn of upper dermis (more superficial than cellulitis), often caused by strep, w/ raised erythematous lesion w/ clear demarcation from normal skin
- Impetigo: infxn of superficial layers, often caused by staph, typically in children, w/ purulent lesions, often on face/extrem, ± bullae, ± gold crust
- Lymphangitis: proximal red streaking ± regional lymphadenopathy
- Toxic shock syndrome can occur w/ staph or strep infxn. Fever, HA, N/V, diarrhea, myalgias, pharyngitis, diffuse rash w/ desquamation, HoTN, shock. BCx may be ⊖.

Microbiology (*CID* 2014;59:e10)

- Primarily strep and staph, including MRSA; may include GNRs in diabetics/immunosupp.
- MRSA (*NEJM* 2005;352:1485 & 2006;355:666) causes up to 75% of purulent skin/soft tissue infxns, depending on local epi (rapidly increasing), often assoc. w/ purulent drainage or exudate. Often TMP-SMX sensitive; variably clindamycin sensitive (may falsely appear susceptible on lab testing, requires confirmation w/ D-test; *NEJM* 2007;357:380).
- Bites: skin (strep, staph) and oral flora (incl anaerobes) + special exposures:

Feature	Microbiology	Clinical	Treatment
Cat bite*	*Pasturella spp*	Rapid onset erythema, swelling, lymphangitis, fever	Amox/clav
Dog bite	*Pasturella* & *Capnocytophaga spp*	Can cause severe sepsis w/ DIC & gangrene in asplenic/cirrhotics and other immunosupp.	[Pip/tazo *or* Carbapnem] ± Vanco
Penetrating injury	*Pseudomonas*	Can be a/w deep tissue abscess	Directed based on suscept.
Gardening	*Sporothrix*	Ulcerating nodules, lymphatic spread	Itraconazole
Salt H_2O or raw oysters/fish	*V. vulnificus*	Hemorrhagic bullae & sepsis (esp. in cirrhotics)	Doxy + Ceftaz/CTX
	Erysipelothrix	Rapid onset, risk of endocarditis	PCN/Amox or FQ
Fresh H_2O	*Aeromonas*	Myonecrosis/rhabdo can occur.	FQ, TMP-SMX, or CTX

*Cat scratch disease caused by Bartonella acquired via cat scratch or bite. Results in lymphadenitis.

Diagnosis
- Largely clinical diagnosis; BCx low yield (~5–10%) but useful if ⊕
- Aspirate of bulla or pus from furuncle or pustule may provide microbiologic dx

Cellulitis Treatment (*NEJM* 2014;370:2238; *CID* 2014;59:e10; *JAMA* 2016;316:325 & 2017;317:2088)

Purulent	Usual Micro	Severity	Treatment
No	β-hemolytic *Strep* > *S. aureus*	Mild	PCN, diclox, cephalosporin or clinda
		Mod	PCN, CTX, cefazolin or clinda
		Severe	Vanc + pip/tazo (± clinda for anti-toxin)
Yes	*S. aureus* (incl. MRSA) >> β-hemolytic *Strep.*	Mild	I&D ± [clinda or TMP-SMZ] (*NEJM* 2017;376:2545)
		Mod	TMP-SMX or doxy; some data for clinda (*NEJM* 2015;372:1093), but MRSA sensitivity variable
		Severe	Vanc, dapto, linezolid (± clinda for anti-toxin)

Mild: no systemic signs of infection; moderate: systemic signs; severe: SIRS or immunocompromised

- Limb elevation; erythema may *worsen* after starting abx b/c bacterial killing → inflam.
- In obese Pts, adequate drug dosing important to avoid treatment failure (*J Infect* 2012;2:128)
- Duration: 5 to up to 14 d. Take pictures & draw margins to track progress.

NECROTIZING SOFT TISSUE INFECTIONS (*NEJM* 2017;377:2253)

Definition
- Includes cellulitis, fasciitis, myositis, myonecrosis (gas gangrene).
- Fulminant tissue destruction, systemic toxicity & high mortality. Surgical emergency.

Risk factors
- Can affect healthy individuals via skin/mucosal breach or traumatic wound, but ↑ risk w/ DM, PVD, EtOH abuse, IVDU, cirrhosis, or other immunosupp.

Microbiology
- Necrotizing fasciitis
- Type I: polymicrobial (mixed aerobes & anaerobes), typically in older Pts w/ above RFs. Fournier's gangrene involves genitalia and/or perineum
- Type II: monomicrobial, usually group A strep, less likely *Staph, Vibrio, Aero.*; a/w TSS
- Clostridial myonecrosis (gas gangrene): *C. perfringens; C. septicum* (large Gram ⊕ rods w/ blunt ends on gram stain). A/w traumatic wounds that create an anaerobic environment ideal for *Clostridia*.

Clinical manifestations
- Erythema, edema, warmth + systemic illness (fever, hemodynamic instability) ± crepitus
- Rapid progression of clinical signs
- May see bullae, change in skin color (purple-red to blue-gray)
- Pain out of proportion to apparent cellulitis; skin hyperesthetic and later anesthetic

Diagnosis

- Clinical dx sufficient to initiate urgent surgical exploration
- Aspiration of necrotic center; BCx; Gram stain; lactic acid and CK for tissue necrosis
- Imaging: noncontrast CT, but do not delay Rx/surgery (*Arch Surg* 2010;145:452)
- Microbiologic dx from Gram stain and culture of surgical specimens

Treatment (*CID* 2014;60:169)

- Urgent surgical exploration with debridement of necrotic tissue
- Antibiotics: [vancomycin or linezolid] + [pip/tazo or carbapenem] + clinda for toxin inhibition Consider vanc + cefepime + metronidazole + clinda to avoid nephrotoxicity from pip/tazo Consider IVIG for GAS toxic shock; consult ID

DIABETIC FOOT INFECTIONS

Leading cause of DM-related hosp. days & nontrauma amputations

Microbiology and severity

- Mild (superficial ulcer, no involvement of deeper structures, erythema <2 cm): usually *S. aureus* or aerobic streptococci
- Moderate (ulcer with involvement of deeper structures, erythema >2 cm): more likely to be chronic and polymicrobial (PsA, enterococci, *Enterobacter*, anaerobes)
- Severe (moderate + systemic sx infx): anaerobic streptococci, *Bacteroides*, *Clostridium*

Initial evaluation

- Cleanse, debride, probe, and obtain deep anaerobic + aerobic cultures
- Assess for PVD: sensation, pulses, ABIs

Diagnosis

- Deep tissue wound cx at time of debridement (ideally prior to antibiotics). Avoid superficial swabs (*only* helpful if ⊕ for *S. aureus* and mild infxn).
- For mod/severe: obtain blood cx, ESR, CRP
- Osteomyelitis should always be ruled out. At ↑ risk if: grossly visible bone or able to probe to bone, ulcer >2 cm, ulcer duration >1–2 wk, ESR >70. If suspicious for osteo, obtain plain films ± MRI (see below).

Treatment (*CID* 2012;54:e132)

- Mild infxn: oral abx. Target skin flora (diclox, cephalexin, or amox/clav); use TMP-SMX or doxy for MRSA.
- Mod/severe infxn: IV abx. Target GPCs (vano, linezolid, or dapto) + GNRs (CTX, levo, or amp/sulb) ± anaerobes (metronidazole or clinda). Add PsA coverage (cefepime or pip-tazo) if: severe, immunocomp, neutropenic, water exposure, burn, puncture, nosocomial.
- Elevation, non–weight-bearing status, wound care, glycemic control, Rx for venous insufficiency and arterial ischemia
- Many require surgery: early, aggressive and repeated debridement; revascularization or amputation may be necessary

OSTEOMYELITIS

Infection of bone due to hematogenous seeding or direct spread from contiguous focus

Microbiology (*Lancet* 2004;364:369)

- Hematogenous: *S. aureus*; mycobacterial infection of vertebral body = Pott's disease
- Contiguous focus (may be acute or chronic)
  - open fracture, orthopedic surgery, etc.: *S. aureus* and *S. epi*
  - skin breakdown + vasc. insuffic. (eg, diabetic foot): polymicrobial
  - GU source (GNR, *Enterococcus*)

Clinical manifestations

- Surrounding soft tissue compromise ± fistula to superficial skin
- ± Fever, malaise, and night sweats (more common in hematogenous than contiguous)
- Vertebral osteomyelitis (esp. IVDU): unremitting, focal back pain, usually febrile (*NEJM* 2010;362:1022)

Diagnosis (*JAMA* 2008;299:806)

- Goal is to obtain cx data of causative organism to avoid long-term empiric abx
- Bone biopsy or tissue cx obtained surgically or via percutaneous biopsy (aspiration bx Se 30–74%) unless ⊕ blood cx. Do not rely on swabs of ulcers or fistulae drainage.
- Physical exam: high suspicion in diabetic foot (see above) if can probe ulcer to bone or ulcer >2 cm^2 (Sp 83%, 90% PPV)
- Blood cultures before antibiotics (more often ⊕ w/ acute hematogenous osteomyelitis)
- CBC, CRP, ESR (>70 greatly ↑ likelihood of osteo; *JAMA* 2008;299:806)
- Imaging
  - Plain radiographs: normal early in disease; lytic lesions seen after 2–6 wk
  - MRI: most sensitive imaging study (overall Se 90%, Sp 82%; *Archives* 2007;167:125)
  - CT: can demonstrate periosteal reaction and cortical and medullary destruction
  - CT & MRI very Se but ↓ Sp; false ⊕ if contig focus w/ periosteal reaction, Charcot Δs
  - Radionuclide imaging: very Se but non-Sp (false ⊕ if soft tissue inflammation)

Treatment

- Antibiotics: based on cx data. Duration depends on Rx strategy/goals of Rx management (eg, 6 wks for vertebral osteo; *Lancet* 2015;385:875). After ≥7 days from either start of IV abx or surgery, if doing well consider (in consultation with ID!) Δ'ing IV to PO (if good bioavailability and bone penetration) (*NEJM* 2019;380:425).
- Surgery should be considered for any of the following: acute osteo that fails to respond to medical Rx, chronic osteo, complications of pyogenic vertebral osteo (eg, neurologic compromise, spinal instability, epidural abscess) or infected prosthesis

EPIDURAL ABSCESS

Etiology

- Hematogenous spread ($^2/_3$): skin infection, soft tissue (dental abscess) or endocarditis
- Direct extension (⅓): vertebral osteo, sacral ulcer, spinal anesthesia or surgery, LP

- Risk factors: diabetes, renal failure, alcoholism, IVDU, immunosupp.
- *S. aureus* most common pathogen, increasing incidence of MRSA

Clinical manifestations

- Back pain (unremitting including midline) + often fever ± nerve root or cord signs

Diagnostic studies

- MRI
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently ⊖)

Treatment

- Antibiotics ± surgery (decompressive laminectomy and debridement) for failure to improve on medical Rx. Emergent surgery for early s/s of cord compression (w/ vertebral osteo and epidural abscess, may see paraplegia 48–72 h after first signs)

INFECTIONS OF THE NERVOUS SYSTEM

ACUTE BACTERIAL MENINGITIS

Clinical manifestations (*NEJM* 2006;354:44; *Lancet* 2012;380:1684)

- Fever (77%), headache (87%), stiff neck (31%), photosensitivity, Δ MS (69%) (defined as GCS <14), seizures (5%); 2 of 4 (fever, HA, stiff neck, Δ MS) present in 95%
- Presentation may be *atypical* (eg, lethargy w/o fever) in elderly and immunosupp.

Physical exam

- Nuchal rigidity (Se 31%), Kernig's sign (Pt supine, hip flexed at 90°, knee flexed at 90°; ⊕ if passive extension of knee → resistance), Brudzinski's sign (Pt supine and limbs supine; ⊕ if passive neck flexion → involuntary hip and/or knee flexion)
  nb, Kernig's or Brudzinski's signs ⊕ in only ~10% of Pts (*Lancet* 2012;380:1684)
- ± Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- ± Funduscopic findings: papilledema, absent venous pulsations
- ± HEENT findings: sinus tenderness, clear rhinorrhea (CSF leak)
- ± Skin findings: petechial rash (*N. meningitidis*), genital or oral ulcers (HSV)

Microbiology in Bacterial Meningitis (*NEJM* 2011;364:2016)	
Etiology	Comments
S. pneumoniae (30–60%)	Assess for distant infxn (eg, Osler's triad = meningitis, PNA, IE) Drug-resistant *S. pneumoniae:* ~40% PCN-resistant (even *intermediate* resistance problematic) ~<10% 3rd-gen. cephalosporin-resistant Vaccine may have reduced rate of invasive disease
N. meningitidis (10–35%)	Primarily in those <30 y; may be a/w petechiae or purpura. Deficiencies in terminal complement predispose to recurrent meningococcemia & rarely meningitis. Vaccine rec for all adolescents, college freshmen living in dorm, military recruits, s/p splenectomy or C5-9 deficiency
H. influenzae (<5%)	↓ Incidence in children b/c vaccine. Look for risk factors in adults (eg, CSF leak, neurosurgical procedure, trauma, mastoiditis).
L. monocytogenes (5–10%)	↑ Incid in elderly, alcoholics or Pts w/ cancer, immunosupp. or iron overload. Outbreaks a/w contaminated dairy & raw vegetables. Despite name, a/w *poly-predominant* pleocytosis.
GNRs (1–10%)	Usually health care associated, postprocedure or in elderly or immunosuppressed
Staphylococci (5%)	Seen with indwelling CSF shunt (*S. epidermidis*) or following neurosurgery or head trauma (*S. aureus*)
Mixed infection	Suspect parameningeal focus or CSF leak
Fungal	Seen if immunosuppressed or after neurosurgery

Sequential approach to bacterial meningitis

(1) Stat BCx → antibiotics + corticosteroids (see below)
(2) Consider CT head (if indicated, see below)
(3) LP (if not contraindicated); yield of CSF cx unlikely to be changed if obtained w/in ~4 h

of initiation of abx

Diagnostic studies (*NEJM* 2017;388:3036)

- Blood cultures ×2 *before abx*
- WBC count: >10,000 in >90% of bacterial meningitis in healthy hosts
- Head CT to r/o mass effect before LP *if* ≥1 high-risk feature: immunosupp., h/o CNS disease, new-onset seizure, focal neuro findings, papilledema (*CID* 2004;39:1267)
- Lumbar puncture (*NEJM* 2006;355:e12)
  CSF Gram stain has 30–90% Se; cx 80–90% Se if LP done prior to abx
  opening pressure typically ↑ in bact meningitis; must measure w/ Pt's legs extended
  rule of 2s: CSF WBC >2k, glc <20, & TP >200 has >98% Sp for bacterial meningitis
  repeat LP only if no clinical response after 48 h of appropriate abx or CSF shunt
- Additional CSF studies based on clinical suspicion: AFB smear & cx, India ink prep, cryptococcal Ag, fungal cx, VDRL, PCR (HSV, VZV, enteroviral), cytology
- Metagenomic next-generation sequencing ↑ dx yield (*NEJM* 2019;380:2327)

Typical CSF Findings in Meningitis

Type	Appearance	Pressure (cm H_2O)	WBC/mm^3 Predom Type	Glc (mg/dL)	TP (mg/dL)
Normal	Clear	9–18	0–5 *lymphs*	50–75	15–40
Bacterial	Cloudy	18–30	100–10,000 *polys*	<45	100–1000
TB	Cloudy	18–30	<500 *lymphs*	<45	100–200
Fungal	Cloudy	18–30	<300 *lymphs*	<45	40–300
Aseptic	Clear	9–18	<300 *polys → lymphs*	50–100	50–100

Treatment of Bacterial Meningitis (*Lancet* 2012;380:1693)	
Clinical Scenario	Empiric Treatment Guidelines*
Normal adult	Ceftriaxone 2 g IV q12h + vancomycin 15–20 mg/kg IV q12h If >50 y or alcoholic: add ampicillin 2 g IV q4h for *Listeria* β-lactam allergy: substitute cipro 400 mg q8h or aztreonam 2 g q6h for CTX. Substitute TMP/SMX for amp.
Immunosuppressed	Ampicillin + ceftazidime 2 g IV q8h + vancomycin
CSF shunts, recent neurosurgery, or head trauma	Vancomycin + ceftazidime 2 g IV q8h (*NEJM* 2010;362:146)
Corticosteroids: dexamethasone 10 mg IV q6h × 4 d → ↓ neuro disability & mortality by ~50% w/ *S. pneumo* & GCS 8–11. Consider steroids in all bacterial meningitis prior to organism identification. Must start before or w/ 1st dose of abx (*NEJM* 2002;347:1549). Nb, do *not* give steroids in cryptococcal meningitis (*NEJM* 2016;374:542).	
Prophylaxis: rifampin (600 mg PO bid × 2 d) or ciprofloxacin (500 mg PO × 1) or ceftriaxone (250 mg IM × 1) for close	

contacts of Pt w/ *N. meningitidis* meningitis
Precautions: droplet precautions until *N. meningitidis* is r/o

*When possible, organism-directed Rx, guided by sensitivities or local patterns of drug resistance should be used. In mouse model, Cftx + Ab directed against plgR and PECAM (blood–brain barrier receptors that allow *S. Pneumoniae* to enter) → ↓ bacteria in the brain & less inflammation (*J Infect Dis* 2018; 218:476).

Prognosis

- For community-acquired *S. pneumo* mort. 19–37%; 30% have long-term neuro sequelae

ASEPTIC MENINGITIS

Definition

- CSF pleocytosis w/ ⊖ blood & CSF cx; typically lymphocyte predominant
- Less likely to be bacterial, but can be infectious or noninfectious

Etiologies (*Neurology* 2006;66:75)

- Viral: enteroviruses [most common; if CSF ⊖ & PCR not available, test nonsterile sites (eg, nasopharyngeal, rectum)] to help r/o], HIV, HSV (type 2 > 1), VZV, mumps, lymphocytic choriomeningitis virus, encephalitis viruses, adenovirus, polio, CMV, EBV, WNV
- Parameningeal focus of infection (eg, brain abscess, epidural abscess, septic thrombophlebitis of dural venous sinuses or subdural empyema)
- Partially treated bacterial meningitis
- TB, fungal, spirochetal (Lyme, syphilis, leptospirosis), rickettsial, *Coxiella*, *Ehrlichia*
- Medications: TMP/SMX, NSAIDs, IVIG, PCN, INH, lamotrigine
- Systemic illness: SLE, sarcoidosis, Behçet's, Sjögren's syndrome, RA
- Neoplasm: intracranial tumors (or cysts), lymphomatous or carcinomatous meningitis (CSF cytology or flow may be reactive and dx may require meningeal bx)

Empiric treatment

- No abx if suspect viral (cell count <500 w/ >50% lymphs, TP <80–100 mg/dL, normal glc, ⊖ Gram stain, not elderly/immunosupp.); o/w start empiric abx, wait for cx data
- If suspect MTb: antimycobacterial Rx + dexamethasone (*NEJM* 2004;351:1741)
- If suspect fungal: ampho lipid formulation, ± 5-fluorouracil

ENCEPHALITIS (*NEJM* 2018;379:557)

Definition

- Infection of brain parenchyma with evidence of neurologic dysfunction

Etiologies (specific etiology found in <20% of cases; *Neurology* 2006;66:75; *CID* 2008;47:303)

- HSV-1 all ages/seasons. If sxs recur after Rx, consider viral relapse vs. autoimmune encephalitis b/c high rates of autoimmune disease wks later (*Lancet Neurol* 2018;17:760).
- VZV 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- Arboviruses: West Nile, Eastern/Western equine, St. Louis, Japanese, Powassan (*NEJM* 2005;353:287): fever, HA, flaccid paralysis, rash. Risk factors for severe renal dis., cancer,

EtOH, DM, HTN (*Am J Trop Med Hyg* 2012;87:179).
- Enteroviruses (coxsackie, echo): viral syndrome; peaks in late summer/early fall
- Others: CMV, EBV, HIV, JC virus (PML), measles, mumps, rubella, rabies, flu, adenovirus
- Non-infectious: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5, anti-mGluR5), endocarditis, brain abscess, toxoplasmosis, TB, toxins, vasculitis, Whipple's disease, subdural hematoma, post-infxn demyelination (eg, ADEM), seizure

Clinical manifestations
- Fever, HA, Δ MS, ± seizures and focal neuro findings (latter atypical for viral *meningitis*)

Diagnostic studies (*CID* 2013;57:1114)
- Lumbar puncture: lymphocytic pleocytosis; PCR for HSV (95% Se & Sp at 2–3 d), VZV, CMV, EBV, HIV, JC, adeno/enterovirus, W. Nile (<60% Se); W. Nile CSF IgM 80% Se
- Consider testing for autoimmune etiologies (anti-NMDAR, etc.) in approp. setting
- MRI (CT if unavail.); HSV w/temporal lobe involvement, W. Nile w/ thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific (temporal lobe focus in HSV)

Treatment
- HSV, VZV: acyclovir 10 mg/kg IV q8h (often empiric Rx given frequency of HSV/VZV)
- CMV: ganciclovir ± foscarnet; supportive care for most other etiologies

---

BELL'S PALSY

Definition & etiology
- Acute idiopathic unilat. facial nerve palsy (CN VII), often presumed HSV-1 reactivation

Clinical manifestations
- Unilateral facial muscle weakness, hyperacusis, ↓ taste/lacrimation/salivation

Diagnosis
- Dx of exclusion: r/o brainstem lesion, Lyme (often bilateral), zoster (incl *sine herpete*), HIV/AIDS, sarcoid (often bilateral)

Treatment (*NEJM* 2007;357:1598; *JAMA* 2009;302:985)
- ~80% recover spontaneously by 9 mo (much lower rate in DM)
- Corticosteroids (prednisolone 25 mg PO bid × 10 d) started w/in 72 h of sx onset improve odds of recovery (note: no conclusive data for use in DM, immunosupp.)
- No conclusive data to support the use of acyclovir or valacyclovir

---

ZOSTER

Definition & etiology

- Zoster = herpes zoster = shingles: acute, unilat., painful dermatomal skin eruption
- VZV reactivation in peripheral nerve distribution from latency in dorsal root ganglion

Clinical manifestations

- Neuritic pain in a dermatomal distribution, then acute dermatomal eruption of clustered rash (vesicles > papules/pustules > macules) in varying stages of evolution
- Consecutive dermatomes may be seen in all Pts; more widespread in immunosupp.
- Lesions in V1 distribution of facial nerve require urgent ophthalmologic evaluation
- Post-herpetic neuralgia (PHN) = severe pain lasting >90 d after episode; may last mos to y, more frequent w/ ↑ age and delay of antiviral Rx

Diagnosis

- Appearance of rash; DFA is most Se from scrape of newly unroofed vesicle. Tzanck does not distinguish HSV or VZV, cx insensitive for VZV (unlike HSV).

Treatment

- Rx if can initiate w/in 72 h of skin lesions in healthy Pt or at *any time* in immunosupp
- Valacyclovir or famciclovir × 7–14 d, or until lesions fully crusted; acyclovir 10 mg/kg IV q8h if dissem. or high-risk Pt (medically ill, immunosupp., V1 zoster w/ ophthalmic s/s, etc.)
- Prevention: Shingrix approved for Pts >50 y. 2 doses separated by 2–6 mos (97% effective at preventing shingles, also ↓ post-herpetic neuralgia).

BACTEREMIA & ENDOCARDITIS

BACTEREMIA

Etiologies

- 1° infxn due to direct inoculation of the blood, frequently assoc w/ intravascular catheters. Catheter-related bloodstream infection = same org from peripheral cx *and* cath tip cx *or* cx drawn from catheter (*CID* 2009;49:1).
- 2° infxn due to infection in another site (eg, UTI, lung, biliary tree, skin) spreading to blood

Microbiology

- Coag-neg staph 34%, *S. aureus* 10%, enterococci 16%, *Candida* 12%, GNRs 5%
- *Clostridium septicum*, *Bacteroides*, & *S. bovis* a/w colon ca (*Gastro* 2018;155:383)
- Bacteremia with encapsulated organisms (*S. pneumo, Neisseria, Haemophilus*, Group A strep) may indicate 1° immunodeficiency (*Clin Microbiol Infect* 2017;8:576)

Risk factors for true bacteremia (*JAMA* 2012;308:502)

- Fever, shaking chills and poor food consumption (*J Hosp Med* 2017;12:510), SIRS (96% Se), IVDU, comorbidities, immunosupp, indwelling lines
- Organism
  - more likely pathogenic: *S. aureus*, β-hemolytic strep, enterococci, GNR, *S. pneumo, Neisseria*
  - less likely pathogenic: coag-neg staph (~10%), diphtheroids, *Propionibacterium* (~0%)
- Time to growth: <24 h → higher risk, >72 h → lower risk (except for slow-growing organisms such as HACEK group)
- Factors increasing likelihood of endocarditis: high-grade bacteremia w/o source, persisting after line removal or drainage of focal source, in hosts at risk for endocarditis or w/ organisms known to cause IE; emboli

Diagnosis

- Obtain BCx prior to abx if possible, ≥2 sets (2 bottles in each set, each w/ 10 cc blood)
- If proven bacteremia, daily surveillance cxs until 48 hrs of ⊖ cxs. May not need for GNRs (*CID* 2017;65:1776).
- If *S. aureus* or *S. lugdunensis* obtain TEE. TTE for high-grade Strep bacteremia. No need for routine echos for GNR bacteremia.

Treatment

- Antibiotics based on Gram stain/culture results; tailor abx to sensitivities
  - empiric therapy for GPC: vanco to cover coag-neg staph and MRSA while awaiting sensi
- *S. aureus* bacteremia: ID consult associated with lower mortality (*CID* 2015;60:1451).

Short-Term Central Venous Catheter-Related Bloodstream Infections (*CID* 2009;49:1)	
S. aureus	Risk of endocarditis in bacteremia: ~25% (*JACC* 1997;30:1072) D/c CVC, TEE to r/o endocarditis; if TEE ⊖ *and* not immunosupp. *and* no intravasc prosthesis, Rx × 2 wk from first ⊖ BCx. If no echo obtained, Rx × 4–6 wk. Preferred abx: MSSA → nafcillin or cefazolin; MRSA → vancomycin
Coag-neg staphylococci	May consider keeping catheter. Catheter retention does not ↓ rate of bacteremia resolution, but a/w ↑ rate of recurrence (*CID* 2009;49:1187). If catheter left in place, Rx × 10–14 d and consider abx or ethanol lock If catheter d/c, Rx × 5–7 d
Enterococcus	D/c catheter & Rx × 7–14 d
GNR	Rx × 7–14 d. Abx based on sensitivities. D/c catheter if *Pseudomonas.*
Fungi	D/c catheter & Rx × 14 d from first ⊖ BCx

- Persistently ⊕ BCx: d/c indwelling catheters, consider metastatic infxn, infected thrombosis or infected prosthetic material (joint, abscess, vascular graft, PPM, etc.)

BACTERIAL ENDOCARDITIS

Definition

- Infection of endothelium of heart (including but not limited to the valves)

Predisposing conditions

- Abnormal valve
  - *High risk:* prior endocarditis, prosthesis, cyanotic congenital heart (unrepaired), VADs, rheumatic heart disease, AoV disease (incl. bicuspid)
  - *Medium risk:* MV disease (including MVP w/ MR or thickened leaflet), HCMP
- Risk of bacteremia: IVDU, indwelling venous catheters, poor dentition, hemodialysis, DM, prosthetic material in heart (eg, pacemaker, ICD, graft)

Modified Duke Criteria	
Major	Minor
• BCx with common endocarditis pathogen (grown in 2 separate cultures) • *Coxiella* serology ≥1:800 • Endocardial involvement, w/ either: echocardiogram w/ vegetation, abscess, or prosthetic dehiscence new valvular regurgitation	• Predisposing condition (see above) • Fever • Vascular phenomena: septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions • Immune phenomena: ⊕ RF, GN, Osler's nodes, Roth spots • ⊕ BCx not meeting major criteria
Definitive (ie, highly probable): 2 major *or* 1 major + 3 minor *or* 5 minor criteria Possible: 1 major + 1 minor *or* 3 minor criteria	

Se ~90%, Sp >95%, NPV ≥92% (*CID* 2000;30:633). *Serologic or molecular tests for other known agents of Cx ⊖ endocarditis (see below) not yet included as major criterion, but may help dx.

Microbiology of Endocarditis				
	Native Valve (NVE)		Prosthetic Valve (PVE)	
Etiology	**Non-IVDA**	**IVDU**	**Early** (≤60 d)	**Late** (>60 d)
S. viridans et al.	**36%**	**13%**	<5%	**20%**
Enterococcus	**11%**	5%	8%	13%
S. aureus	**28%**	**68%**	**36%**	**20%**
S. epidermidis	**9%**	<5%	**17%**	**20%**
GNR	<5%	**<5%**	**6%**	<5%
Other	<5%	<5%	10%	10%
Fungal[a]	1%	1%	9%	3%
Culture ⊖[b]	11%	<5%	17%	12%

[a]↑ risk w/ DM, indwelling lines, immunosupp. [b]Cx ⊖ = abiotrophic strep, HACEK (*Haemophilus para-influenzae* & *aphrophilus, Actinobacillus, Cardiobacterium, Eikenella* and *Kingella*), *T. whipplei*, *Bartonella, Coxiella, Chlamydia, Legionella, Brucella* (*JAMA* 2007;297:1354; *Annals* 2007;147:829; *J Clin Microbiol* 2012;50:216)

Clinical manifestations (*Lancet* 2016;387:882)

- Persistent bacteremia: fever (80–90%), rigors, night sweats, anorexia, wt loss, fatigue
- Valvular or perivalvular infection: CHF, conduction abnormalities
- Septic emboli: stroke, PE (if right-sided), mycotic aneurysm, MI (coronary artery embolism), CNS, kidneys, spleen, joints
- Immune complex phenomena: arthritis, glomerulonephritis, ⊕ RF, ↑ ESR
- *Subacute* (less-virulent pathogens) can p/w fatigue, nonspecific sx in Pts w/o risk factors

Physical exam

- HEENT: Roth spots (retinal hemorrhage + pale center), petechiae (conjunctivae, palate)
- Cardiac: murmur (85%), new valve regurgitation (40–85%) ± thrill (fenestrated valve or ruptured chordae), muffled sounds (PV). *Frequent exams* for Δ murmurs, s/s CHF.
- Extremities
  Janeway lesions (septic emboli → nontender, hemorrhagic macules on palms or soles)
  Osler's nodes (immune complexes → tender nodules on pads of digits)
  proximal nail bed splinter hemorrhages (8–15%); petechiae (33%); clubbing; arthritis
- Δ MS or focal deficits, vertebral tenderness
- Devices: erythema, tenderness or drainage at catheter site, PM/ICD pocket tenderness

Diagnosis (*CID* 2010;51:131; *EHJ* 2015;36:3075; *Circ* 2015;132:1435)

- Blood cultures (*before abx*): 3 sets (aerobic & anaerobic bottles) from different sites, ideally spaced ≥1 h apart. ✔ BCx (at least 2 sets) after appropriate abx have been initiated to document clearance; repeat q24–48h until ⊖.
- ECG (on admission and at regular intervals) to assess for new conduction abnormalities
- Echocardiogram: *TTE in all*. Obtain TEE if (i) TTE nondx (ii) TTE ⊖ but high suspicion, (iii) high-risk (prosthetic valve, prior IE, congenital heart dis.), or (iv) suspect progressive or invasive infxn (eg, persistent bacteremia or fever, new conduction abnl, etc.)

Method	Sensitivity		
	NVE	PVE	Abscess
Transthoracic (TTE)	39–58%	33%	18–63%
Transesophageal (TEE)	>90%	86%	76–100%

(*Mayo Clin Proc* 2014;89:799; *Circ* 2015;132:1435; *Eur Radiol* 2015; 25:2125; *J Am Soc Echo* 2016;29:315)

- Addition of PET/CT or MRI helpful to assess for periannular complications in PVE
- Brain/spine imaging necessary in those who develop severe HA, neurologic deficits, meningeal signs. Consider in any patient with left-sided endocarditis (*Circ* 2015;132:1435).
- Cx ⊖ endocarditis: may be due to abx prior to BCx. PCR, bacterial 16S ribosomal RNA, serol. may be helpful. Detailed hx: animal exposure, travel, unpast. dairy, etc. ID eval.

Treatment (*Circ* 2015;132:1435)	
Organism	Specific Considerations
Empiric	NVE or PVE >12 mo post-op: Vanc + CTX PVE <12 mo post op: Vanc + CTX + gent
Strep	*S. bovis* a/w colon cancer. Penicillin, Amp, CTX
Staph	• MRSA: vanc or dapto; MSSA: nafcillin or cefazolin • Obtain ID consult • Vanc inferior to beta lactam for long-term MSSA Rx • For PCN allergy w/ MSSA, undergo desensitization • Do not use cefazolin for CNS involvement b/c poor penetration • Rif (+ AG × 2 wk to prevent resistance) should be added in PVE • *S. lugdunensis* is *virulent* and should be treated like *S. aureus*
Enterococcus	Ampicillin + [CTX or gent]; VRE needs linezolid or dapto
GNRs	HACEK: CTX. *Pseudomonas*: 2 anti-Pseudomonal agents [eg, B-lactam + (AG or quinolone)]; consult ID.
Fungi	Liposomal ampho or micafungin. Risk factors: TPN, lines, pacemaker/ICD, prothesis, IVDU. *Ophtho consult for candidemia.*
Early surgical consult for any prosthetic valve infection regardless of organism	

- De-escalate abx to organism-directed therapy once sensitivities return
- Repeat BCx q24–48h until Pt defervesces and BCx ⊖
- Anticoag. controversial; d/c for ≥2 wk if PVE and CNS embolic event. Can continue antiplatelet Rx if no CNS event in all comers, but no proven benefit to adding.
- Monitor for complications of endocarditis (CHF, conduction block, new emboli, etc., which can occur even on abx) and of abx Rx (interstitial nephritis, ARF, neutropenia, etc.)
- Duration of Rx: usually 4–6 wk

  After ≥10d IV abx, if doing well, and depending on organism, Pt, & abx choices, may consider Δ'ing to PO in consultation with ID (*NEJM* 2019;380:415)

  Uncomplicated right-sided NVE or PCN-S strep spp → 2 wk may be comparable

Indications for surgery (*EHJ* 2015;36:3075)

- Severe valvular dysfunction → refractory CHF: *emergent* if refractory cardiogenic shock (ie, despite ICU-level Rx); *urgent* (w/in days) if persistent refractory heart failure; *elective* (w/in wks) if asx severe AI or MR. Consult cardiac surgery early.

- Uncontrolled infxn (typically urgent surgery w/in days): periannular abscess (10–40% NV 60–100% PVE), heart block, fistula, worsening conduction, PVE w/ dehiscence, ↑ veg. size or persistent sepsis (eg, ⊕ BCx after ~1 wk of appropriate IV abx & no drainable metastatic focus or other identifiable cause; complicated if due to septic emboli to lung)
- Organism: consider surgery for *S. aureus*, fungal or multiRx-resistant organisms
- Prosthetic valve: dysfunction or dehiscence
- Systemic embolism (20–50%): risk 4.8/1000 Pt days in 1st wk, 1.7/1000 thereafter. Urgent surgery if L-sided w/ >10 mm veg & severe AI/MR (*NEJM* 2012;366:2466) or if recurrent emboli, embolism & >10 mm veg, or >15 mm veg despite approp. abx.
- Cerebral emboli no longer considered contraindic to surgery unless severe stroke or hemorrhage (then ideally wait 1 mo) (*Stroke* 2006;37:2094)

Prognosis

- NVE: non-IVDU *S. aureus* → 30–45% mortality; IVDU *S. aureus* (often right-sided) → 10–15% mortality; SBE → 10–15% mortality
- PVE → 23% mortality

Endocarditis Prophylaxis (*Circ* 2007;116:1736)	
Cardiac conditions*	Prosthetic valve; previous NVE; congenital heart disease (CHD) including unrepaired or incompletely repaired cyanotic CHD (palliative shunts or conduits), 1st 6 mo after completely repaired CHD using prosthetic material; cardiac transplant recipients w/ valvulopathy (Prophylaxis no longer rec. in acquired valvular dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCMP)
Procedures*	Dental: manipulation of gingival tissue or periapical region of teeth or perf oral mucosa (eg, extraction, periodontal, implant, root canal, cleaning) Respiratory: incision or biopsy of respiratory mucosa (no prophylaxis for GI or GU procedures)
Regimens	Oral: amoxicillin 2 g 30–60 min before Unable to take PO: amp 2 g IM/IV or cefazolin or Cftx 1 g IM/IV PCN-allergic: clinda 600 mg PO/IM/IV

*Pts should meet both indications (high-risk condition & high-risk procedure) to qualify for Ppx

TUBERCULOSIS

Epidemiology

- U.S.: 10–15 million infected (15× ↑ risk if foreign-born or minority); worldwide: ~2 billion
- Multidrug-resistant (MDR) TB: resistant to INH & rifampin. Can occur as 1° infxn.
- Extensively drug-resistant (XDR) TB resistant to INH, RIF, FQ, and injectables
- Risk factors (*NEJM* 2011;364:1441)
  - *Acquisition:* immigrant from high-prevalence area, homeless, IVDU or medically underserved, resident or worker in jail or long-term facility, healthcare worker, close contact to Pt w/ active TB
  - *Reactivation:* risk is 5% in first 2 yr, 5–10% over lifetime, but higher if HIV ⊕, immunosupp. incl. biologics, CKD (HD), uncontrolled DM, cancer, transplant, malnourished, underweight, smoker, IVDU, alcohol

Microbiology & natural history

- Transmission of *Mycobacterium tuberculosis* via small-particle aerosols (droplet nuclei)
- 90% of infected normal hosts will never develop clinically evident disease
- Localized disease: healing & calcification *or* progressive 1° TB (at site of infection)
- Hematogenous spread: latent infection ± reactivation TB *or* progressive dissem. TB

Screening for latent TB

- Whom to screen: high-prevalence and high-risk populations (HIV ⊕ Pts should be tested as part of initial evaluation and annually thereafter)
- How to screen
- IFN-γ release assays (IGRA): Ag-stimulated IFN-γ release from patient's T-cells. Preferred to PPD due to ↑ Sp in BCG vaccine Pts (*Annals* 2008;149:177).
- Tuberculin skin test (TST or also known as PPD): inject purified protein interdermally then examine for wheal 48–72 hrs later. Interpret based on max diameter of induration.

Size of Reaction	Persons considered to have ⊕ test (*NEJM* 2002;347:1860)
>5 mm	HIV ⊕ or immunosupp (eg, prednisone 15 mg/d × >1 mo) Close contacts of Pt w/ active TB; CXR w/ apical fibrosis c/w TB
>10 mm	All other high-risk or high-prevalence populations Recent conversion (↑ in induration by >10 mm in last 2 y)
>15 mm	Everyone else
False ⊖	Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB mycobacteria (NTM), malignancy
False ⊕	Improper reading, cross-reaction with NTM, BCG vaccination (although usually <10 mm by adulthood)
Booster effect	↑ induration b/c immunologic boost by prior skin test in prev sensitized individual (by TB, NTM or BCG). Test ⊖ → ⊕ but *not* true conversion due to *recent* infxn. 2nd test true baseline. Can be 1 y after initial test.

- Neither screening test rules in/out active TB. Use both IGRA & PPD combined to ↑ Se (to 80–90%). Relies on host immune system, therefore limited Se in immunocompromised (*J Clin Epi* 2010;63:257; *CID* 2011;52:1031).

Clinical manifestations (*Lancet* 2016;387:1211)

- Primary TB pneumonia: middle or lower lobe consolidation, ± effusion, ± cavitation
- TB pleurisy: can occur w/ primary or reactivation. Due to breakdown of granuloma w/ spilling of contents into pleural cavity and local inflammation. Pulmonary effusion ± pericardial and peritoneal effusions (tuberculous polyserositis).
- Reactivation TB pulmonary disease: apical infiltrate ± volume loss ± cavitation
- Miliary TB: acute or insidious; due to hematogenous dissemination; usually in immunosupp, DM, EtOH, elderly or malnourished. Constitutional sx (fever, night sweats, weight loss) usually prominent. Pulm disease w/ millet seed-like lesions (2–4 mm) on CXR or chest CT (latter more Se) present in 60–80% of those w/ miliary TB.
- Extrapulmonary TB: lymphadenitis, pericarditis, peritonitis, meningitis, nephritis ± sterile pyuria, osteomyelitis (vertebral = Pott's disease), hepatitis, splenitis, cutaneous, arthritis
- TB and HIV: HIV ⊕ at ↑ risk infxn, progressive 1° infxn & reactivation. Risk of progression from infxn to disease >8–10%/y, higher risk with ↓ CD4. Reinfection (also w/ MDR) significant, esp. in hyperendemic areas.

Diagnostic studies for active TB (*high index of suspicion is key!*)

- AFB smear (rapid dx) and culture (↑ Se & allows sensitivity testing) of sputum, BAL, pleura, etc.; *avoid FQ* if considering TB (can compromise dx yield)
- Gene Xpert PCR (rapid dx) can also detect rifampin resistance; validated on nonbloody sputum only. Sp 98% & Se 74% independent of HIV status (*AJRCCM* 2014;189;1426).
- PCR: 94–97% Se c/w smear; 40–77% Se c/w culture (*JAMA* 2009;301:1014)
- CXR: classically fibrocavitary apical disease in reactivation vs. middle & lower lobe consolidation in 1° TB but distinction imperfect. HIV ⊕ assoc. w/ nonapical disease regardless of timing (*JAMA* 2005;293:2740).
- Adenosine deaminase testing: useful in extrapulmonary sites; best validated for ascites

Treatment of latent TB

- Treat Pts who are ⊕ based on guidelines or any exposed HIV ⊕ or immunocompromised Pt (*NEJM* 2015;372:2127; *Eur Respir J* 2015;46:1563)
- R/o active disease in any Pt w/ suggestive s/s before starting INH (cough, fever, nightsweats), CXR (though may be nl in immunosupp.)

Scenario	Prophylaxis Regimen
PPD/IGRA ⊕ (regardless of HIV status), or contact case INH resistant	1st line: Rifampin × 4 mo (non-inferior to INH, greater adherence and lower hepatotoxicity) (*NEJM* 2018;5:440). *Alternative:* [INH 5 mg/kg + vitamin B6 × 9 mo] *or* [INH + Rifapentine weekly × 12 wk]
Contact case known or suspected to have MDR TB	No proven regimen: ? PZA + EMB, ? PZA + FQ

(INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; EMB, ethambutol; FQ, fluoroquinolone)

- ✔ LFTs monthly if receiving INH (risk ↑ w/ age; *Chest* 2005;128:116): if 5× ULN *or* sx → stop TB meds & re-eval

Patient isolation

- Decision based on likelihood. Consider when cough, dyspnea, hemoptysis + 1 risk factor (HIV ⊕, foreign born, substance use disorder, homeless, recent incarceration, prior TB or exposure).
- Discontinue if alternative dx, AFB smear neg ×3, or TB treated for 2 wk & AFB neg

Treatment of active tuberculosis (*NEJM* 2015;373:2149; *Lancet* 2016;387:1211)

- Treatment requires several drugs to prevent resistance (see below)
- Suspect MDR TB if prior TB Rx, travel to area w/ ↑ rates of MDR (India, China, Russia, South Africa), exposure to person w/ likely MDR-TB, poor Rx adherence, INH resis. in community ≥4% (includes most of U.S.), extrapulm. TB, HIV ⊕ (*NEJM* 2008;359:636)
- Screen for HIV. If ⊕ → consult ID re: timing of concurrent HIV Rx
- "Paradoxical *worsening*" of sx can occur after starting Rx. More common w/ extrapulm TB & more frequent/severe w/ concurrent immune reconstitution (eg, HIV ⊕ Pts started on ARVs, Pts taken off immunosuppression). *Must r/o Rx failure* (repeat Cx, imaging, etc.).

Antituberculous Medications		
Drug	Dose	Adverse Effects*
Isoniazid (INH)	300 mg PO qd	Hepatitis, periph neuropathy (↓ risk by suppl. vit B_6), drug-induced lupus
Rifampin (RIF)	600 mg PO qd	Orange tint of body fluids, GI upset, hepatitis, hypersensitivity, fever, drug interactions, avoid EtOH
Pyrazinamide (PZA)	25 mg/kg PO qd	Hepatitis, hyperuricemia, arthritis
Ethambutol (EMB)	15–25 mg/kg PO qd	Optic neuritis
Streptomycin (SM)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Amikacin (AMK)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin)	400 mg PO qd	GI upset, tendinopathy, ↑ QTc

*Risk of hepatitis ↑ w/ pre-existing liver disease. Consult ID if mod to severe liver disease, and consider holding/replacing PZA or INH.

Scenario	Antituberculous Treatment Regimens
Pulmonary TB ≥4% INH-resist. in community (includes most of U.S.)	INH + RIF + PZA + (EMB) until suscept. known If *sensitive* to INH & RIF → INH + RIF + PZA × 2 mo, *then* → INH + RIF × 4 mo If *resistant*, see next row
Drug-resistant TB (INH-R, RIF-R or MDR/XDR)	*Consult ID specialist* (*NEJM* 2008;359:636)
Extrapulmonary TB	*Consult ID specialist*
TB in HIV ⊕ patient	*Consult ID specialist*

Individualize duration based on host, disease form, and rate of clinical/microbiologic improvement

HIV/AIDS

Definition & Clinical Manifestations

- Acute HIV: mono-like syndrome → rash, lymphadenopathy, fever, oral ulcers, pharyngitis, myalgias, diarrhea. Presents ~2–6 wk after infxn.
- AIDS: HIV + CD4 <200/mm^3 *or* AIDS-defining opportunistic infection (OI) or malignancy

Epidemiology

- ~1 million Americans living w/ HIV (1 in 8 unaware); ~36 million worldwide
- Highest at risk are men who have sex with men (MSM) and African Americans
- Routes: sexual (risk is 0.1–1% per sex act w/o ARV), IVDU, transfusions, needlesticks (0.3%), vertical (15–40% w/o ARV)

Prophylaxis (*NEJM* 2015;373:2237; *Lancet* 2016;387:53; *J Infect Dis* 2018;218:16)

- Preexposure (PrEP): TDF/FTC qd effective & safe in high-risk, adherent populations. Use in heterosexuals or MSM w/: (1) serodiscordant partner, (2) inconsistent condom use, or (3) STI w/in 6 mo; or IVDU w/ equipment sharing or high-risk for HIV (*JAMA* 2019;321:2203). On-demand PrEP effective option for MSM (44–86% ↓). ✔ renal fxn, STIs, & HIV q3 mo.
- Postexposure (PEP): present <72 hr after high-risk exposure from HIV+ source (case-by-case decision if HIV status unknown). Test baseline HIV, STIs, HBV, HCV. Rx: 2 NRTIs (usually TDF/FTC) + RAL or DTG × 4 wk. Consider initiating PrEP.
- Treatment is prevention: early Rx of HIV ⊕ Pt prevents transmission to partners (*NEJM* 2016;375:830). Risk of transmission w/ unprotected sex w/ undetectable viral load is ~0% (*JAMA* 2016;316:171; *Lancet HIV* 2018;5:e438).

Screening and Diagnosis

- Screen all ages 13–64 once in lifetime & every pregnancy. High risk (IVDU, sex workers, MSM >1 partner) screen annually (*JAMA* 2018;320:379).
- HIV Ab/p24Ag (ELISA assay): ⊕ 1–12 wk after acute infxn; >99% Se; 1° screening test
- If ⊕, Ab differentiation assay confirms and differentiates HIV-1 vs. -2 (*MMWR* 2013;62:489)
- HIV RNA PCR viral load in plasma; assay range is 20–10 million copies/mL; ~2% false ⊕, but usually low # copies; in contrast, should be very high (>750 k) in 1° infxn
- CD4 count: not a dx test, b/c can be HIV ⊕ w/ normal CD4 or be HIV ⊖ w/ low CD4

Approach to newly diagnosed HIV ⊕ Pt (*JAMA* 2018;320:379)

- Document HIV infection; counsel re: treatment options, adherence, & disclosure
- Lab evaluation: CD4 count, HIV VL & genotype, CBC w/ diff., Cr, lytes, LFTs, A1c, & fasting lipids; PPD or IGRA, toxo, syphilis, *Chlamydia* & gonorrhea screens, Hep A/B/C serologies; G6PD (if PCP ppx), Pap smear/anal pap in ♀/♂; ± CMV IgG, baseline CXR

- Initiate ARV early (same day prior to labs/genotype and w/ *guidance from HIV specialist*) regardless of CD4 level because ↓ mortality (*NEJM* 2015;373:795)
- Regimens include: 2 NRTI (eg, TAF + FTC) + *either* int. inhib or boosted PI (eg, DRV/r)

Common Antiretrovirals (ARVs)		Common Side Effects
NRTI	abacavir (ABC; Ziagen) emtricitabine (FTC; Emtriva) lamivudine (3TC; Epivir) tenofovir (TAF or TDF) zidovudine (AZT; Retrovir)	*Class:* GI intol, lipoatrophy, lactic acidosis ABC: hypersensitivity (3%), ✔ HLA-B*5701 AZT: BM suppression (esp. macrocytic anemia) TDF: renal toxicity TAF: minimal renal toxicity
NNRTI	efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune) rilpivirine (RPV; Edurant)	*Class:* rash, hepatitis, mixed CYP450 inducer/inhib EFV: CNS effects (incl depression) NVP: rash and hypersensitivity [risk factors are female, CD4 >250, pregnancy (∴ avoid)]
PI	atazanavir (ATV; Reyataz) darunavir (DRV; Prezista) lopinavir/riton. (LPV/r; Kaletra) ritonavir (RTV; Norvir)	*Class:* GI intol; hepatotoxicity; inhibit CYP450 (caution w/ statins); T2DM; truncal obesity; hyperlipid (less w/ ATV); MI (*NEJM* 2007;356:1723) ATV: crystalluria → nephrolithiasis DRV: rash (10%); possible sulfa cross-reactivity
FI	enfuvirtide (T20; Fuzeon)	Injection site reaction
EI	maraviroc (MVC; Selzentry)	Dizziness, hepatotoxicity; ✔ CCR5 tropism assay
II	bictegravir (BIC; Biktarvy) dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress)	Class: diarrhea & other GI intol; ↑ CPK DTG ↑ metformin levels; monitor glc DTG a/w neural tube defects
B*	ritonavir (r); cobicistat (COBI)	Drug interactions (inhibit CYP450)

NRTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, nonnucleoside RTI; PI, protease inhibitor; FI, fusion inhibitor; EI, entry inhibitor (CCR5 antagonist); II, integrase inhibitor; *booster to give w/ other ARVs; several multiclass combination pills exist

- Initiation of ARVs may *transiently worsen* existing OIs (TB, MAC, CMV, others) due to immune reconstitution inflammatory syndrome (IRIS). Prednisone during 1st 4 wk of ARVs ↓ risk for TB-associated IRIS (*NEJM* 2018;379:1915).

Approach to previously established HIV ⊕ Pt

- H&P (mucocutaneous, neurocognitive, OIs, malignancies, STDs); meds
- Review ARVs (past and current); if any must be interrupted, *stop all* to ↓ risk of resistance
- Failing regimen = unable to achieve undetectable viral load, ↑ viral load, ↓ CD4 count or clinical deterioration (with detectable viral load consider genotypic or phenotypic assay)

OI Prophylaxis (https://aidsinfo.nih.gov/guidelines & *JAMA* 2018;320:379)		
OI	Indication	1° Prophylaxis
Tuberculosis	⊕ PPD (≥5 mm)/IGRA *or* high-risk exposure	Rifampin × 4 mo (noninferior to INH, but ✔ for drug interactions) *or* INH + vit B_6 × 9 mo
Pneumocystis jiroveci (PCP)	CD4 <200/mm^3 *or* CD4 <14% *or* thrush	TMP-SMX DS or SS qd or DS tiw *or* dapsone 100 mg qd *or* atovaquone 1500 mg qd *or* pentamidine 300 mg inh q4wk
Toxoplasmosis	CD4 <100/mm^3 *and* ⊕ *Toxo* IgG	TMP-SMX DS qd *or* dapsone 50 mg qd + pyrimeth. 50 mg qwk + leucovorin 25 qwk

MAC	Ppx no longer rec. if effective ART initiated
Stop 1° prophylaxis if CD4 >initiation threshold >3–6 mo on ARVs	
Stop 2° prophylaxis (maintenance therapy for prior OI; drugs and doses differ by OI) if clinical resolution or stabilization and CD4 thresholds have been exceeded × 3–6 mo	

COMPLICATIONS OF HIV/AIDS

CD4 Count	Complications
Any CD4 count	Influenza, HAV, HBV, HPV, VZV, *S. pneumo*, TB
<500	Constitutional sx; noninfectious disease (CVD, bone, oncologic) Mucocutaneous: Kaposi's sarcoma; seborrheic dermatitis; oral hairy leukoplakia; lymphoma; candidiasis; HSV Recurrent bacterial infections, TB (pulm and extrapulm); neurosyphilis
<200	*PCP, Toxo, Bartonella, Crypto, Histo* (if endemic), *Coccidio*
<50–100	CMV, MAC, CNS lymphoma, PML, death (<50 is medical emergency) Invasive aspergillosis, bacillary angiomatosis (dissem. *Bartonella*)

Fever

- Etiologies (*Infect Dis Clin North Am* 2007;21:1013)
  - infxn (82–90%): MAC, TB, CMV, early PCP, *Histo*, *Crypto*, *Coccidio*, *Toxo*, endocarditis
  - noninfectious: lymphoma, drug reaction. Non 1° HIV itself rarely (<5%) cause of fever.
- Workup: guided by CD4 count, s/s, epi, & exposures
  - CBC, chem, LFTs, BCx, CXR, UA, mycobact. & fungal cx, ✔ meds, ? ✔ chest & abd CT
  - CD4 <100–200 → serum crypto Ag, LP, urinary *Histo* Ag, CMV PCR
  - pulmonary s/s → CXR; ABG; sputum for bacterial cx, PCP, AFB; bronchoscopy
  - diarrhea → stool cx, O&P, AFB; direct visualization with bx on colonoscopy
  - cytopenias → BM bx for, path & cx of aspirate including for mycobacteria & fungi

Cutaneous

- Seborrheic dermatitis; eosinophilic folliculitis; warts (HPV); HSV & VZV; MRSA skin & soft tissue infxns; scabies; candidiasis; eczema; prurigo nodularis; psoriasis; drug eruption; subungual onychomycosis (at nail bed)
- Molluscum contagiosum (poxvirus): 2–5 mm pearly papules w/ central umbilication
- Kaposi's sarcoma (KSHV or HHV8): red-purple nonblanching nodular lesions
- Bacillary angiomatosis (disseminated *Bartonella*): friable violaceous vascular papules

Ophthalmologic

- CMV retinitis (CD4 usu <50); Rx: gan- or valganciclovir, ganciclovir implant or cidofovir
- HZV, VZV, syphilis (any CD4 count, *treat as neurosyphilis*) or *Toxo:* CD4 usually <100

Oral

- Aphthous ulcers; KS; thrush (oral candidiasis): curd-like patches typically w/ burning or pain; oral hairy leukoplakia: painless proliferation of papillae w/ adherent white

coating usually on lateral tongue, caused by EBV but not precancerous

Endocrine/metabolic

- Hypogonadism; adrenal insufficiency (CMV, MAC, TB, HIV or med-related); wasting osteopenia/porosis (at all CD4 counts); fragility fractures
- Lipodystrophy: central obesity, peripheral lipoatrophy, dyslipidemia, hyperglycemia

Cardiovascular (*JACC* 2013;61:511)

- CAD (HIV incr risk indep of classic risk fx); dilated CMP; pulm HTN; pericarditis/effusion
- Higher rates of VTE, stroke, worse outcomes after MI (*JAIDS* 2012;60:351; *Circ* 2013;127:1767)

Pulmonary

Radiographic Pattern	Common Causes
Normal	Early PCP
Diffuse interstitial infiltrates	PCP, TB, viral, or disseminated fungal
Focal consolidation or masses	Bacterial or fungal, TB, KS
Cavitary lesions	TB, non-TB mycobacteria, aspergillus, other fungal, bacterial (incl MRSA, *Nocardia, Rhodococcus*)
Pleural effusion	TB, bacterial or fungal, KS, lymphoma

- *Pneumocystis jiroveci* (PCP) pneumonia (CD4 <200) (*NEJM* 1990;323:1444)
  constitutional sx, fever, night sweats, dyspnea on exertion, nonproductive cough
  CXR w/ interstitial pattern, ↓ P_aO_2, ↑ A-a ∇, ↑ LDH, ⊕ PCP sputum stain, ⊕ β-glucan
  Rx if P_aO_2 >70: TMP-SMX 15–20 mg of TMP/kg divided tid, avg dose = DS 2 tabs PO tid
  Rx if P_aO_2 <70 or A-a gradient >35: prednisone before abx (40 mg PO bid; ↓ after 5 d)
  HIV smokers are much more likely to die from lung cancer than OI (*JAMA* 2017;177:1613)

Gastrointestinal & hepatobiliary

- Esophagitis: *Candida*, CMV (solitary, lg serpiginous), HSV (multiple, small shallow), aphthous ulcers, pills; EGD if no thrush or no response to empiric antifungals
- Enterocolitis: *bacterial* (esp. if acute: shigella, salmonella, *C. diff*); *protozoal* (esp. if chronic: Giardia, Entamoeba, etc.); *viral* (CMV, adeno); *fungal* (histo); MAC; AIDS enteropathy; TB enteritis
- GI bleeding: CMV, KS, lymphoma, histo; proctitis: HSV, CMV, *LGV, N. gonorrhoeae*
- Hepatitis: HBV, HCV, CMV, MAC, TB, histo, drug-induced
- AIDS cholangiopathy: often a/w CMV or *Cryptosporidium or Microsporidium* (at ↓ CD4)

Renal

- HIV-assoc. nephropathy (collapsing FSGS); nephrotoxic drugs (eg, TDF → prox tub dysfxn)

Hematologic/oncologic (*NEJM* 2018;378:1029)

- Anemia: ACD, BM infiltration by infxn or tumor, drug toxicity, hemolysis
- Leukopenia; thrombocytopenia (bone marrow involvement, ITP); infection, ↑ globulin

- Non-Hodgkin lymphoma: ↑ frequency with any CD4 count, but incidence ↑ with ↓ CD4
- CNS lymphoma: CD4 count <50, EBV-associated
- Kaposi's sarcoma (HHV-8): at any CD4 count, incidence ↑ b/c CD4 ↓, usu. MSM
  Mucocut. (violacious lesions); *pulmonary* (nodules, infiltrates, LAN); *GI* (bleed, obstruct.)
- Cervical/anal CA (HPV high risk in MSM); ↑ rates of liver (a/w HBV/HCV), gastric

Neurologic

- Meningitis *Crypto* (dx w/ CSF; serum CrAg 90% Se), bact (inc. *Listeria*), viral (HSV, CMV, 1° HIV), TB, histo, *Coccidio*, lymphoma; neurosyphilis (cranial nerve palsies)
- Space-occupying lesions: may present as HA, focal deficits or Δ MS. Workup: MRI, brain bx if suspect non-*Toxo* etiology (*Toxo* sero ⊖) or no response to 2 wk of empiric anti-*Toxo* Rx (if *Toxo*, 50% respond by d3, 91% by d14; *NEJM* 1993;329:995)

Etiology	Imaging Appearance	Diagnostic Studies
Toxoplasmosis	Enhancing lesions, typically in basal ganglia (can be multiple)	⊕ *Toxo* serology (Se ~85%)
CNS lymphoma	Enhancing ring lesion (single 60% of the time)	⊕ CSF PCR for EBV ⊕ SPECT or PET scan
Progressive multifocal leukoencephalopathy (PML)	Multiple nonenhancing lesions in white matter	⊕ CSF PCR for JC virus
Other: abscess, nocardiosis, crypto, TB, CMV, HIV	Variable	Biopsy

- AIDS dementia complex: memory loss, gait disorder, spasticity (usually at CD4 ↓)
- Depression: ↑ rates of suicide/depression
- Myelopathy: infxn (CMV, HSV), cord compression (epidural abscess, lymphoma)
- Peripheral neuropathy: meds, HIV, CMV, demyelinating

Disseminated *Mycobacterium avium* complex (DMAC)

- Fever, night sweats, wt loss, HSM, diarrhea, pancytopenia. Enteritis and mesenteric lymphadenitis if CD4 <150, bacillemia if <50. Rx: clarithro/azithro + ethambutol ± rifabutin.

Cytomegalovirus (CMV)

- Usually reactivation with ↓ CD4. Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. CMV VL may be ⊖. Rx: ganciclovir, valganciclovir, foscarnet or cidofovir.

TICK-BORNE DISEASES

Distinguishing Features of Tick-Borne Illnesses					
Disease	**Rash**	**↓ WBC**	**Anemia**	**↓ Plts**	**↑ LFTs**
Lyme	80%: erythema migrans	–	–	–	+
RMSF	90%: petechiae, palms/soles	–	+	+	+++
Borrelia miyamotoi	<10%	++	+	+++	+++
Ehrlichiosis (HME)	25%: maculopapular, petechiae	+++	++	++++	++++
Anaplasmosis (HGA)	<5%	+++	+	+++	++++
Babesia	–	+	++++ (lysis)	++++	+++

–: <15%, +: 15–25%, ++: 25–50%, +++: 50–75%, ++++: >75%

LYME DISEASE

Microbiology

- Spirochete *B. burgdorferi* (consider coinfection w/ *Anaplasma, Babesia, B. miyamotoi*)
- Transmitted by ticks (*Ixodes*, deer tick); infxn usually requires tick attached >36–48 h

Epidemiology

- Most common vector-borne illness in U.S.; peak incidence in summer (May–Aug)
- Majority of cases in MN, WI, New England, northern mid-Atlantic, northern CA
- Humans contact ticks usually in fields with low brush near wooded areas

Clinical Manifestations	
Stage	Manifestations
Stage 1 (early localized) 3–30 d after bite	Pathogenesis: local effects of spirochete. *General:* flu-like illness *Derm* (~80%): erythema migrans (EM) = erythematous patches w/ central clearing, ~6–38 cm in size & often not "annular"
Stage 2 (early dissem.) wks to mos after bite	Pathogenesis: spirochetemia and immune response *General:* fatigue, malaise, LAN, HA; fever uncommon *Derm:* multiple (1–100) annular lesions ≈ EM *Rheum* (~10%): migratory arthralgias (knee & hip) & myalgias *Neurologic* (~15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis *Cardiac* (~8%): conduction block, myopericarditis
Stage 3 (late persistent) mos to yrs after bite	Pathogenesis: immune response *Derm* (rare in U.S.): acrodermatitis chronica atrophicans, panniculitis *Rheum* (~60%, espec. if not Rx'd): recurrent mono- or oligoarthritis of large joints (classically knee), synovitis *Neurologic* (rare!): subacute encephalomyelitis, polyneuropathy

(*CID* 2006;43:1089; *Lancet* 2012;379:461; *NEJM* 2014;370:1724)

Diagnostic studies

- *EM present:* confirmed in appropriate geographic setting; no need for testing (likely sero ⊖)
- *EM absent* (ie, stage 2 or 3 disease): 2-step testing
  1st step: ELISA screen (false ⊕ common, false ⊖ w/ early abx or <6 wk after tick bite)
  2nd step: if ⊕ ELISA, confirm with Western blot (↑ Sp)
- ✔ CSF if suspected neuro disease: ⊕ CSF Ab if $(IgG_{CSF}/IgG_{serum})/(alb_{CSF}/alb_{serum}) > 1$

Treatment (*NEJM* 2014;370:1724; *JAMA* 2016;315:1767 & 2461)

- Prophylaxis: tick avoidance, protective clothing, tick ✔ q24h, DEET
  Chemoprophylaxis w/ doxycycline 200 mg PO × 1 *only* if *all* of the following:
  1. *Ixodes scapularis* tick attached ≥36 h
  2. Local Lyme carriage in ticks ≥20% (peak season in endemic area)
  3. Abx can be given w/in ≤72 h of tick bite
  4. No contraindication to doxy (eg, preg, allergy, age <8 y)

  If criteria 1–4 met, NNT to prevent 1 case ~50; w/o doxy, risk of Lyme after tick bite 1–3%
  Regardless of Ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- Abx (ISDA 2019): *if* clin. manifest. *and* ⊕ serology in endemic area (unless isol. EM)
  Isolated EM: doxy 100 mg PO bid × 10 d (altern: cefurox or amox × 14 d or azithro × 7 d)
  Arthritis: doxy 100 mg PO bid × 28 d (alternative: cefurox or amox × 28 d)
  Carditis or meningitis: CTX 2 g IV q24h or doxy 100 mg PO bid (IV vs. PO depends on severity, clinical improvement) × 2–3 wk
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

---

BABESIOSIS

Microbiology & epidemiology

- Infxn w/ parasite *Babesia microti* (U.S.), transmitted by *Ixodes* ticks; also a/w transfusion
- Europe & U.S. (more commonly MN, WI, coastal areas & islands of MA, NY, NJ, RI, CT)
- Peak incidence June–August (*MMWR* 2012;61:505)

Clinical manifestations (typically 1–4 wk after tick exposure; <9 wk if transfusion)

- Range from asx to fevers, sweats, myalgias, & HA to severe hemolytic anemia, hemoglobinuria, & death (degree of parasitemia correlates roughly with severity)
- Risk factors for severe disease: asplenia, ↓ cellular immunity, TNF inhib, ↑ age, pregnancy

Diagnosis (*NEJM* 2012;366:2397)

- Clinical syndrome + blood smear w/ intraerythrocytic parasites
- Repeat smears (q12–24h) if sx persist despite negative initial smear
- PCR serum if smear ⊖ and high clinical suspicion, serum IgG can help but some false ⊕

Treatment (*JAMA* 2016;315:1767)

- Atovaquone & azithro for mild/mod illness; call ID if severe (azithro/atovaquone/clinda)
- Duration depends on host; immunosupp Pts often need longer Rx
- Exchange transfusion if parasitemia >10%, severe hemolysis or SIRS

EHRLICHIOSIS/ANAPLASMOSIS

Microbiology

- Gram ⊖ obligate intracellular bacterium; human monocytic ehrlichiosis (*E. chaffeensis*, HME); human granulocytic anaplasmosis (*A. phagocytophilum*, HGA)
- Transmission: HME by *Amblyomma americanum*, *Dermacentor variabilis;* HGA by *Ixodes*

Epidemiology

- HGA cases typically in New Engl, mid-Atl, MN; HME in SE and south-central U.S.
- Peak incidence spring and early summer; can be transmitted by blood transfusion

Clinical manifestations (typically w/in 3 wk of tick exposure)

- Asx or nonspecific: fever, myalgias, malaise, HA, cough, dyspnea; onset often acute
- Laboratory: leukopenia, thrombocytopenia, ↑ aminotransferases, LDH, Aφ, renal insuff
- More severe disease can occur with bacterial superinfection in HGA

Diagnosis

- Acute: intraleukocytic morulae on peripheral blood smear (rare); PCR; later: serology

Treatment (*JAMA* 2016;315:1767)

- Start Rx based on clinical suspicion; definitive dx requires PCR (may not detect all spp.)
- Doxycycline 100 mg PO bid (often × 10 d); should defervesce in ≤48 h, else reconsider dx

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Microbiology & epidemiology

- Infection with *Rickettsia rickettsii* (Gram ⊖ obligate intracellular bacterium)
- Transmitted by *Dermacentor variabilis, D. andersoni* (dog tick); peak in spring/early summer
- Occurs in mid-Atl, SE, Midwest, New Engl, NW, Canada, Mexico, Central & S. America
- Consider other rickettsial spp.: *R. akari* (Rickettsial pox), *R. conorii* (Mediterranean spotted fever), *R. africae* (African tick bite fever), *R. felis* (Flea rickettsiosis)

Clinical manifestations (typically w/in 1 wk of tick exposure)

- Nonspecific: fever, HA, ΔMS, myalgias, N/V, occasionally abdominal pain
- Rash (2–5 d *after* onset) = *centripetal:* starts on ankles and wrists → trunk, palms, & soles; progresses from macular to maculopapular to petechial
- Severe cases → vasculitis, hypoperfusion/shock, end-organ damage; more likely in elderly
- Up to 75% mortality if untreated, 5–10% even w/ Rx (esp. if delayed) (*NEJM* 2005;353:551)

Diagnosis

- Usually a clinical dx; *requires early clinical suspicion* given risks of delayed Rx
- Acute illness dx by skin bx for rickettsiae (Se ~70%); 7–10 d after sx onset, serology ⊕

Treatment

- Doxycycline 100 mg PO bid *(give empirically if clinical suspicion)*

TULAREMIA

Microbiology

- Infxn w/ *Francisella tularensis* via contact w/ animal tissue, aerosol, tick/insect bite

Clinical manifestations (typically w/in 2–10 d of exposure)

- Acute onset of fever, HA, nausea; ulcer w/ black eschar at site of entry; LAN; PNA

Diagnosis & treatment

- Hazardous and difficult to Cx, alert lab. Serology ⊕ by wk 2. PCR by research lab.
- Streptomycin or gentamicin × 7–14 d; empiric Rx may be needed given challenges in dx

FEVER SYNDROMES

Temperature ≥100.4°F or ≥*38°C*

Diagnostic approach

- Thorough history including ROS, PMH/PSH, immunizations, including from childhood
- Fever curve (holding antipyretics); less likely to mount fever if: chronic renal or liver disease, extremes of age, protein calorie malnutrition, immunosuppression, steroid use
- Exposures: travel, occupation or hobbies, animals and insects, sexual contacts, TB; consider age, geography, season and incubation time in relation to exposures
- Physical exam: complete exam w/ focus on mucous membranes & conjunctiva; cardiac murmurs; liver and spleen size; skin, genitals, lymph nodes, & joints; complete neuro exam incl cranial nerves and meningeal signs
- If rash: location, duration, progression/Δ in appearance, was prodrome present

FEVER OF UNKNOWN ORIGIN (FUO)

Definition & etiologies

- Fever (as per above def) on >1 occasion during ≥3 wk & no dx despite 1 wk of evaluation
- More likely to be *unusual manifestation of common disease* than an uncommon disease
- In Pts with HIV: >75% causes are infectious, but *rarely due to HIV itself*
- Frequent reassessment needed to identify focal signs and progression of disease

Category	Etiologies of Classic FUO (*Archives* 2003;163:545; *Medicine* 2007;86:26)
Infection ~30%	Tuberculosis: disseminated or extrapulm disease can have normal CXR, PPD, sputum AFB; bx (lung, liver, bone marrow) for granulomas has 80–90% yield in miliary disease Abscess: dental, paraspinal, hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic abscess or prostatitis, appendicitis Endocarditis: consider HACEK orgs, *Bartonella*, *Legionella*, *Coxiella* Osteomyelitis, sinusitis, Lyme, typhoid, 1° CMV or EBV, malaria, *Babesia*
Connective tissue disease ~30%	Giant cell arteritis/PMR: headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, ↑ ESR Adult-onset Still's: evanescent truncal rash, LAN, pharyngitis, ↑↑ ferritin PAN, ANCA ⊕, other vascul.; SLE, RA, psoriatic or reactive arthritis
Neoplasm ~20%	Lymphoma: LAN, HSM, ↓ Hct or plt, ↑ LDH; leukemia, myelodysplasia Renal cell carcinoma: microscopic hematuria, ↑ Hct HCC, pancreatic and colon cancers, sarcomas, mastocytosis Atrial myxomas: obstruction, embolism, constitutional symptoms
Misc ~20%	Drugs, factitious, DVT/PE, hematoma Thyroiditis or thyroid storm, adrenal insufficiency, pheochromocytoma Granulomatous hepatitis (many causes), sarcoidosis, Kikuchi's, Behçet's Familial Mediterranean fever (peritonitis, episodic fever, pleuritis; ↑ WBC & ESR during attacks); other defects in innate immunity

Workup

- Focus by H&P, incl: CBC w/ diff, lytes, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulin, LDH, CK, SPEP, 3 sets BCx (off of abx), U/A, UCx, PPD or IGRA, HIV Ab ± PCR, heterophile Ab (EBV serologies if), CMV antigen, Hep serologies if LFTs abnl
- Stop unnecessary meds (only 20% with a med cause have eos or rash), reassess 1–3 wk
- Imaging: CXR, chest & abd CT, consider tagged WBC, gallium scan, PET, TTE, LENI
- Consider temporal artery bx if ↑ ESR and age >60, particularly if other s/s
- Consider BM aspirate & bx (esp. if signs of marrow infiltration) or liver bx (esp. if ↑ Aϕ): even w/o localizing s/s, yield may be up to 24% (path and cx) (*Archives* 2009;169:2018)
- Pursue abnormalities raised by above w/u (eg, bx, MRI, etc., for dx, *not* screening)

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic)
- Empiric glucocorticoids not indicated unless strong suspicion for specific rheumatologic dx
- Up to 30% of cases remain undiagnosed, most spontaneously defervesce (wks to mos)

FEVER AND RASH

Approach to diagnostic workup

- Meningococcemia, endocarditis, RMSF, sepsis, toxic shock need urgent dx & Rx
- Workup: CBC w/ diff, lytes, BUN/Cr, LFTs, LDH, CK, U/A, HIV Ab ± PCR, BCx (off abx)
- To narrow Ddx: characterize time course of rash, progression & morphology
- Erythema multiforme: symmetric "target" lesions often of palms, soles, & mucous memb
  Infxn etiol: HSV 1/2, *Mycoplasma*, syphilis, tick-borne diseases, etc.
  Non-infxn etiol: meds (eg, NSAIDs, sulfa), malignancy, autoimmune & rheum disease
- Erythema nodosum: tender erythematous or violaceous nodules usually symmetric on LE
  Infxn etiol: Strep, TB, EBV, *Bartonella*, HBV, psittacosis, fungal, *L. venereum*, etc.
  Non-infxn etiol: sarcoidosis, IBD, Behçet's, other rheum, pregnancy/OCP use
- Pursue specific dx based on exposure hx & exam, including serologies, viral swab PCR, antigen tests and possibly skin biopsy ± exam of vesicular or bullae fluid if present
- Etiologies more broad in immunosupp. Pts, dx testing should be earlier and more extensive; higher risk of critical illness due to disseminated or rapidly progressive infxns

Variable	Possible Etiology
Summer/fall > other seasons	Enterovirus
Winter	Parvovirus, Meningococcemia
Spring/summer	Measles/rubella, Lyme, RMSF
Year-round	Adenovirus, *Mycoplasma*
Cat and dog exposure	*Bartonella, Pasteurella, Toxoplasma, Capnocytophaga*
Tick exposure	Lyme, RMSF, Ehrlichiosis, Anaplasmosis
Adult <30 y	Mononucleosis (EBV or CMV)

Inadequate immunization	Measles, Rubella, VZV, influenza
Sexually active	HIV, syphilis, disseminated gonococcal infection, HSV2
Consider noninfectious causes: allergy/DRESS, DVT, phlebitis, vasculitides, neutrophilic dermatoses, gout, connective tissues dis., malignancy, foreign body rxn	

Treatment

- Empiric abx *not* indicated (unless Pt neutropenic or critically ill)
- Consider important empiric isolation precautions (ie, varicella → airborne/contact; measles → airborne; meningococcus → droplet) while workup pending

FEVER IN A RETURNED TRAVELER

Region or Exposure	Common Etiologies
Sub-Saharan Africa	Malaria >> dengue, rickettsial disease, enteric disease
Southeast Asia	Dengue > malaria, enteric disease (*S. typhi*), Chikungunya
Central & S. America	Enteric disease, malaria, dengue, Zika
Caribbean & Mexico	Dengue >> Chikungunya > malaria. Also consider Zika.
Middle East	Middle East Respiratory Syndrome
Freshwater swimming	Schistosomiasis, leptospirosis
Unpurified drinking water	Enteric disease (*E. coli* >> *S. typhi*, *Campylobacter*, hepatitis E > *Vibrio cholerae*), amebic liver abscess
Lacking immunizations	HAV/HBV, *S. typhi*, influenza, measles, rubella, yellow fever
Animal bite	Rabies
African "safari"	Rickettsial disease, African trypanosomiasis
Adult <30 years	Mononucleosis (EBV or CMV)

(*NEJM* 2017;376:548)

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Emerging pathogens: Influenza occurs year-round in the tropics. Chikungunya and dengue w/ ↑ areas of transmission, hemorrhagic fevers primarily in Central Africa.
- Consider domestic infxns, STIs, & non-infxn causes. Enteric parasites rarely cause fever.

Select clinical manifestations

- Ebola: fever in traveler from area with active transmission of Ebola w/in 21 d: isolate & contact state health department (http://www.cdc.gov/vhf/ebola)
- Malaria: nonspecific symptoms including diarrhea, myalgias, cough, altered mental status
- Dengue: nonspecific symptoms including headache, severe myalgias, rash/petechiae
- Chikungunya: nonspecific symptoms including joint pain, moderate myalgias, fever
- Typhoid (*Lancet* 2015;385:1136): constipation, abd pain, possible rash, relative bradycardia
- Rickettsial disease: headache, myalgias, lymphadenopathy, possible rash/eschar
- Zika: fever, rash, arthralgia, H/A, conjunctivitis (http://www.cdc.gov.zika)

Workup

- Routine testing: CBC w/ diff, lytes, LFTs, BCx, UA, rapid malaria test
- Fever in a traveler from a malaria zone is malaria until proven otherwise; consider a

medical emergency → hospitalization & empiric Rx. One ⊖ smear does *not* r/o.

- Other tests based on s/s, labs, exposure, incubation period, geography and seasonality. O&P exam, CXR, blood smears for filaria/Babesiosis/*Borrelia*, serologies, STI & HIV, PPD or IGRA, bone marrow aspirate, bx of lymph nodes or skin lesions, CSF studies.

NOTES

PITUITARY DISORDERS

HYPOPITUITARY SYNDROMES (*Lancet* 2016;388:2403)

Etiologies

- Primary: surgery, radiation (develops after avg 4–5 y), tumors (primary or metastatic), infection, infiltration (sarcoid, hemochromatosis), autoimmune, ischemia (including Sheehan's syndrome caused by pituitary infarction intrapartum), carotid aneurysms, cavernous sinus thrombosis, trauma, medications (eg, ipilimumab), apoplexy
- Secondary (hypothalamic dysfunction or stalk interruption): tumors (including craniopharyngioma), infection, infiltration, radiation, surgery, trauma

Clinical manifestations

- Hormonal deficiencies: ACTH, TSH, FSH and LH, GH, prolactin, and ADH
- Panhypopituitarism: deficiencies in multiple hormonal axes and including ADH
- Mass effect: headache, visual field Δs, cranial nerve palsies, galactorrhea

Central adrenal insufficiency: ↓ ACTH

- Sx similar to 1° adrenal insufficiency (see "Adrenal Disorders") *except:*
  no salt cravings or hyperkalemia (b/c aldo preserved)
  no hyperpigmentation (b/c ACTH/MSH is not ↑)

Central hypothyroidism: ↓ TSH

- Sx of central hypothyroidism similar to 1° (see "Thyroid Disorders") *except* absence of goiter
- Dx with free T_4 in addition to TSH, as TSH may be low or *inappropriately normal*

Hypoprolactinemia: ↓ prolactin

- Inability to lactate

Growth hormone deficiency: ↓ GH

- ↑ chronic risk for osteoporosis, fatigue, weight gain
- Dx with failure to ↑ GH w/ appropriate stimulus (eg, insulin tolerance test, glucagon stimulation, and macimorelin stimulation)
- GH replacement in adults controversial (*Annals* 2003;35:419)

Central hypogonadism: ↓ FSH & LH

- Clinical manifestations: ↓ libido, impotence, oligomenorrhea or amenorrhea, infertility, ↓ muscle mass, osteoporosis
- Physical exam: ↓ testicular size; loss of axillary, pubic and body hair
- Dx with: ↓ a.m. testosterone or estradiol (also assess SHBG, esp. in obese) and ↓ or normal FSH/LH (all levels ↓ in acute illness, ∴ do not measure in hospitalized Pts)
- Treatment: testosterone or estrogen replacement *vs.* correction of the underlying cause

Central diabetes insipidus: ↓ ADH

- Typically from mass lesion extrinsic to sella; pituitary tumor does not typically present w/ DI
- Clinical manifestations: *severe* polyuria, *mild* hypernatremia (*severe* if ↓ access to H_2O)
- Diagnostic studies: see "Sodium and Water Homeostasis"

Pituitary apoplexy (*Endocr Rev* 2015;36:622)

- Rapid expansion of pituitary tumor (typically adenoma) due to hemorrhage or infarction
- Sx include excruciating headache, diploplia, hypopituitarism
- Rx: immediate high-dose glucocorticoids; prompt surgical decompression if severe neurologic impairment or Δ MS; conservative management if mild

Diagnostic evaluation

- Hormonal studies
  Chronic: ↓ target gland hormone + ↓ or normal trophic pituitary hormone
  Acute: target gland hormonal studies may be *normal*
  Partial hypopituitarism is more common than panhypopituitarism
- Pituitary MRI: pituitary protocol (contrast enhanced) recommended

Treatment

- Replace deficient target gland hormones
- Most important deficiencies to recognize and treat in inpatients are *adrenal insufficiency* and *hypothyroidism;* if both present, treat with glucocorticoids first, then replace thyroid hormone so as not to precipitate adrenal crisis

---

HYPERPITUITARY SYNDROMES

Pituitary tumors (*JAMA* 2017;317:516)

- Pathophysiology: adenoma → excess of trophic hormone (if tumor fxnal, but 30–40% not) and potentially *deficiencies* in other trophic hormones due to compression; cosecretion of PRL and growth hormone in 10% of prolactinomas
- Clinical manifestations: syndromes due to oversecretion of hormones (see below)
  ± mass effect: headache, visual Δs, diplopia, cranial neuropathies
- Workup: MRI brain pituitary protocol, hormone levels, ± visual field testing
  if <10 mm, no mass effect, no hormonal effects, can f/up q3–6mo

Hyperprolactinemia (*NEJM* 2010;362:1219; *JCEM* 2011;96:273)

- Etiology
  Prolactinoma (50% of pituitary adenomas)
  Stalk compression due to nonprolactinoma → ↓ inhibitory dopamine → ↑ PRL (mild)
- Physiology: PRL induces lactation and inhibits GnRH → ↓ FSH & LH
- Clinical manifestations: amenorrhea, galactorrhea, infertility, ↓ libido, impotence
- Diagnostic studies
  ↑ PRL (✔ *fasting* levels), but elevated in many situations, ∴ r/o pregnancy or exogenous estrogens, hypothyroidism, dopamine agonists (eg, psych meds, antiemetics), renal failure (↓ clearance), cirrhosis, stress, ↑ carb diet. Watch for *hook*

effect: assay artifact yielding falsely low PRL if very high serum PRL levels; retest with sample dilution.

MRI brain pituitary protocol

- Treatment

If asx (no HA, galactorrhea, hypogonadal sx) & microadenoma (<10 mm), follow w/ MRI

If sx or macroadenoma (≥10 mm) options include:

Medical with dopamine agonist such as cabergoline (70–100% success rate) or bromocriptine (not as well tol); side effects include N/V, orthostasis, nasal congestion

Surgical: transsphenoidal surgery (main indications: failed or cannot tolerate medical Rx, GH cosecretion or neurologic sx not improving); 10–20% recurrence rate

Radiation: if medical or surgical therapy have failed or are not tolerated

Acromegaly (↑ GH; 10% of adenomas; *NEJM* 2006;355:2558; *JCEM* 2014;99:3933)

- Physiology: stimulates secretion of insulin-like growth factor 1 (IGF-1)
- Clinical manifestations: ↑ soft tissue, arthralgias, jaw enlargement, headache, carpal tunnel syndrome, macroglossia, hoarseness, sleep apnea, amenorrhea, impotence, diabetes mellitus, acanthosis/skin tags, ↑ sweating, HTN/CMP, colonic polyps
- Diagnostic studies: *no utility in checking random GH levels because of pulsatile secretion* ↑ IGF-1 (somatomedin C); ± ↑ PRL; OGTT → GH *not* suppressed to <1 (<0.3 if newer assay) ng/mL; pituitary MRI to evaluate for tumor
- Treatment: surgery, octreotide (long- and short-acting preparations), dopamine agonists (if PRL co-secretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/o Rx 2–3× ↑ mortality, risk of pituitary insufficiency, colon cancer

Cushing's disease (↑ ACTH): 10–15% of adenomas; see "Adrenal Disorders"

Central hyperthyroidism (↑ TSH, ↑ α-subunit): extremely rare; see "Thyroid Disorders"

↑ FSH & LH: often non-fxn, may present as *hypopituitarism* b/c compression effects

Multiple Endocrine Neoplasia (MEN) Syndromes	
Type	Main Features
1 (*MENIN* inactiv.)	Parathyroid hyperplasia/adenomas → hypercalcemia (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn)
2A (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (*RET* proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas

Autoimmune Polyglandular Syndromes (APS) (*NEJM* 2018;378:1132)	
Type	Features
I (child onset)	Mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency
II (adult onset)	Adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1

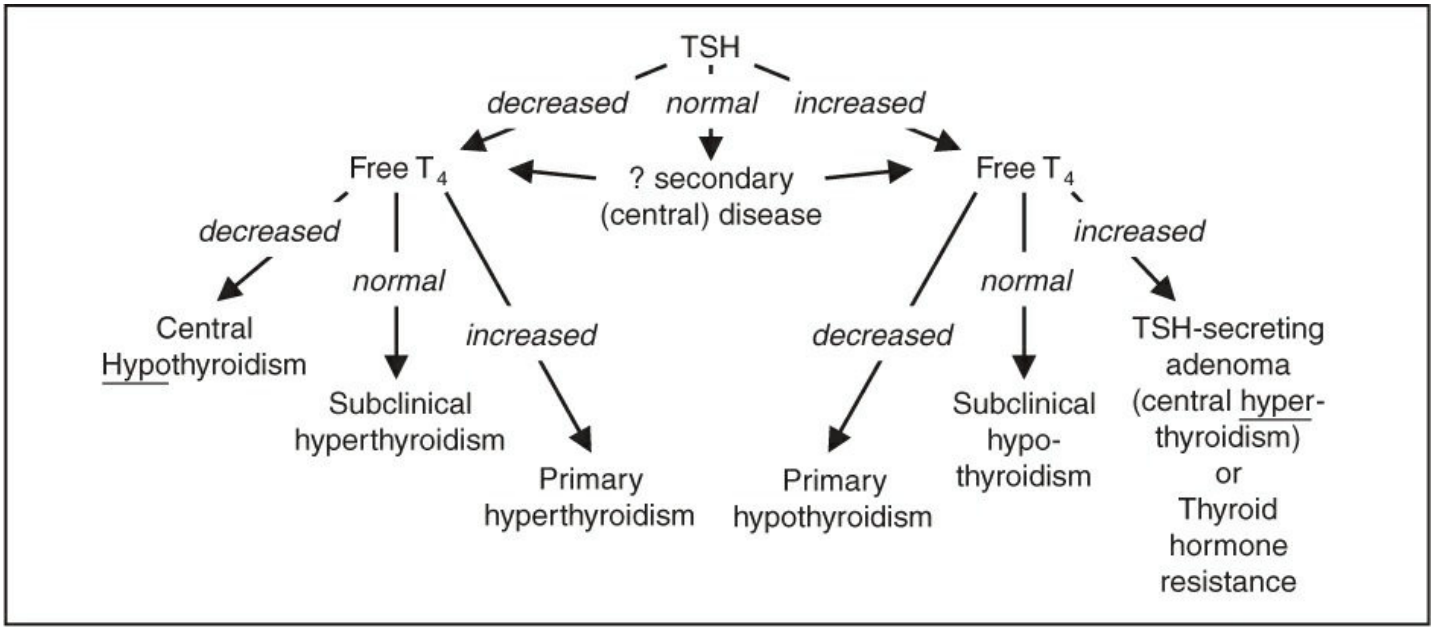
THYROID DISORDERS

Common Diagnostic Tests in Thyroid Disorders	
Test	Comments
Thyroid-stimulating hormone (TSH)	*Most sensitive test* to detect 1° hypo- and hyperthyroidism. Used as primary screening test for thyroid disease. ↓'d by dopamine, glucocorticoids, severe illness. May not be accurate in central hypothyroidism.
Free T_4 (fT_4)	Unbound T_4, not influenced by TBG. Checked in a variety of thyroid states including *hyperthyroidism* & *central hypothyroidism*
Total T_3	*Total* serum concentrations of T3 (liothyronine). Useful when evaluating for *hyperthyroidism*.
Antithyroid peroxidase Ab (anti-TPO)	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless subacute thyroiditis and Graves' disease (low titer)

(*Lancet* 2001;357:619 & *Thyroid* 2003;13:19)

Specialized Diagnostic Tests in Thyroid Disorders	
Test	Comments
Total T_4	*Total* serum concentrations (∴ influenced by TBG). Checked if concern that TSH and free T4 are not accurate.
Free T_3	Unbound T_3, low clinical utility
Reverse T_3	Inactive, ↑'d in sick euthyroid syndrome. Rarely used clinically.
Thyroid stimulating Abs (TSI)	Thyroid-stimulating Ig (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) seen in Graves' disease. Diagnostic of Graves' disease in high titer.
Thyroglobulin	↑'d in goiter, hyperthyroidism and thyroiditis ↓'d in factitious ingestion of thyroid hormone Tumor marker for thyroid cancer only after total thyroidectomy and radioiodine therapy
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T_4): estrogen (OCP, preg.), hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T_4): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary
Radioactive iodine uptake (RAIU) scan	Useful to differentiate causes of hyperthyroidism ↑ uptake: Graves' disease, goiter or hot nodule no uptake: subacute painful (de Quervain's) or silent thyroiditis, exogenous thyroid hormone, recent iodine load, struma ovarii or antithyroid drugs

Figure 7-1 Approach to TSH levels



HYPOTHYROIDISM

Etiologies

- Primary (>90% of cases of hypothyroidism; ↓ free T_4, ↑ TSH)
  - Goitrous: Hashimoto's thyroiditis (after hyperthyroid phase of thyroiditis), iodine deficiency, lithium, amiodarone
  - Nongoitrous: surgical destruction, s/p radioactive iodine or XRT, amiodarone
- Secondary (central): ↓ free T_4; TSH low, inappropriately nl, or slightly high (although functionally inactive due to abnormal glycosylation); due to hypothalamic or pituitary failure

Hashimoto's thyroiditis

- Autoimmune destruction with patchy lymphocytic infiltration
- Associated with other autoimmune disease and may be part of APS Type II
- ⊕ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations (*Annals* 2009;151:ITC61)

- Early: weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, menorrhagia, dry skin, coarse brittle hair, brittle nails, carpal tunnel syndrome, delayed DTRs ("hung up" reflexes), diastolic HTN, hyperlipidemia
- Late: slow speech, hoarseness, loss of outer third of eyebrows, myxedema (nonpitting skin thickening due to ↑ glycosaminoglycans), periorbital puffiness, bradycardia, pleural, pericardial, & peritoneal effusions, atherosclerosis
- Myxedema crisis: hypothermia, hypotension, hypoventilation, Δ MS (including coma) hyponatremia, hypoglycemia; often precipitated by infection or major cardiopulmonary or neurologic illness (*Med Clin North Am* 2012;96:385)

Diagnostic studies (*Lancet* 2017;390:1550)

- ↓ free T_4; ↑ TSH in 1° hypothyroidism; ⊕ antithyroid Ab (TPO) in Hashimoto's thyroiditis
- May see hyponatremia, hypoglycemia, anemia, ↑ LDL, ↓ HDL and ↑ CK

- Screening recommended for pregnant women

Treatment of overt hypothyroidism

- Levothyroxine (1.5–1.7 µg/kg/d), re ✔ TSH q5–6wk & titrate until euthyroid (can take mos)
- *Lower starting dose* (0.3–0.5 µg/kg/d) if at risk for ischemic heart disease or elderly
- ↑ dose typically needed if:
  - poor GI absorption: meds that ↓ absorption (iron, calcium, cholestyramine, sucralfate, PPI), celiac disease, IBD
  - meds that accelerate T_4 catabolism (eg, phenytoin, phenobarbital)
  - initiation of estrogen replacement; pregnancy (~30% ↑ by wk 8): TSH goals change by trimester: 1st = 0.1–4.0 mIU/L, 2nd & 3rd = gradual return of TSH to nonpregnant nl range (*Thyroid* 2017;3:315)

Subclinical hypothyroidism (*NEJM* 2017;376:2556; *JAMA* 2019;322:153)

- Mild ↑ TSH and normal free T_4 with only subtle or no sx
- If TSH <7 or ⊖ anti-TPO Ab, ~½ resolve after 2 y (*JCEM* 2012;97:1962) if ↑ titers of antithyroid Abs, progression to overt hypothyroidism is ~4%/y
- No clear benefit to Rx (*NEJM* 2017;376:2534). In practice, follow expectantly or Rx to improve mild sx or dyslipidemia. Experts often Rx if TSH >10 mU/L, goiter, pregnancy or infertility.

Myxedema coma (ie, profound hypothyroidism; *Med Clin North Am* 2012;96:385)

- Presentation: hypothermia, hypotension, hypoventilation, Δ MS (coma rare), hyponatremia, hypoglycemia; often precipitated by infxn or major cardiopulmonary or neurologic illness
- Treatment: supportive care most important. Slow metabolism of drugs can lead to coma. Correction of hypothyroidism takes time. Load 5–8 µg/kg T_4 IV, then 50–100 µg IV qd; b/c peripheral conversion impaired, may also give 5–10 µg T_3 IV q8h if unstable w/ bradycardia and/or hypothermia (T_3 more arrhythmogenic); must give empiric *adrenal replacement therapy* first as ↓ adrenal reserves in myxedema coma.

HYPERTHYROIDISM

Etiologies (*Lancet* 2016;388:906)

- Graves' disease (60–80% of thyrotoxicosis)
- Thyroiditis: thyrotoxic phase of subacute (granulomatous) or painless (lymphocytic)
- Toxic adenomas (single or multinodular goiter)
- Extremely rare: TSH-secreting pituitary tumor or pituitary resistant to thyroid hormone (↑ TSH, ↑ free T_4)
- Misc: amiodarone, iodine-induced, thyrotoxicosis factitia, struma ovarii (3% of ovarian dermoid tumors and teratomas), hCG-secreting tumors (eg, choriocarcinoma), large deposits of metastatic follicular thyroid cancer

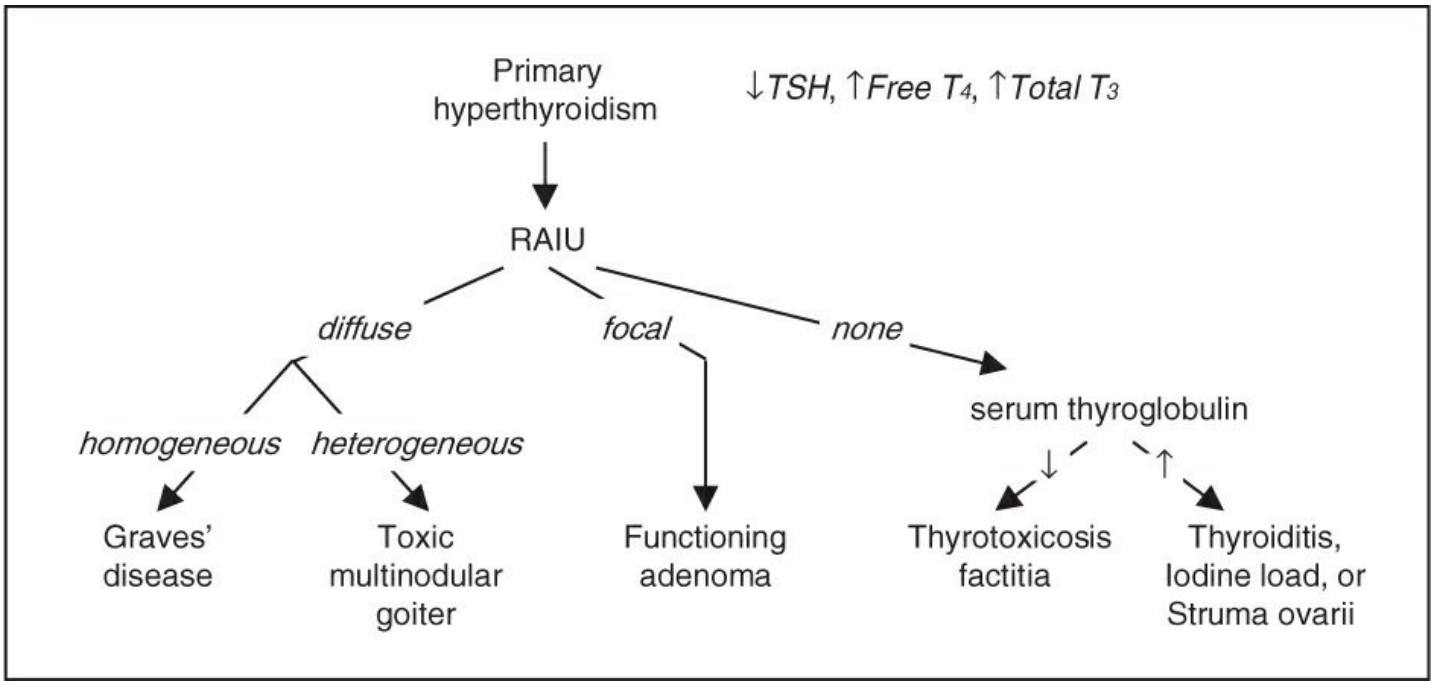
Clinical manifestations

- Restlessness, sweating, tremor, moist warm skin, fine hair, tachycardia, AF, weight loss, ↑ frequency of stools, menstrual irregularities, hyperreflexia, osteoporosis, stare and lid lag (due to sympathetic overactivity)
- Apathetic thyrotoxicosis: seen in elderly who can present with lethargy as only sx

Laboratory testing

- ↑ free T_4 and total T_3; ↓ TSH (except in TSH-secreting tumors)
- RAIU scan is very useful study to differentiate causes (see table on page 7-3); cannot do if recent IV contrast or amio load b/c iodine blocks uptake, so ✔ autoantibodies instead
- Rarely need to ✔ for autoantibodies except in pregnancy (to assess risk of fetal Graves')
- May see hypercalciuria ± hypercalcemia, ↑ Aϕ, anemia

Figure 7-2 Workup of primary hyperthyroidism



Graves' disease (*NEJM* 2016;375:1552)

- ♀:♂ ratio is 5–10:1, most Pts between 40 and 60 y at dx
- ⊕ thyroid antibodies: TSI or TBII (⊕ in 80%), anti-TPO, antithyroglobulin; ANA
- Clinical manifestations in addition to those of hyperthyroidism (see above):
  - Goiter: diffuse, nontender, w/ thyroid bruit
  - Ophthalmopathy (*NEJM* 2010;362:726): seen in 50%; up to 90% if formally tested. Periorbital edema, lid retraction, proptosis, conjunctivitis, diplopia (EOM infiltration); associated w/ smoking. Stare and lid lag seen in any type of hyperthyroidism.
  - Pretibial myxedema (3%): infiltrative dermopathy

Thyroiditis (*NEJM* 2003;348:2646; *Med Clin North Am* 2012;96:223)

- Acute: bacterial infection (very rare in U.S. except postsurgical), typically *Staph/Strep* spp.
- Subacute: transient thyrotoxicosis → transient hypothyroidism → normal thyroid fxn

Painful (viral, granulomatous or de Quervain's): fever, ↑ ESR; Rx = NSAIDs, ASA, steroids

Silent (postpartum, autoimmune including Hashimoto's, or lymphocytic): painless, ⊕ TPO Abs; if postpartum, can recur with subsequent pregnancies

Other: meds (amiodarone, lithium, TKIs), palpation thyroiditis, post-radiation

Treatment (*Thyroid* 2011;21:593)

- β-blockers: control tachycardia (propranolol also ↓ $T_4 \rightarrow T_3$ conversion)
- Graves' disease: either antithyroid drugs or radioactive iodine (*JAMA* 2015;314:2544)
  - methimazole: 70% chance of recurrence after 1 y; side effects include pruritus, rash, arthralgia, fever, N/V and *agranulocytosis* in 0.5%. PTU: 2nd line (risk of hepatocellular necrosis; TID dosing; slower effect; *JCEM* 2007;92:2157). For both, need to ✔ LFTs, WBC, TSH at baseline and in follow-up.
  - radioactive iodine (RAI) (*NEJM* 2011;364:542): typically done as outPt; preRx w/ antithyroid drugs in selected Pts w/ CV disease or elderly to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pts become hypothyroid
  - surgery: less commonly chosen for Graves', usually for Pts w/ obstructive goiter or ophthalmopathy
- Ophthalmopathy: can worsen after RAI; prophylax w/ prednisone in high-risk Pts; can be Rx'd w/ radiation and/or surgical decompression of orbits (*NEJM* 2009;360:994)
- Toxic adenoma or toxic multinodular goiter: RAI or surgery (methimazole preRx for surgery, in selected patients before RAI)

Subclinical hyperthyroidism (*NEJM* 2018;378:2411)

- Mild ↓ TSH and normal free T_4 with only subtle or no sx
- ~15% → overt hyperthyroidism in 2 y; ↑ risk of AF, CHD, fracture (*JAMA* 2015;313:2055)
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

Thyroid storm (extremely rare in hyperthyroidism; *JCEM* 2015;2:451)

- Presentation: delirium, fever, tachycardia, systolic HTN w/ wide pulse pressure and ↓ MAP, GI symptoms; 20–30% mortality
- Diagnosis: no universally accepted criteria. Biochemical hyperthyroidism + severe sx, consider additional dx that may explain/contribute to sx.
- Treatment: β-blocker, PTU or methimazole, iopanoic acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, ± steroids (↓ $T_4 \rightarrow T_3$)

NONTHYROIDAL ILLNESS (SICK EUTHYROID SYNDROME) (*J Endocrinol* 2010;205:1)

- TFT abnormalities in Pts w/ severe nonthyroidal illness (∴ in acute illness, ✔ TFTs only if ↑ concern for thyroid disease); *may* have acquired transient central hypothyroidism
- If thyroid dysfxn suspected in critically ill Pt, TSH alone not reliable; must measure total T_4, free T_4, & T_3
- Mild illness: ↓ $T_4 \rightarrow T_3$ conversion, ↑ $rT_3 \rightarrow$ ↓ T_3; in severe illness: ↓ TBG & albumin, ↑↑

$rT_3 \rightarrow \downarrow\downarrow T_3$, ↑ degradation of T_4, central ↓ TSH → $\downarrow\downarrow T_3$, $\downarrow\downarrow T_4$, ↓ free T_4, ↓ TSH

- Recovery phase: ↑ TSH followed by recovery of T_4 and then T_3
- Replacement thyroxine *not* helpful or recommended for critically ill Pts w/ ↓ T_3 and T_4 unless other s/s of hypothyroidism

AMIODARONE AND THYROID DISEASE

Overview (*JCEM* 2010;95:2529)

- 6 mg iodine per 200-mg tablet; risk of thyroid dysfunction lower with lower doses
- ✔ TSH prior to therapy, at 4-mo intervals on amio, and for 1 y after if amio d/c'd

Hypothyroidism (occurs in ~10%; more common in iodine-replete areas)

- Pathophysiology
  - (1) Wolff-Chaikoff effect: iodine load ↓ I^- uptake, organification and release of T_4 & T_3
  - (2) inhibits $T_4 \rightarrow T_3$ conversion
  - (3) ? direct/immune-mediated thyroid destruction
- Normal individuals: ↓ T_4; then escape Wolff-Chaikoff effect and have ↑ T_4, ↓ T_3, ↑ TSH; then TSH normalizes (after 1–3 mo)
- Susceptible individuals (eg, subclinical Hashimoto's, ∴ ✔ anti-TPO) do *not* escape effects
- Treatment: thyroxine to normalize TSH; may need larger than usual dose

Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts *in iodine-deficient areas*)

- Type 1 = underlying multinodular goiter or autonomous thyroid tissue
  Jod-Basedow effect: iodine load → ↑ synthesis of T_4 and T_3 in autonomous tissue
- Type 2 = destructive thyroiditis
  ↑ release of preformed T_4 & T_3 → hyperthyroidism → hypothyroidism → recovery
- Doppler U/S: type 1 w/ ↑ thyroid blood flow; type 2 w/ ↓ flow
- Treatment: not absolutely necessary to d/c amio b/c amio ↓ $T_4 \rightarrow T_3$ conversion
  methimazole for type 1; steroids (eg, 40 mg prednisone qd) for type 2 often difficult to distinguish, so Rx for both typically initiated (*JCEM* 2001;86:3) consider thyroidectomy in severely ill patient

THYROID CANCER (*NEJM* 2015;373:2347; *Thyroid* 2016;26:1)

Thyroid nodules (*JAMA* 2018;319:914)

- Prevalence 5–10% (50–60% if screen with U/S), ♀ > ♂, ~7–15% malignant
- Screening U/S recommended if FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules or multinodular goiter
- Features a/w ↑ risk of malig: age <20 or >70 y, ♂, h/o neck XRT, hard & immobile mass, cervical LAN, dysphonia
- U/S features a/w benign dx: cystic nodules, "spongiform" sonographic pattern
- Worrisome findings: hypoechoic, solid, irregular borders, microCa^{2+}, height>width, >20

mm
- Indications for FNA: >10-mm nodule w/ suspicious features

Papillary thyroid cancer
- Most common form (85% of differentiated thyroid cancers); peak incidence 30 to 50 y
- Risk factors: childhood radiation exposure, FHx in 1° relative, familial syndrome
- Low-risk, mort. 1–2% at 20 y; mets to neck LN common, but prognosis remains good
- Rx is surgery; after surgical resection, RAI if medium or high risk (*Lancet* 2013;381:1046 & 1058)

Follicular thyroid cancer
- Peak incidence 40 to 60 y, ♀:♂ 3:1; RFs: childhood radiation; FHx; familial syndrome
- Mortality 10–20% at 20 y; mets frequently distal due to hematogenous spread
- Hurthle cell carcinoma: pathologic dx; variant a/w poorer prognosis and ↑ recurrence rate

Anaplastic thyroid cancer (*Endo Metab Clin North Am* 2008;37:525)
- ♀:♂ 1.5–2:1; poorly differentiated, extremely aggressive, mortality 90% at 5 y
- P/w rapidly growing fixed & hard neck mass, regional or distant spread in 90% at dx
- Rx options include surgery, radiation, trach, chemo, investigational clinical trials

Medullary thyroid cancer
- Neuroendocrine tumor of C cells, peak incidence 40 to 60 y, a/w MEN2A and MEN2B
- Most commonly solitary nodule; calcitonin production and level used to trend dz progression, dx w/ FNA (Se 50–80%); mortality 25–50% at 5 y
- Surgery first-line treatment

ADRENAL DISORDERS

CUSHING'S SYNDROME (HYPERCORTISOLISM) (*NEJM* 2017;376:1451)

Cushing's syndrome = cortisol excess
Cushing's disease = Cushing's syndrome 2° to pituitary ACTH hypersecretion

Etiologies of hypercortisolism

- Most commonly iatrogenic caused by exogenous glucocorticoids (though underreported)
- Cushing's disease (60–70%): ACTH-secreting pituitary adenoma (usually microadenoma) or hyperplasia
- Adrenal tumor (15–25%): adenoma or (rarely) carcinoma
- Ectopic ACTH (5–10%): SCLC, carcinoid, islet cell tumors, medullary thyroid cancer, pheo

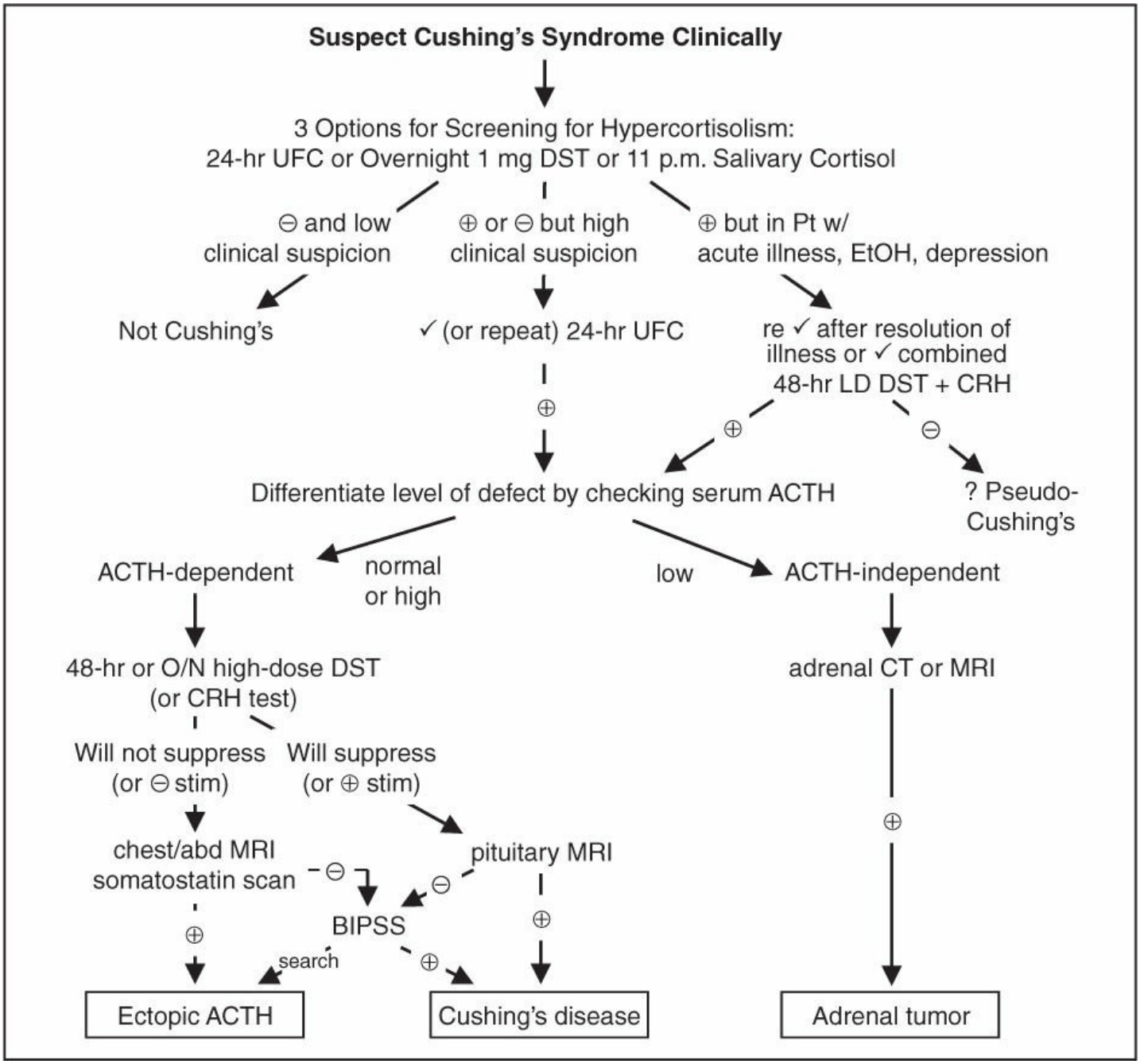
Clinical manifestations (*Lancet* 2006;367:13)

- *Nonspecific:* glucose intolerance or DM, HTN, obesity, oligo- or amenorrhea, osteoporosis
- *More specific:* central obesity w/ extremity wasting, dorsocervical fat pads, spont. bruising
- *Most specific:* proximal myopathy, rounded facies, facial plethora, wide purple striae
- Other: depression, insomnia, psychosis, impaired cognition, hypokalemia, acne, hirsutism, hyperpigmentation (if ↑ ACTH), fungal skin infxns, nephrolithiasis, polyuria

Diagnosis

- Typically performed in *outPt* setting
- *Very difficult as inPt b/c hypercortisolism from acute illness and hosp.*

Figure 7-3 Approach to suspected Cushing's syndrome (*JCEM* 2008;93:1526)



CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol
Overnight 1 mg DST = give 1 mg at 11 p.m.; ✔ 8 a.m. serum cortisol (suppression if <1.8 μg/dL); <5% false ⊕ (primarily used to evaluate subclinical Cushing's in adrenal "incidentalomas")
11 p.m. salivary cortisol = abnl if level ↑; 24-h UFC = abnl if level ↑, > 4× ULN virtually diagnostic
48-h LD DST + CRH = 0.5 mg q6h × 2 d, then IV CRH 2 h later; ✔ serum cortisol 15 min later (⊕ = >1.4 μg/dL)
48-h LD DST = 0.5 mg q6h × 2 d; ✔ 24-h UFC at base. & during last 24 h of dex (suppress if <10% of base)
48-h HD DST = 2 mg q6h × 2 d; ✔ 24-h UFC as per LD DST
O/N HD DST = 8 mg at 11 p.m.; ✔ 9 a.m. serum cortisol (suppression if <32% of baseline)
CRH test = 1 μg/kg IV; ✔ cortisol and ACTH (⊕ stim if > 35% ↑ in ACTH or >20% ↑ in cortisol above baseline)
BIPSS, bilat. Inferior petrosal sinus vein sampling; ✔ petrosal:pewwripheral ACTH ratio (⊕ = 2 basal, >3 after CRH)

Treatment of Cushing's syndrome (*JCEM* 2015;100:2807)

- Surgical: resection of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor, or bilat surgical adrenalectomy if unable to control source of ACTH
- Medical: cabergoline, pasireotide, mitotane, ketoconazole, or metyrapone to ↓ cortisol, and/or mifepristone to block cortisol action at glucocorticoid receptor; frequently used as bridge to surgery or when surgery contraindicated

- Radiation: can do pituitary XRT, but not effective immediately (takes 6 mo to 2 y)
- Glucocorticoid replacement therapy × 6–36 mo after TSS (lifelong glucocorticoid + mineralocorticoid replacement if medical or surgical adrenalectomy)

HYPERALDOSTERONISM

Etiologies

- Primary (adrenal disorders, renin-independent increase in aldosterone; *JCEM* 2015;100:1) adrenal hyperplasia (60–70%), adenoma (Conn's syndrome, 30–40%), carcinoma glucocorticoid-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- Secondary (extra-adrenal disorders, ↑ aldosterone is renin-dependent)
  Primary reninism: renin-secreting tumor (rare)
  Secondary reninism: renovascular disease: RAS, malignant hypertension; edematous states w/ ↓ effective arterial volume: CHF, cirrhosis, nephrotic syndrome; hypovolemia, diuretics, T2D, Bartter's (defective Na/K/2Cl transporter ≈ receiving loop diuretic), Gitelman's (defective renal Na/Cl transporter ≈ receiving thiazide diuretic)
- Nonaldosterone mineralocorticoid excess mimics hyperaldosteronism
  11β-HSD defic. (→ lack of inactivation of cortisol, which binds to mineralocorticoid recept.)
  Black licorice (glycyrrhizic acid inhibits 11β-HSD), extreme hypercortisolism (overwhelming 11β-HSD), exogenous mineralocorticoids
  Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

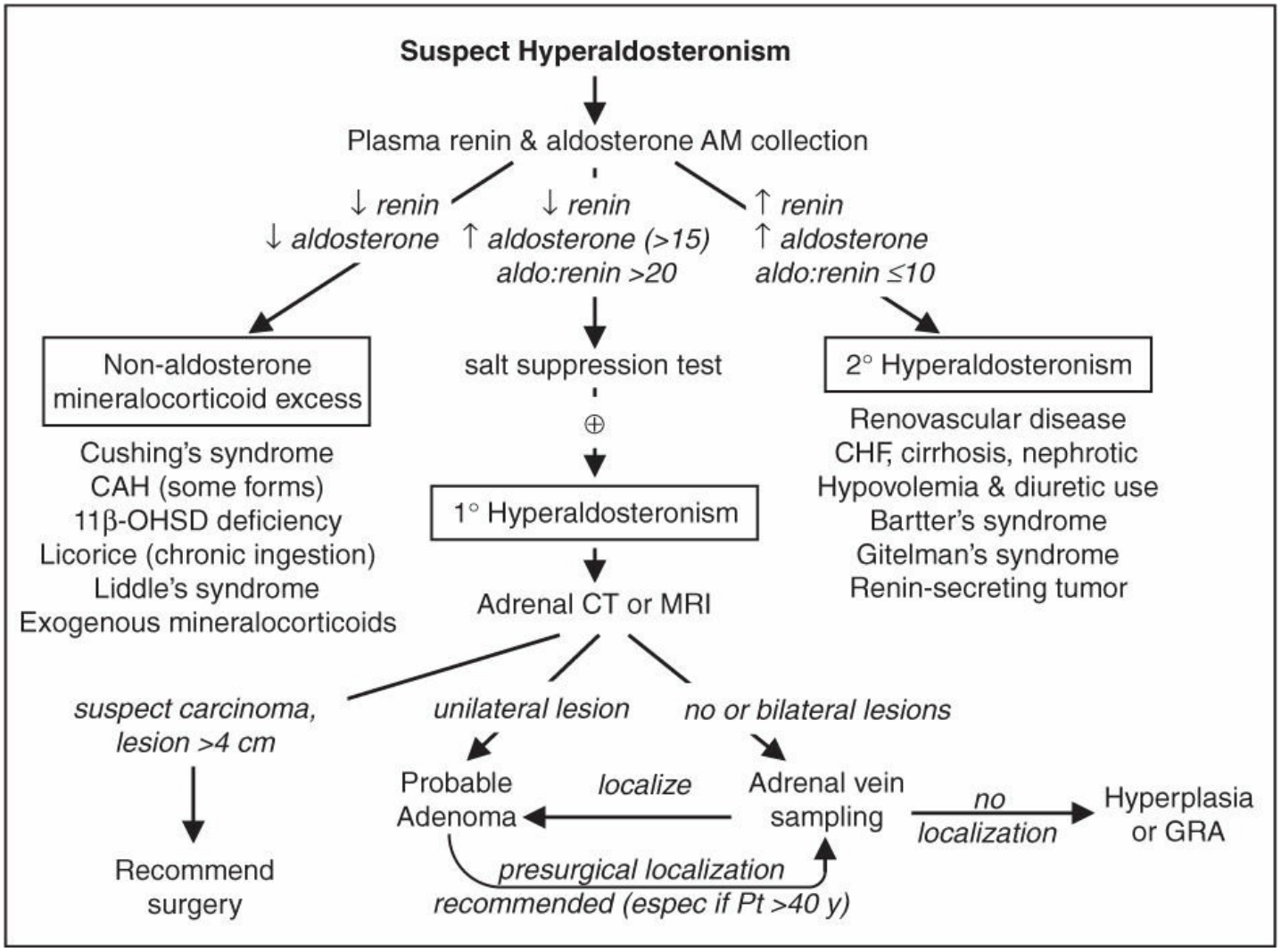
Clinical manifestations

- Mild-to-moderate HTN (11% of Pts w/ HTN refractory to 3 drugs; *Lancet* 2008;371:1921) headache, muscle weakness, polyuria, polydipsia; no peripheral edema because of "escape" from Na retention; malignant HTN is rare
- Classically hypokalemia (but often normal), metabolic alkalosis, mild hypernatremia

Diagnostic studies (*JCEM* 2008;93:3266; *SCNA* 2014;94:643)

- 5–10% of Pts w/ HTN; ∴ screen if HTN + hypoK, adrenal mass, refractory/early onset HTN
- Screening: aldo (>15–20 ng/dL) *and* plasma aldo:renin ratio (>20 if 1°) obtain 8 a.m. paired values (*off* spironolactone & eplerenone for 6 wk); Se & Sp >85%
- ACEI/ARB, diuretics, CCB can ↑ renin activity → ↓ PAC/PRA ratio and βBs may ↑ PAC/PRA ratio;∴ avoid. α-blockers generally best to control HTN during dx testing.
- Confirm with sodium suppression test (fail to suppress aldo after sodium load) oral salt load (+ KCl) × 3 d, ✔ 24-h urine (⊕ if urinary aldo >12 μg/d while urinary Na >200 mEq/d) *or* 2L NS over 4 h, measure plasma aldo at end of infusion (⊕ if aldo >5 ng/dL)

Figure 7-4 Approach to suspected hyperaldosteronism



Treatment (*Surg Clin N Am* 2014;94:643)

- Adenoma → adrenalectomy vs. medical Rx w/ spironolactone or eplerenone
- Hyperplasia → spironolactone or eplerenone; GRA → glucocorticoids ± spironolactone
- Carcinoma → adrenalectomy

ADRENAL INSUFFICIENCY

Etiologies

- Primary = adrenocortical disease = *Addison's disease*
  - autoimmune: isolated or in assoc w/ APS (see table on page 7-2)
  - infection: TB, CMV, histoplasmosis, paracoccidioidomycosis
  - vascular: hemorrhage (usually in setting of sepsis), adrenal vein thrombosis, HIT, trauma
  - metastatic disease: (90% of adrenals must be destroyed to cause insufficiency)
  - deposition diseases: hemochromatosis, amyloidosis, sarcoidosis
  - drugs: azole antifungals, etomidate (even after single dose), rifampin, anticonvulsants
- Secondary = pituitary failure of ACTH secretion (but aldosterone intact b/c RAA axis)
  - any cause of primary or secondary hypopituitarism (see "Pituitary Disorders")
  - glucocorticoid therapy (can occur after ≤2 wk of "suppressive doses"; dose effect

variable; even <10 mg of prednisone daily chronically can be suppressive)
megestrol (a progestin with some glucocorticoid activity)

Clinical manifestations (*Lancet* 2014;383:2152)

- Primary or secondary: weakness and fatigability (99%), anorexia (99%), orthostatic hypotension (90%), nausea (86%), vomiting (75%), hyponatremia (88%)
- Primary only (extra s/s due to lack of aldosterone and ↑ ACTH): marked orthostatic hypotension (because volume depleted), salt craving, hyperpigmentation (seen in creases, mucous membranes, pressure areas, nipples), hyperkalemia
- Secondary only: ± other manifestations of hypopituitarism (see "Pituitary Disorders")

Diagnostic studies (*JCEM* 2016;101:364)

- Early a.m. serum cortisol: <3 µg/dL virtually diagnostic; ≥18 µg/dL generally consistent with intact adrenal function (see Appendix for examples of test results)
- Standard (250 µg) cosyntropin stimulation test (testing ability of ACTH → ↑ cortisol)
  normal = 60-min (or 30-min) post-ACTH cortisol ≥18 µg/dL
  abnormal in *primary* b/c adrenal gland diseased and unable to give adequate output
  abnormal in *chronic* secondary b/c adrenals atrophied and unable to respond
  (very rarely, may be *normal* in *acute pituitary injury* b/c adrenals still able to respond → use early a.m. cortisol instead)
  All glucocorticoids (incl creams, inh. & drops) affect test. Must know exposure to interpret.
- Other tests (w/ guidance by endocrinologist): renin, aldosterone, insulin-induced hypoglycemia (measure serum cortisol response); metyrapone (blocks cortisol synthesis and therefore stimulates ACTH, measure plasma 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels)
- Other lab abnormalities: hypoglycemia, eosinophilia, lymphocytosis, ± neutropenia
- ACTH: ↑ in 1°, ↓ or low-normal in 2°
- Imaging studies to consider
  pituitary MRI to detect anatomical abnormalities
  adrenal CT: small, noncalcified adrenals in autoimmune, enlarged in metastatic disease, hemorrhage, infection or deposition (although they may be normal-appearing)

Treatment

- *Acute* insufficiency: volume resusc. w/ normal saline + hydrocortisone IV (see below)
- *Chronic* insufficiency: (1) prednisone ~4–5 mg PO qam or hydrocortisone 15–25 mg PO qd (⅔ a.m., ⅓ early p.m.); (2) fludrocortisone (*not* needed in 2° adrenal insufficiency) 0.05–0.2 mg PO qam (*JCEM* 2018;103:376); (3) backup dexamethasone 4-mg IM prefilled syringe given to Pt for emergency situations

Adrenal insufficiency & critical illness (*NEJM* 2003;348:727; *JAMA* 2009;301:2362)

- Low cortisol binding proteins; ∴ dx of adrenal insufficiency problematic (*NEJM* 2013;368:1477)
- Adrenal insufficiency rare in most cases of shock unless adrenal infarction or bleed, Waterhouse-Friderichson, CNS or pituitary bleed
- Reasonable to perform ACTH stim ASAP in HoTN Pt w/ suspicion for adrenal

insufficiency
- Can consider above dx criteria, but decision for Rx should also be based on clinical assessment due to risk of false ⊖ and ⊕ results in context of altered physiology
- If concerned, initiate corticosteroids early: use hydrocortisone 50–100 mg IV q8h; prior to ACTH stim test, use dexamethasone 2–4 mg IV q6h + fludrocortisone 50 μg daily
- Controversial data for empiric steroids in all critically ill Pts (see "Sepsis")

Adrenal crisis in adrenal insufficiency (*Lancet Diabetes & Endo* 2015;3:216)
- Precipitants: bilateral adrenal hemorrhage or infarction, pituitary infarction, pre-existing adrenal insufficiency + serious infection or GI illness
- Presentation: shock + anorexia, N/V, abd pain, weakness, fatigue, confusion, coma, fever
- Lab findings: hyponatremia, hyperkalemia (1°)
- Rx: hydrocortisone 50–100 mg IV q8 + IVF; do not delay for dx tests

PHEOCHROMOCYTOMA & PARAGANGLIOMA

Clinical manifestations (five Ps) (*Lancet* 2005;366:665)
- Neuroendocrine neoplasm leads to inappropriate and paroxysmal release of adrenergic agents including epinephrine, norephinephrine, and rarely dopamine
- Pressure (hypertension, paroxysmal in 50%, severe & resistant to Rx, occ orthostatic)
- Pain (headache, chest pain)
- Palpitations (tachycardia, tremor, wt loss, fever)
- Perspiration (profuse)
- Pallor (vasoconstrictive spell)
- Paroxysms can be triggered by meds (eg, β-blockers) abdominal manipulation
- Associated with MEN2A/2B, von Hippel Lindau, NF1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C and D) or *TMEM127* mutations
- Up to 40% of pheos/paragangliomas thought to have underlying genetic etiology; genetic testing frequently recommended

Diagnostic studies (*JCEM* 2014;99:1915)
- 24° urinary fractionated metanephrines: 85–97% Se, 69–95% Sp. Screening test of choice if low-risk (b/c false ⊕ with severe illness, renal failure, OSA, labetalol due to assay interference, acetaminophen, TCAs, medications containing sympathomimetics).
- Plasma-free metanephrines: 89–100% Se, 79–97% Sp (*JAMA* 2002;287:1427). Screening test of choice if high risk, but ↑ rate of false ⊕ in low-prevalence population. False ⊕ rate lower if patient supine for 30 min (estimated 2.8× ↑ false ⊕ if seated).
- Adrenal CT generally better than MRI; PET for known metastatic disease or to localize nonadrenal mass but usually easy to find; consider MIBG scintigraphy if CT/MRI ⊖
- Consider genetic testing if bilateral disease, young Pt, ⊕ FHx, extra-adrenal

Treatment
- α-blockade first (usually phenoxybenzamine) ± β-blockade (often propranolol) → surgery
- Preoperative volume expansion is critical due to possible hypotension after tumor excision

ADRENAL INCIDENTALOMAS

Epidemiology

- 4% of Pts undergoing abdominal CT scan have incidentally discovered adrenal mass; prevalence ↑ with age

Differential diagnosis

- Nonfunctioning mass: adenoma, cysts, abscesses, granuloma, hemorrhage, lipoma, myelolipoma, primary or metastatic malignancy
- Functioning mass: pheochromocytoma, adenoma (cortisol, aldosterone, sex hormones), nonclassical CAH, other endocrine tumor, carcinoma

Hormonal workup (*NEJM* 2007;356:601; *EJE* 2016;175:G1)

- Rule out subclinical Cushing's syndrome *in all Pts* using 1 mg overnight DST (Sp 91%). Abnormal results require confirmatory testing.
- Rule out hyperaldosteronism *if hypertensive* w/ plasma aldo & renin (see above)
- Rule out pheochromocytoma *in ALL Pts* (b/c of morbidity unRx'd pheo) using 24-h urine fractionated metanephrines or plasma-free metanephrines

Malignancy workup

- CT and MRI characteristics may suggest adenoma vs. carcinoma
  Benign features: unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min; size <4 cm; smooth margins, homogenous and hypodense appearance; can follow such incidentalomas w/ periodic scans
  Suspicious features: size >6 cm or ↑ size on repeat scan; irregular margins, heterogeneous, dense or vascular appearance; h/o malignancy or young age. Such incidentalomas warrant resection or repeat scan at short interval.
- Rule out metastatic cancer (and infection) in Pts w/ h/o cancer; ~50% of adrenal incidentalomas are malignant

Follow-up

- If hormonal workup ⊖ and appearance benign, yearly fxnal testing for 4 y w/ follow-up imaging at 6, 12, & 24 mo reasonable approach, but controversial

CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders					
Ca	PTH	Disease	PO_4	25-(OH)D	1,25-$(OH)_2$D
↑	↑↑	Hyperparathyroidism (1° and 3°)	↓	↓ to nl	↑
	↑ or nl	Familial hypocalciuric hypercalcemia	↓	nl	nl
	↓	Malignancy	var.	var.	var.
		Vitamin D excess	↑	↑	var.
		Milk-alkali syndrome, thiazides	↓	nl	nl
		↑ Bone turnover	↑	var.	var.
↓	↑↑	Pseudohypoparathyroidism	↑	nl	↓
	↑	Vitamin D deficiency	↓	↓↓	nl / ↓
		Chronic renal failure (2° hyperpara)	↑	var.	↓
	var.	Acute calcium sequestration	var.	var.	var.
	↓	Hypoparathyroidism	↑	nl	↓

Pitfalls in measuring calcium

- Physiologically active Ca is free or ionized (ICa). Serum Ca reflects total calcium (bound + unbound) and ∴ influenced by albumin (main Ca-binding protein).
- Corrected Ca (mg/dL) = measured Ca (mg/dL) + {0.8 × [4 – albumin (g/dL)]}
- Alkalosis will cause more Ca to be bound to albumin (∴ total Ca may be normal but ↓ ICa)
- Best to measure ionized Ca directly *(but accuracy is lab dependent)*

HYPERCALCEMIA

Etiologies of Hypercalcemia	
Category	Etiologies
Hyperparathyroidism (HPT) (*NEJM* 2018;379:105; *Lancet* 2018;391:168)	1°: adenoma (85%), hyperplasia (15–20%; spont. vs. MEN1/2A), carcinoma (<1%), meds (Lithium → ↑ PTH) 3°: after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery
Familial hypocalciuric hypercalcemia (FHH)	Inact. mut. in Ca-sensing receptor (FHH1), Gα11 (FHH2), AP2S1 (FHH3) → ↑ Ca set point; ± mild ↑ PTH Acquired form due to autoAb vs. Ca-sensing receptor (rare) FE_{Ca} [(24-h U_{Ca}/serum Ca) / (24-h U_{Cr}/serum Cr)] <0.01
Malignancy (*JCEM* 2015;100:2024)	PTH-related peptide (PTHrP) → humoral ↑ Ca of malignancy (eg, squamous cell cancers, renal, breast, bladder) Cytokines → ↑ osteoclast activity (eg, hematologic malig) ↑ 1,25-$(OH)_2$D (eg, rare lymphomas) Local osteolysis (eg, breast cancer, myeloma)
Vitamin D excess	Granulomas (sarcoid, TB, histo, GPA) → ↑ 1-OHase → ↑ 1,25-$(OH)_2$D. Vitamin D

	intoxication.
↑ Bone turnover	Hyperthyroidism, immobilization + Paget's disease, vitamin A
Miscellaneous	Thiazides; Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency
Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° HPT, 10% CKD → 3° HPT	

(*JCEM* 2005;90:6316; *NEJM* 2013;368:644)

Clinical manifestations ("bones, stones, abdominal groans, and psychic moans")

- Hypercalcemic crisis (usually when Ca >13–15): polyuria, dehydration, ΔMS
  Ca toxic to renal tubules → blocks ADH activity, causes vasoconstriction and ↓ GFR → polyuria but Ca reabsorption → ↑ serum Ca → ↑ nephrotoxicity and CNS sx
- Osteopenia, fractures, and osteitis fibrosa cystica (latter seen in severe hyperpara. only → ↑ osteoclast activity → cysts, fibrous nodules, salt & pepper appearance on X-ray)
- Nephrolithiasis, nephrocalcinosis, nephrogenic DI
- Abdominal pain, anorexia, nausea, vomiting, constipation, pancreatitis, PUD
- Fatigue, weakness, depression, confusion, coma, ↓ DTRs, short QT interval
- 1° HPT: 80% asx, 20% nephrolithiasis, osteoporosis, etc.

Diagnostic studies

- Hyperparathyroidism (HPT) and malignancy account for 90% of cases of ↑ Ca; HPT more likely if asx or chronic; malignancy (usually overt) more likely if acute or sx
- Ca, alb, ICa, PTH (may be inapprop. normal in 1° HPT & FHH; *JAMA* 2014;312:2680), PO_4;
  ↑ or high nl PTH: 24-h U_{Ca} >200 mg → HPT; 24-h U_{Ca} <100 mg & FE_{Ca} <0.01 → FHH
  ↓ PTH: ✔ PTHrP, Aϕ, & search for malig (eg, CT, mammogram, SPEP/UPEP) and ✔ vit D: ↑ 25-(OH)D → meds; ↑ 1,25-$(OH)_2$D → granuloma (✔ CXR, ACE, r/o lymph)

Acute Treatment of Hypercalcemia

Treatment	Onset	Duration	Comments
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
± Furosemide	h	during Rx	Use cautiously, only if volume overloaded
Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis
Calcitonin	h	2–3 d	Quickly develop tachyphylaxis
Glucocorticoids	days	days	? Useful in some malig, granulomatous disorders & vitamin D intox.
Denosumab (*JCEM* 2014;99:3144)	days	months	Monoclonal Ab against RANKL; typically used in hyperCa of malignancy; not renally cleared
Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

(*BMJ* 2015;350:h2723)

Treatment of asymptomatic 1° HPT (*JCEM* 2014;99:3561)

- Surgery if: age <50 y; serum Ca >1 mg/dL >ULN; CrCl <60 mL/min, DEXA T score <–2.5
- If surgery declined/deferred, can Rx with cinacalcet (↓ Ca & PTH but may not ↑ BMD)
- If not yet candidate for surgery: ✔ serum Ca & Cr annually and BMD q2y

Calciphylaxis (calcific uremic arteriolopathy)

- Calcification of media of small- to med-sized blood vessels of dermis & SC fat
- Ischemia & skin necrosis. See "Chronic Kidney Disease" for further details.

HYPOCALCEMIA

Etiologies of Hypocalcemia	
Category	Etiologies
Hypoparathyroidism (*NEJM* 2019;380:1738)	Iatrogenic (s/p thyroidectomy, rarely after parathyroidectomy); sporadic; familial (APS1, activating Ca-sensing receptor mutations; see page 7-2); Wilson's, hemochromatosis; hypoMg (↓ secretion and effect); activating Ca-sensing receptor autoAb
Pseudo- hypoparathyroidism (*JCEM* 2011;96:3020)	Ia and Ib: PTH end-organ resistance (∴ ↑ serum PTH) Ia: + skeletal abnormalities, short stature, & retardation Pseudopseudohypoparathyroidism = Ia syndrome but *nl* Ca & PTH
Vit D defic. or resist (*NEJM* 2011;364:248; *JCEM* 2012;97:1153)	Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations)
Chronic renal failure	↓ 1,25-$(OH)_2$D production, ↑ PO_4 from ↓ clearance
Accelerated net bone formation	Postparathyroidectomy, Paget's disease (*NEJM* 2013;368:644), osteoblastic metastases
Calcium sequestration	Pancreatitis, citrate excess (after blood transfusions), acute ↑↑ PO_4 (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

Clinical manifestations

- Neuromuscular irritability: perioral paresthesias, cramps, ⊕ Trousseau's (inflation of BP cuff ≥3 min → carpal spasm), ⊕ Chvostek's (tapping facial nerve → contraction of facial muscles), laryngospasm; irritability, depression, psychosis, seizures, ↑ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO_4 → ↓ bone/cartilage mineralization, growth failure, bone pain, muscle weakness
- Renal osteodystrophy (↓ vit D & ↑ PTH in renal failure): osteomalacia [↓ mineralization of bone due to ↓ Ca and 1,25-$(OH)_2$D] & osteitis fibrosa cystica (due to ↑ PTH)

Diagnostic studies

- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-$(OH)_2$D (if renal failure or rickets), Cr, Mg, PO_4, Aϕ, U_{Ca}

Treatment (also treat concomitant vitamin D deficiency)

- Severely symptomatic: Ca gluconate (1–2 g IV over 20 min) + oral Ca + calcitriol (but

takes hrs to work) ± Mg (50–100 mEq/d); 10% $CaCl_2$ in codes or via CVL

- Consider Ca gtt or PO to follow b/c effect of IV bolus typically lasts only a few hours
- Chronic (depends on etiol.): oral Ca (1–3 g/d; citrate better absorbed than carbonate, esp. if achlorhydria or on PPI) and typically calcitriol (0.25–2 mcg/d), and replete vit. D defic. Consider thiazide to ↓ urinary Ca or recombinant PTH 1-84 (if hypopara).
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol or analogue

DIABETES MELLITUS

Definition (*Diabetes Care* 2019;42:S13)

- Either Hb_{A1c} ≥6.5, fasting glc ≥126 mg/dL, or glc 2 h after OGTT ≥200 mg/dL × 2 (for any test) or single random glc ≥200 mg/dL w/ classic sx of hyperglycemia; all tests equally reasonable (nb, may be ⊕ on one test but not another); OGTT preferred during preg
- Blood glc higher than normal, but not frank DM ("prediabetics," ~40% U.S. population)
  Hb_{A1c} 5.7–6.4%, impaired fasting glc (IFG) 100–125 mg/dL, or 2 h prandial glc 140–199
  Preventing progression to DM: diet & exercise (58% ↓), metformin (31% ↓; *NEJM* 2002;346:393), TZD (60% ↓; *Lancet* 2006;368:1096)

Categories

- Type 1 (*Lancet* 2018;391:2449): islet cell destruction; absolute insulin deficiency; ketosis in absence of insulin; prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk if ⊕ FHx; HLA associations; anti-GAD, anti-islet cell & anti-insulin autoAb
- Type 2 (*Lancet* 2017;389:2239): insulin resistance + relative insulin ↓; prevalence 6%; onset generally later in life; no HLA assoc.; risk factors: age, ⊕ FHx, obesity, sedentary lifestyle
- Type 2 DM p/w DKA ("ketosis-prone type 2 diabetes" or "Flatbush diabetes"): most often seen in nonwhite, ± anti-GAD Ab, eventually may not require insulin (*Endo Rev* 2008;29:292)
- Mature-Onset Diabetes of the Young (MODY): autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (*NEJM* 2001;345:971)
- Secondary causes of diabetes: exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), endocrinopathies (Cushing's disease, acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

Clinical manifestations

- Polyuria, polydipsia, polyphagia with unexplained weight loss; can also be asymptomatic

Diabetes Treatment Options	
Medication (↓ Hb_{A1C})	Comments
Metformin (~1–1.5%)	↓ hepatic gluconeogenesis. Mild wt ↓. *1st line for T2D.* Rare lactic acidosis. Caution if GFR 30–45; contra. if <30. Poss CV benefit.
DPP-4 inhibitors (~0.5–1%)	Block degrad. GLP-1 & GIP → ↑ insulin. ↑ risk of HF w/ saxagliptin (*NEJM* 2013;369:1317), not w/ others.
GLP-1 receptor agonists	↑ glc-depend insulin secretion. Wt ↓, N/V.

(~1–1.5%)	↓ CVD/MI/stroke, espec. if ASCVD. ↓ prog of albuminuria.
SGLT-2 inhibitors (~0.5–1%)	↑ glucosuria. Wt ↓. Genital infxn. ↓ CVD/HHF. ↓ CVD & MI if ASCVD. ↓ prog. of renal disease.
Sulfonylureas (SU) (~1.5%)	↑ insulin secretion. Hypoglycemia; wt gain.
Thiazolidinediones (TZD) (~1%)	↑ insulin sens. in adipose & muscle. Wt ↑, fluid retention & CHF. Hepatox. ↑ MI w/ rosiglitazone? Contraindic. in HF & liver dysfxn.
Glinides (~1%)	↑ insulin secretion; hypoglycemia; wt gain
α-glucosidase inhib. (0.5–1%)	↓ intestinal CHO absorption. Abd pain, flatulence.
Pramlintide (~0.5%)	Delays gastric emptying & ↓ glucagon. N/V
Insulin (variable)	Hypoglycemia; wt gain. Mandatory in T1D; consider in T2D if oral Rx inadequate.
Gastric bypass	Wt ↓↓↓; can cause remission DM (*NEJM* 2014;370:2002)

(*Diabetes Care* 2019;42:S90; *Lancet* 2019;393:31; *Circ* 2019;139:2022; *NEJM* 2019;380:2295)

Insulin Preparations (*Diabetes Care* 2019;42:S90)

Type (example)	**Onset**	**Peak**	**Duration**	**Comments**
Rapid (lispro, aspart)	Immed	1-2 h	<4 h	Give immediately before meal
Short (regular)	~30 min	2–3 h	5–8 h	Give ~30 min before meal
Intermed. (NPH)	2–3 h	4–8 h	10–14 h	Can cause protamine Ab prod
Long (glargine, detemir)	1–2 h	n/a	12–24 h	Once-daily basal insulin

Complications (*NEJM* 2004;350:48; 2016;374:1455; *CJASN* 2017;12:1366)

- Retinopathy
  nonproliferative: "dot & blot" and retinal hemorrhages, cotton-wool/protein exudates
  proliferative: neovascularization, vitreous hemorrhage, retinal detachment, blindness
  treatment: photocoagulation, surgery, intravitreal bevacizumab injections
- Nephropathy: microalbuminuria → proteinuria ± nephrotic syndrome → renal failure
  diffuse glomerular basement membrane thickening/nodular pattern (Kimmelstiel-Wilson)
  usually accompanied by retinopathy; lack of retinopathy suggests another cause
  treatment: strict BP control using ACE inhibitors or ARBs (*Mayo Clin Proc* 2011;86:444), SGLT-2 inhib (*NEJM* 2016;375:323 & 2019;380:2295), low-protein diet, dialysis or transplant
- Neuropathy: *peripheral:* symmetric distal sensory loss, paresthesias, ± motor loss
  autonomic: gastroparesis, constipation, neurogenic bladder, erectile dysfxn, orthostasis
  mononeuropathy: sudden-onset peripheral or CN deficit (footdrop, CN III > VI > IV)
- Accelerated atherosclerosis: coronary, cerebral and peripheral arterial beds
- Infections: UTI, osteomyelitis of foot, candidiasis, mucormycosis, necrotizing external otitis
- Dermatologic: necrobiosis lipoidica diabeticorum, lipodystrophy, acanthosis nigricans

Outpatient screening and treatment goals (*Diabetes Care* 2019;42:S61, S81, S103)

- ✔ Hb_{A1C} q3–6mo, goal <7% for most Pts. Goal <6.5% if low-risk hypoglycemia; ≤8% if h/o severe hypoglycemia, elderly or other comorbid. Microvascular & macrovascular

complic. ↓ by strict glycemic control in T1D (*NEJM* 2005;353:2643) & T2D (*NEJM* 2015;372:2197).

- Microalbuminuria screening yearly with spot microalbumin/Cr ratio, goal <30 mg/g
- Wt loss (dietary/drugs) can regress or resolve DM (*Endo Rev* 2018;39:79; *NEJM* 2018;379:1107)
- BP ≤130/80 if high CV risk, ≤140/90 if lower risk; benefit of ACEI/ARB
- Lipids: statin initiation in all diabetics age 40–75 if LDL-C >70 (see "Lipids")
- ASA in 2° prevention; ? role in 1°, balancing ↓ MACE & ↑ bleeding (*NEJM* 2018;379:1529)
- Dilated retinal exam and comprehensive foot exam yearly

Management of hyperglycemia in inPts (for ICU: see "Sepsis") (*ClinTher* 2013;35:724)

- Identify reversible causes/precipitants (dextrose IVF, glucocorticoids, postop, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or q6h if NPO), Hb_{A1C}
- Treatment goals: avoid hypoglycemia, extreme hyperglycemia (>180 mg/dL)
- Transition to inPt
  - T1D: do not stop basal insulin (can → DKA)
  - T2D: stopping oral DM meds generally preferred to avoid hypoglycemia or med interaction (except if short stay, excellent outPt cntl, no plan for IV contrast, nl diet). *If Pt w/ known insulin needs do not rely on sliding scale alone* (*Diabetes Care* 2018;41:S144).
- Starting new insulin regimen
  - Basal = 0.2–0.4 u/kg/d NPH Q12h or detemir or glargine
  - + correction insulin for BG >150 mg/dl
  - + prandial insulin if eating: 0.05–0.1 μ/kg/meal lispro, aspart, or regular
- *When NPO*
  - T1D: continue basal insulin at current dose or 75% depending on BG control
  - T2D: continue basal insulin at 25–75% depending on BG control and level of insulin resistance. Hold all prandial insulin.
- Discharge regimen: similar to admission regimen unless poor outPt cntl or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outPt follow-up.

DIABETIC KETOACIDOSIS (DKA)

Precipitants (the I's)

- Insulin defic. (ie, failure to take enough insulin); Iatrogenesis (glucocorticoids; SGLT2 inhibitors—can be w/o marked hyperglycemia; *Diabetes Care* 2016;39:532)
- Infection (pneumonia, UTI) or Inflammation (pancreatitis, cholecystitis)
- Ischemia or Infarction (myocardial, cerebral, gut); Intoxication (alcohol, drugs)

Pathophysiology (*NEJM* 2015;372:546)

- Occurs in T1D (and in ketosis-prone T2D); ↑ glucagon and ↓ insulin
- Hyperglycemia due to: ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glucose uptake into cells
- Ketosis due to: insulin deficiency → mobilization and oxidation of fatty acids, ↑ substrate for ketogenesis, ↑ ketogenic state of the liver, ↓ ketone clearance

Clinical manifestations (*Diabetes Care* 2009;32:1335 & 2016;39:S99)

- Polyuria, polydipsia, & dehydration → ↑ HR, HoTN, dry mucous membranes, ↓ skin turgor
- N/V, abdominal pain (either due to intra-abdominal process or DKA), ileus
- Kussmaul's respirations (deep) to compensate for metabolic acidosis with odor of acetone
- Δ MS → somnolence, stupor, coma; mortality ~1% even at tertiary care centers

Diagnostic studies

- ↑ Anion gap metabolic acidosis: can later develop nonanion gap acidosis due to urinary loss of ketones (HCO_3 equivalents) and fluid resuscitation with chloride
- Ketosis: ⊕ urine and serum ketones (predominant ketone is β-OH-butyrate, but acetoacetate measured by assay; urine ketones may be ⊕ in fasting normal Pts)
- ↑ Serum glc; ↑ BUN & Cr (dehydration ± artifact due to ketones interfering w/ some assays)
- Hyponatremia: corrected Na = measured Na + [2.4 × (measured glc – 100)/100]
- ↓ or ↑ K (but even if serum K is elevated, usually *total body K depleted*); ↓ total body phos
- Leukocytosis, ↑ amylase (even if no pancreatitis)

Typical DKA "Flow Sheet" Setup

VS	UOP	pH	HCO_3	AG	Ketones	Glc	K	PO_4	IVF	Insulin

Note: Main ketone produced is β-OH-butyrate (βOHB), *but ketone measured by nitroprusside is acetoacetate (Ac-Ac). As DKA is treated, βOHB → Ac-Ac, ∴ AG can decrease while measured ketones can increase.*

Treatment of DKA (*BMJ* 2015;28:351)	
R/o possible precipitants	Infection, intra-abdominal process, MI, etc. (see above)
Aggressive hydration	NS 10–14 mL/kg/h, tailor to dehydration & CV status
Insulin	10 U IV push followed by 0.1 U/kg/h Continue insulin drip until AG normal If glc <250 and AG still high → add dextrose to IVF and continue insulin to metabolize ketones AG normal → SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <4.5 insulin promotes K entry into cells → ↓ serum K careful K repletion in Pts with renal failure HCO_3: ? replete if pH <7 or if cardiac instability PO_4: replete if <1

HYPEROSMOLAR HYPERGLYCEMIC STATE

Definition, precipitants, pathophysiology (*Med Clin North Am* 2017;101:587)

- Extreme hyperglycemia (w/o ketoacidosis) + hyperosm. + Δ MS in T2D (typically elderly)
- Precip same as for DKA, but also include dehydration and renal failure
- Hyperglycemia → osmotic diuresis → vol depletion → prerenal azotemia → ↑ glc, etc.

Clinical manifestations & dx studies (*Diabetes Care* 2014;37:3214)

- Volume depletion and Δ MS
- ↑ serum glc (usually >600 mg/dL) and ↑ meas. serum osmolality (>320 mOsm/L)

effective Osm = 2 × Na (mEq/L) + glc (mg/dL)/18

- No ketoacidosis; usually ↑ BUN & Cr; [Na] depends on hyperglycemia & dehydration

Treatment

- Rule-out possible precipitants; ~15% mortality due to precipitating factors
- Aggressive hydration: initially NS, then 1/2 NS, average fluid loss up to 8–10 L
- Insulin (eg, 10 U IV followed by 0.05–0.1 U/kg/h)

HYPOGLYCEMIA

Clinical manifestations (glucose <~55 mg/dL)

- CNS: headache, visual Δs, Δ MS, weakness, seizure, LOC (neuroglycopenic sx)
- Autonomic: diaphoresis, palpitations, tremor (adrenergic sx)

Etiologies in diabetics

- Excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance)
- β-blockers can mask adrenergic symptoms of hypoglycemia

Etiologies in nondiabetics

- ↑ insulin: exogenous insulin, sulfonylureas, insulinoma, anti-insulin antibodies
- ↓ glucose production: hypopituitarism, adrenal insufficiency, glucagon deficiency, hepatic failure, renal failure, CHF, alcoholism, sepsis, severe malnutrition
- ↑ IGF-II: non-islet tumor
- Postprandial, esp. postgastrectomy or gastric bypass: excessive response to glc load
- Low glc w/o sx can be normal

Evaluation in nondiabetics (*JCEM* 2009;94:709)

- If clinically ill: take measures to avoid recurrent hypoglycemia; ✔ BUN, Cr, LFTs, TFTs, prealbumin; IGF-I/IGF-II ratio when appropriate
- If otherwise healthy: 72-h fast w/ monitored blood glc; stop for neuroglycopenic sx
- *At time of hypoglycemia:* insulin, C peptide (↑ w/ insulinoma and sulfonylureas, ↓ w/ exogenous insulin), β-OH-butyrate, sulfonylurea levels
- At end of fast, give 1 mg glucagon IV and measure response of plasma glc before feeding

Treatment

- Glucose tablets, paste, fruit juice are first-line Rx for Pts who can take POs
- 25–50 g of D_{50} IV; if no access, glucagon 0.5–1 mg IM or SC (side effect: N/V)

LIPID DISORDERS

Measurements

- Lipoproteins = lipids (cholesteryl esters & triglycerides) + phospholipids + proteins
  include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL typically calculated: LDL-C = TC – HDL-C – (TG/5)
  underestim. if TG >400 or LDL-C <70 mg/dL; ∴ directly measure LDL-C
  levels stable up to 24 h after ACS, then ↓ and may take 6 wk to return to nl
- PEx clues: tendon xanthomas (eg, Achilles), imply LDL >300 mg/dL; eruptive xanthomas on extensor surfaces imply TG >1000 mg/dL; xanthelasma (yellowish streaks on eyelids)
- Metabolic syndrome (≥3 of following): waist ≥40″ (♂) or ≥35″ (♀); TG ≥150; HDL <40 mg/dL (♂) or <50 mg/dL (♀); BP ≥130/85 mmHg; fasting glc ≥100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = LDL particle bound to apo(a) via apoB; genetic variants a/w MI (*NEJM* 2009;361:2518)

Dyslipidemias

- 1°: *familial hyperchol.* (FH, 1:500): defective LDL receptor; ↑↑ chol, nl TG; ↑ CAD; *familial hypertrig.* (FHTG, 1:500): ↑ TG, ± ↑ chol, ↓ HDL, pancreatitis; and many others
- 2°: DM (↑ TG, ↓ HDL), hypothyroidism (↑ LDL, ↑ TG), nephrotic syndrome (↑ LDL, ↑ TG), liver failure (↓ LDL), alcohol (↑ TG, ↑ HDL), thiazides (↑ LDL, ↑ TG), protease inhib (↑ TG)

Drug Treatment				
Drug	**↓ LDL**	**↑ HDL**	**↓ TG**	**Side Effects/Comments**
Statins	20–60%	5–10%	10–25%	↑ ALT in 0.5–3%; ✓ before starting and then prn Myalgias <10%, rhabdo <0.1%, dose-dependent ↑ risk of DM; screen if risk factors (*ATVB* 2019;39:e38)
Ezetimibe	~24%	—	—	Well tolerated
PCSK9i	~60%	5–10%	15–25%	mAb inj SC q2w or q4w; siRNA under development
Fibrates	5–15%	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Ω-3 FA	5% ↑	3%	25–50%	EPA & DHA at doses of up to 4 g/d No benefit to low-dose supplementation

Resins ↓ LDL-C by ~20%, but not well tolerated; niacin ↑ HDL-C and ↓ TG & LDL-C; no effect on CV outcomes.

Treatment of LDL-C (*Lancet* 2014;384:607)

- Statins: every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (*Lancet* 2010;376:1670)
- Ezetimibe: ↓ major vascular events incl MI & stroke when added to statin post-ACS, w/ magnitude of benefit consistent w/ LDL-statin relationship (IMPROVE-IT, *NEJM*

2015;372:2387)

- PCSK9 inhibitors: ~60% ↓ LDL-C on top of statin, as monoRx, and in FH (*EHJ* 2014;35:2249); ↓ CV outcomes (*NEJM* 2017;376:1713 & 2018;379:2097)

Treatment of other lipid fractions (*Lancet* 2014;384:618 & 626)

- HDL-C: low levels a/w ↑ risk of MI, but no clinical benefit shown by raising
- Triglycerides: reasonable to treat levels >500–1000 mg/dL w/ fibrates or Ω-3 FA to ↓ risk of pancreatitis; genetically-mediated lower levels a/w ↓ risk of CAD (*NEJM* 2014;371:22); modest benefit of fibrates on CV outcomes (*NEJM* 2010;362:1563 & 2013;368:1800); high-dose Ω-3 FA (4 g/d of EPA) ↓ CV outcomes in Pts w/ ASCVD or DM (*NEJM* 2019:380:11)
- Lp(a): consider ↓ to <50 mg/dL in intermed- to high-risk Pts (*EHJ* 2010;31:2844)

2018 ACC/AHA Cholesterol Guidelines (*Circ* 2019;139:e1082)		
Population		Recommendation
Very high-risk ASCVD*		High-intensity statin; add EZE then PCSK9i if LDL-C ≥70
Clinical ASCVD		High-intensity statin (? mod if >75 y), add EZE if LDL-C ≥70
LDL-C ≥190 mg/dL		High-intensity statin; add EZE or PCKS9i if LDL-C ≥100
DM, age 40–75 y		High-intensity statin (? moderate if no CV RFs)
Age 40–75 y (and none of above); *calc 10-y risk*	≥20%	High-intensity statin
	7.5%–<20%	Moderate-intensity statin; if uncertain consider CAC
	5–<7.5%	Moderate-intensity statin reasonable
	<5%	Emphasize lifestyle

ASCVD incl h/o ACS, stable angina, art. revasc, stroke, TIA, PAD. *Multiple major ASCVD events (MI, stroke, sx PAD) or 1 major event + multiple high-risk conditions (age ≥65, DM, HTN, CKD, smoking, FH, prior PCI/CABG). 10-y CV Risk Score: http://my.americanheart.org/cvriskcalculator. Additional risk factors to consider: LDL-C ≥160 mg/dl, met. synd.,CKD, FHx premature ASCVD, hsCRP ≥2 mg/l, Lp(a) ≥50 mg/dl, ABI <0.9, high-risk ethnic groups.

Statin Doses & LDL-C Reduction (doubling of dose → 6% further ↓ LDL-C)								
Intensity	**↓ LDL-C**	**Rosuva**	**Atorva**	**Simva**	**Prava**	**Lova**	**Fluva**	**Pitava**
High	**≥50%**	20–40	40–80	(80)				
Mod	**30–50%**	5–10	10–20	20–40	40–80	40	80	2–4
Low	**<30%**			10	10–20	20	20–40	1

APPROACH TO RHEUMATIC DISEASE

Approach to patient with joint pain

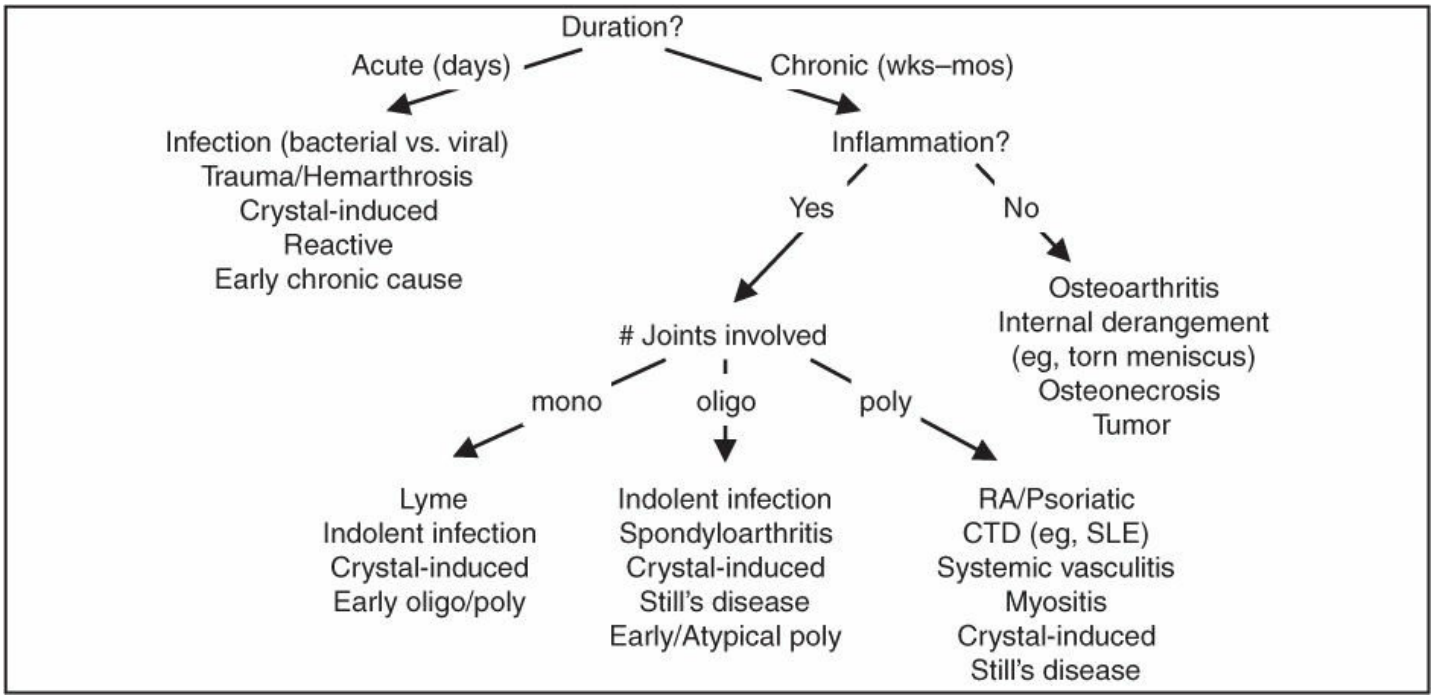
- Articular vs. periarticular (bursitis, tendinitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- Inflammatory vs. noninflammatory pain: *features of inflammatory pain* include swelling, warmth or redness in specific joint, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise. Assess for extra-articular features.
- Physical exam: localize complaint, identify objective signs of inflammation, and assess number and pattern of affected joints
- The physical exam is only *50–70% sensitive* for detecting inflammatory arthritis

Key Physical Exam Findings in Joint Pain

	Articular (Joint) Disease			*Periarticular/Soft Tissue*	
Physical Exam	**OA**	**Inflammatory Arthritis[a]**	**Arthralgia**	**Bursitis or Tendinitis**	**Myofascial**
Swelling	Varies	Yes	No	Yes	No
Erythema	No	Varies	No	Yes	No
Warmth	No	Yes	No	Yes	No
Tenderness	Joint line	Yes	Varies	Periarticular	Yes
ROM[b]	Limited	Limited	Full or limited	Full, often limited by pain	Full
Pain w/ active or passive	Both	Both	Usually both	Active > passive	Usually both

[a]May initially present as arthralgia w/o overt arthritis. [b]Range of motion of joint or joint a/w bursa or tendon.

Figure 8-1 Approach to arthritis



Analysis of Joint Fluid				
Test	**Normal**	**Noninflamm**	**Inflammatory**	**Septic**
Appearance	Clear	Clear, yellow	Clear to opaque yellow-white	Opaque
WBC/mm^3	<200	<2000	>2000	>2000 *(usually >50k*)*
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Intracellular crystals	⊖	⊖	⊕ in some (eg, gout)	May be ⊖ or ⊕ if concurrent gout/CPPD

*WBC count of aspirated fluid in septic bursitis often < WBC count in septic arthritis.

Radiologic features of major arthritides

- OA: plain films: asym joint space narrowing (JSN), osteophytes, subchondral sclerosis & cysts; subchondral "gull-wing" erosions may be seen in less-common erosive OA; MRI may show early disease not seen on plain films; U/S ≈ MRI for structural damage ⊖
- RA: plain films: symmetric JSN, early = periarticular osteopenia; late = marginal erosions; subluxations; MRI & U/S can detect early and subclinical disease; MRI ≈ U/S for erosions
- Gout: plain films: early = nonspec swelling; late = tophus, joint erosions w/ overhanging edges; U/S for detection of microtophi (double-contour sign); dual-energy CT (DECT): identify articular/periarticular UrA deposits vs. calcium deposits; MRI ≈ U/S for erosions
- Spondyloarthritis: e/o sacroiliitis: plain films: early = pseudo-widening SI joint space, late = sclerosis, erosions, ankylosis; SI MRI ↑ Se for early Δ; U/S ≈ MRI to detect enthesitis

Comparison of Major Arthritides				
Feature	**Primary OA**	**RA**	**Gout/CPPD**	**Spondyloarthritis**
Onset	Gradual	Gradual	Acute	Variable
Inflammation	⊖	⊕	⊕	⊕
Pathology	Degeneration	Pannus	Microtophi	Enthesitis
# of joints	Poly	Poly	Mono to poly	Oligo or poly
Typical joint involvement	Hips, knees, spine, 1st CMC DIP, PIP	MCP, PIP wrists, feet, ankles, knees	MTP feet, ankles, knees	Sacroiliac spine large periph
Joints often *spared*	MCP, shoulder, elbow, wrist	L & T spine, DIPs	Spine	*Any joint can be involved*
Special articular findings	Bouchard's & Heberden's nodes	Ulnar dev. swan neck boutonnière deformities	Urate/CPPD crystals tophi	Dactylitis enthesitis (eg, Achilles) bamboo spine syndesmophytes
Extra-articular features		SC nodules pulmonary sicca	Olec. bursitis renal stones	Psoriasis, IBD, uveitis, urethritis conjunctivitis
Lab data	Normal	Often ⊕ RF & anti-CCP	↑ UrA (may be nl during flare)	± HLA-B27

INFLAMMATORY MARKER & AUTOANTIBODY TESTING

Inflammatory markers (*Mod Rheumatol* 2009;19:469)

- ESR: *indirect* measure of inflammation [↑ RBC aggregation due to acute-phase proteins (fibrinogen & Ig) in blood]; slow to rise; may ↑ w/ age, preg., anemia, obesity. Ddx for >100: malig. esp. MM, lymphoma; GCA or other vasculitis; ESRD; endocarditis, TB, osteo.
- CRP: *direct* measure of inflammation (protein produced by liver, part of innate immune system); *typically rises and falls before the ESR* w/ treatment/resolution of process

Autoantibody testing (*Best Pract Res Clin Rheumatol* 2014;28:907)

- ANA (anti-nuclear Ab): *screening test* for Ab directed against nuclear proteins; found in autoimmune conditions; most useful in testing for suspected connective tissue diseases
- Order ANA only when *clinical suspicion for CTD* b/c nonspecific: 1:40 (very low ⊕, 25–30% of healthy Pts); 1:80 (low ⊕, 10–15% of healthy Pts); ≥1:160 (⊕, 5% of healthy Pts). May be ⊕ in Pts prior to clin manifest (*NEJM* 2003;349:1526; *Arthritis Res Ther* 2011;13:1).
- If ANA ⊕ and high clinical suspicion for CTD, consider testing for Ab against dsDNA, Smith, Ro/La, RNP, Scl-70 and myositis-specific Abs (*highly specific* for various CTD)
- ANA does *not* correlate well w/ disease activity, ∴ no clinical value in serial testing
- "False ⊕" ANA: AIH, PBC, thyroid disease, certain infxns and malignancies, IBD, IPF
- RF and anti-CCP (see "Rheumatoid Arthritis")

DDX & APPROACH TO COMMON INPATIENT RHEUM PRESENTATIONS

Presentation	Rheum Ddx	Rheum Lab Workup
Fever of unknown origin	GCA/PMR, adult-onset Still's, SLE, inflammatory arthritis, Takayasu's, PAN, ANCA ⊕ vasc, cryo, HSP	ESR, CRP, ANA, RF, ANCA, ± cryo
Pulmonary hypertension	Scleroderma (limited > diffuse), MCTD, SLE, PM/DM (less common)	ANA, Scl-70, centromere, RNA Pol III, RNP
Diff alveolar hemorrhage	ANCA ⊕ vasculitis, Goodpasture's, SLE, APS	ANCA, GBM, ANA, C3/C4
Interstitial lung disease	Scleroderma (diffuse > limited), sarcoid, RA, DM/PM, antisynthetase syndrome, Sjögren's, MCTD, SLE (esp. pleura), ANCA ⊕ vasc (esp. MPA)	ANA, Scl-70, RF/anti-CCP, CK, aldolase, ± myositis specific Abs, Jo-1, Ro/La, ANCA
Pleuro- pericarditis	SLE, RA, MCTD, DM/PM, ANCA ⊕ vasc, Sjögren's, PAN	ANA, dsDNA, Sm, RNP, Ro/La, RF, anti-CCP, ANCA
Acute kidney injury (+active sed. or s/s c/w CTD)	SLE (GN or nephrotic), ANCA ⊕ vasc (GN), scleroderma renal crisis (diffuse), Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's (GN), cryo, APS	ANA, dsDNA, Smith, Ro/La, RNP, C3/C4, Scl-70 & RNA Pol III (SRC), ANCA, GBM, cryos, APS panel
Neuropathy	ANCA ⊕ vasc, SLE, RA, PAN, Sjögren's, cryo, sarcoid	ANA, Ro/La, ANCA, cryo RF/anti-CCP, HCV, HBV

RHEUMATOID ARTHRITIS (RA)

Definition & epidemiology (*Lancet* 2016;388:2023)

- Chronic, symmetric, debilitating, and destructive inflammatory polyarthritis characterized by proliferative synovial tissue (pannus) formation in affected joints
- Pathogenesis involves over-production of TNF, IL-1, and IL-6 (∴ used as drug targets)
- Risk stems from combination of genetic (~50% of risk), environmental influences (eg, smoking, silica dust), and Pt factors (periodontal disease, Δs in gut microbiome)
- HLA-DRB1 haplotype a/w disease suscept., severity, & response to Rx (JAMA 2015;313:1645)
- Prevalence = 1% adults and 5% of ♀ >70 y; ♀ to ♂ ratio = 3:1; peak incidence 50–75 y

Clinical manifestations (*Medicine* 2010;38:167)

- Usually insidious onset pain, swelling, & impaired function of joints w/ prolonged morning stiffness for ≥6 wk (typically PIPs, MCPs, wrists, knees, ankles, MTPs, cervical spine)
- Typically polyarticular (60% small joints, 30% large joints, 10% both), may be monoarticular (knee, shoulder, wrist) early in course; rheumatoid joints more susceptible to infection
- Joint deformities: ulnar deviation, swan neck (MCP flexion, PIP hyperextension, DIP flexion), boutonnière (PIP flexion, DIP hyperextension), cock-up deformities (toes)
- C1–C2 instability → myelopathy, ∴✔ C-spine flex/ext films prior to elective intubation
- Constitutional symptoms: *low-grade* fever, weight loss, malaise
- Extra-articular manifestations (18–41% of Pts) can occur at any time; ↑ frequency in seropositive (⊕ RF or anti-CCP) and with active disease (*Autoimmun Rev* 2011;11:123)

Extra-Articular Manifestations (EAMs)	
Skin	Rheumatoid nodules (20–30%, usually sero ⊕): extensor surface, bursae; can be in lung, heart, sclera Raynaud's, pyoderma gangrenosum, cutan. vasculitis (ulcers, purpura, etc.)
Pulm	ILD, airway disease, pleuritis, effusions (low glc), nodules, pulm HTN; precedes joint sx in 20% of cases; RA med toxicity (MTX, ? anti-TNF & anti- CD20) (*Curr Opin Pulm Med* 2011;362:367)
CV	Accel. athero w/ ↑ risk of MI & CV death, pericarditis (effusions in ⅓ of sero ⊕), myocarditis, AF, coronary/systemic vasculitis. (*Arth Rheum* 2015;67:2311)
Nervous	Mono/polyneuritis multiplex, CNS vasculitis, stroke, nerve entrapment
Ocular	Scleritis, episcleritis, keratoconjunctivitis sicca (2° Sjögren's)
Heme	Anemia of chronic disease, neutropenia (Felty's syndrome: 1%, typically long- standing RA + splenomegaly; large granular lymphocyte leukemia: bone marrow infiltrated w/ lymphocytes ± myeloid hypoplasia), NHL, amyloidosis
Renal	Glomerulonephritis (usually mesangial), nephrotic syndrome (2° amyloidosis), nephrotoxicity from RA meds
Vasculitis	Small & medium vessels (usually ↑ RF titer, long-standing RA); pericarditis, ulcers, scleritis, & neuropathy most common (*Curr Opin Rheum* 2009;21:35)

Laboratory & radiologic studies (*JAMA* 2018;320:1360)

- RF (IgM/IgA/IgG anti-IgGAb) ⊕ in ~70% of Pts w/ RA; also seen in other rheumatic diseases (SLE, Sjögren's), infection (SBE, hepatitis, TB), cryo, ~5% of healthy population
- Anti-CCP (Ab to cyclic citrullinated peptide): ⊕ in ~80% of Pts w/ RA, similar Se (~70%), but more Sp (>90%) than RF particularly for early RA (*Arth Rheum* 2009;61:1472); a/w increased joint damage and low remission rates
- ~20% are seronegative (RF *and* anti-CCP negative)
- ↑ ESR/CRP but nl in ~30%; ⊕ ANA in ~40%; ↑ globulin during periods of active disease
- Radiographs of hands and wrists: periarticular osteopenia, bone erosions, joint subluxation
- Increasing use of MSK U/S to diagnosis synovitis and erosive disease

ACR/EULAR classification criteria (*Arth Rheum* 2010;62:2569)

- Used in clinical research, but not in clinical practice
- Relevant for Pts with ≥1 joint with synovitis not better explained by another disease
- Likelihood of RA ↑ w/ higher # (espec. ≥4) of small joints involved, ⊕ RF or anti-CCP (espec. high titer), ANA, ↑ ESR or CRP, and duration ≥6 wk

Management (*Lancet* 2017;389:2328 & 2338; *JAMA* 2018;320:1360)

- Early dx and Rx (esp DMARD) w/ frequent follow-up and escalation of Rx as needed with goal to achieve clinical remission or low disease activity
- ↓ time to remission ≈ ↑ length of sustained remission (*Arthritis Res Ther* 2010;12:R97)
- Sero-⊕ disease (eg, RF or anti-CCP) a/w aggressive joint disease & EAM
- At dx, start *both* rapid-acting agent (to acutely ↓ inflammation) and Disease-Modifying Anti-Rheumatic Drug (DMARD) (typically take 1–3 mo to have max effect)
- *Rapid-acting drugs:*
  - NSAIDs or COX-2 inhibitors: ↑ CV risk, GI adverse events, AKI; consider starting w/ PPI
  - glucocorticoids: low dose (<20 mg/d oral) or joint injection
  - NSAIDs + glucocorticoids: ↑↑ GI events; give PPI and minimize long-term concurrent use
- *DMARDs (see RA therapeutics below):*
  - Methotrexate (1st line unless CKD, hepatitis, EtOH or lung disease), alternatives include sulfasalazine or leflunomide; consider HCQ if seronegative and mild disease
  - If inadequate response after 3 mo (despite DMARD dose escalation) consider:
    - combination Rx w/ other DMARDs (eg, "triple therapy" w/ MTX, SAS and HCQ)
      or
    - adding biologic (anti-TNF typically 1st line unless contraindication)
    - MTX/SAS/HCQ non-inferior to etanercept/MTX (*NEJM* 2013;369:307)
    - JAK inhib: if fail biologics vs. initial DMARD (*NEJM* 2017;376:652; *Lancet* 2018;391:2503 & 2513)
- Given ↑ r/o early CV morbidity/mortality, try to ↓ risk w/ lifestyle mgmt, lipid & DM screening

RA Therapeutics (*Arth Rheum* 2016;68:1)		

Class	Drug	Side Effects
Traditional DMARDs	Methotrexate (MTX) Leflunomide Sulfasalazine (SAS)	MTX: GI distress, stomatitis, ILD, myelosuppression, hepatotoxicity Supplement MTX ± SAS w/ folate ✔ *G6PD prior to SAS*
Biologic DMARDs (all anti-TNF ≈ efficacy; if inadequate resp to anti- TNF try non-TNF)	Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab CTLA4-Ig: abatacept Anti-IL-6R Ab: tocilizumab (studied as mono-Rx w/o MTX); sarilumab Anti-CD20: rituximab Anti-IL-1R: anakinra *Never use 2 biologics together*	↑ risk bacterial/fungal/viral infxn ✔ TB, Hep B/C before starting Immunize against Zoster + Pneumococcus Anti-TNF: ? risk for CHF & CNS demyelinating disease Anti-IL-6R: risk of GI perf. Rituximab: infusion reaction
Other	Hydroxychloroquine (HCQ) JAK inhib: tofacitinib (TF), baricitinib, others Rarely: cyclosporine, azathioprine, gold	HCQ: retinopathy, rash JAK inhib: infxn, ↑ Cr, ↑ LFTs, HTN CsA: nephrotox, HTN, gum hyperplasia

(*Lancet* 2013;381:451,918, & 1541; *NEJM* 2012;367:495 & 508, & 369:307; *JAMA* 2016;316:1172)

ADULT-ONSET STILL'S DISEASE & RELAPSING POLYCHONDRITIS

Adult-onset Still's disease (*J Rheumatol* 1992;19:424; *Autoimmun Rev* 2014;13:708)

- Rare autoinflammatory synd; ♂ = ♀ w/ typical onset 16–35 y; sx evolve over wks to mos
- Dx if 5 criteria are present & ≥2 major; exclude infxn, malig, other rheumatic, drug rxn
  - Major: fever ≥39°C for ≥1 wk (usually daily or twice daily high-spiking fever); arthralgias/arthritis ≥2 wk; Still's rash (qv); ↑ WBC w/ 80% PMN
  - Minor: sore throat; LAN; HSM; ↑ AST/ALT/LDH; negative ANA & RF
- Still's rash (>85%): nonpruritic macular or maculopapular salmon-colored rash; usually trunk or extremities; may be precipitated by trauma (Koebner phenomenon), warm water
- Plain films: soft tissue swelling (*early*) → cartilage loss, erosions, carpal ankylosis (*late*)
- Treatment: NSAIDs; steroids; steroid-sparing (MTX, anakinra, anti-TNF, tocilizumab)
- Variable clinical course: 20% w/ long-term remission; 30% remit-relapse; ~50% chronic (esp. arthritis); ↑ risk of macrophage activation syndrome (life threatening)

Relapsing polychondritis (*Rheum Dis Clin NA* 2013;39:263)

- Inflammatory destruction of cartilaginous structures; onset usually age 40–60 y, ♂ = ♀
- Subacute onset of red, painful, and swollen cartilage; ultimately atrophic & deformed
- Common clinical features: bilateral auricular chondritis; nonerosive inflammatory arthritis; nasal chondritis; ocular inflammation; laryngeal or tracheal chondritis; cochlear and/or vestibular dysfxn
- 40% of cases a/w immunologic disorder (eg, RA, SLE, vasc., Sjögren's), cancer or MDS
- Clinical diagnosis based on exam with multiple sites of cartilaginous inflammation
- Labs: ↑ ESR & CRP, leukocytosis, eosinophilia, anemia of chronic inflammation
- Bx (not req for dx): proteoglycan depletion, perichondrial inflammation and replacement with granulation tissue and fibrosis; immunofluorescence with Ig and C3 deposits
- Screen for pulm (PFTs, CXR/CT, ± bronch) and cardiac (ECG, TTE) involvement
- Therapy guided by disease activity and severity: steroids 1st line; NSAIDs, dapsone for sx control of arthralgias and mild disease; MTX, AZA, or biologics for steroid-sparing; cyclophosphamide for organ-threatening disease

CRYSTAL DEPOSITION ARTHRITIDES

Comparison of Gout and Pseudogout		
	Gout (*NEJM* 2011;364:443)	Pseudogout (*Rheum* 2009;48:711)
Acute clinical	*S*udden onset painful *mono- articular* arthritis (classically podagra [MTP of great toe]) or bursitis; frequently nocturnal May be *polyarticular* in subseq flares Can mimic cellulitis (esp in foot)	Mono- or asymmetric oligoarthritis (esp knees, wrists and MCP joints); rare axial involvement (eg, crowned dens syndrome)
Chronic clinical	Solid crystal deposition (tophus) in joints (esp. toes, fingers, wrists, knees) & tissue (esp. olecranon bursa, pinna, Achilles)	"Pseudo-RA" w/ polyarticular arthritis w/ morning stiffness or "Pseudo-OA"
Assoc. conditions	Metabolic syndrome; CKD; CHF	3 H's: Hyperparathyroidism, Hypo-magnesemia, Hemochromatosis
Crystal	Monosodium urate (MSU)	Calcium pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, negatively birefringent (yellow)	Rhomboid-shaped, weakly positively birefringent (blue)
Radio- graphic findings	Early = nonspecific tissue swelling Late = tophus, joint erosions w/ overhanging edges "Double contour sign" on MSK US DECT: UrA vs Ca deposits	Chondrocalcinosis: linear densities within articular cartilage; often found in menisci, fibrocartilage of wrist, hands, symphysis pubis
Other	a/w uric acid stones; urate nephropathy	✔ Ca, Mg, Fe, ferritin, TIBC, UrA, PTH in young or severe cases

**Crystals should be intracellular; infection can coexist with acute attacks, ∴ always ✔ Gram stain & Cx*

GOUT

Definition & epidemiology (*Lancet* 2016;388:2039)

- Humans lack enzyme to metabolize urate (end-product of purine metabolism)
- MSU crystal deposition promotes inflammation in joints and peri-articular tissue;
- ♂ > ♀ (9:1); peak incidence 5th decade; most common cause of inflammatory arthritis in ♂ over 30 y; *rare* in premenopausal ♀ (estrogens promote renal urate excretion)

Etiologies (*Ann Rheum Dis* 2012;71:1448)

- UrA underexcretion (85–90%): meds (eg, diuretics); idiopathic; ↓ renal function; obesity
- Uric acid (UrA) overproduction (10–15%): ↑ meat, seafood, EtOH, psoriasis, idiopathic, myelo- and lymphoproliferative disease, chronic hemolytic anemia, cytotoxic drugs, rare inherited enzyme defic, genetic variants (*Lancet* 2008;372:1953)

Diagnosis

- ↑ UrA is not diagnostic: 25% of measurements nl during flare; ± ↑ WBC & ESR
- Arthrocentesis is gold standard: negatively birefringent needle-shaped MSU crystals
- 2015 ACR/EULAR Classification Criteria (*Ann Rheum Dis* 2015;74:1789) used 1° in research

Acute treatment (*Ann Rheum Dis* 2017;76:29)

- No superior option; start w/in 24 h of sx onset; continue until acute flare resolves; for severe cases, consider combination therapy; rest and ice; w/o treatment self-limited in 3–10 d
- Continue urate-lowering therapy during attack if already taking

Acute Treatment for Gout		
Drug	Initial Dose	Comments
NSAIDs (nonselect or COX-2)	Full anti-inflammatory dose → tapering	Gastritis & GIB; avoid in CKD & CVD ≈ efficacy among NSAIDs never compared with colchicine
Colchicine (PO; IV no longer available in U.S.)	1.2 mg then 0.6 mg 1 h later → 0.6 mg bid	N/V, diarrhea (↑ w/ ↑ dose); ↓ dose in renal insufficiency (however, not nephrotoxic) a/w BM supp., myopathy, neuropathy
Corticosteroids (PO, IA, IV, IM) *or* Corticotropin	eg, prednisone ~0.5 mg/kg/d × 5–10 d ± taper	Rule out joint infection 1st Comparable to NSAID as 1st-line treatment Corticosteroid injection if <3 joints
IL-1 inhibitors (*Curr Opin Rheumatol* 2015;27:156)	anakinra (100 mg SC qd × 3 d) canakinumab (150 mg SC × 1)	↑↑ cost; anakinra a/w injection site pain (*Arthritis Res Ther* 2007;9:R28) Canakinumab approved in EU (*Ann Rheum Dis* 2012;71:1839; *Arth Rheum* 2010;62:3064)

Chronic treatment (*Ann Rheum Dis* 2017;76:29)

- Approach: if ≥2 attacks/y, polyarticular attack, tophus, joint erosions, GFR <60, or urolithiasis → start urate-lowering therapy + pharmacologic ppx to ↓ risk of acute attacks
- Urate-lowering therapy (ULT): goal UrA <6 mg/dL or < 5 mg/dl if tophi; when starting ULT, always give with pharm ppx as below; *do NOT d/c during acute attack or due to AKI*
- Pharmacologic prophylaxis: continue 6 mo w/ above Rx or longer if frequent attacks: low-dose colchicine (~50% ↓ risk of acute flare; *J Rheum* 2004;31:2429), NSAIDs (less evidence; *Ann Rheum Dis* 2006;65:1312), low-dose steroids, IL-1 inhibitors (see above)
- Lifestyle Δs (*Rheum Dis Clin NA* 2014;40:581): ↓ intake of meat, EtOH & seafood, ↑ low-fat dairy products, wt loss, avoid dehydration

Urate-Lowering Therapy (Chronic Treatment for Gout)		
Drug (route)	Mechanism	Comments
Allopurinol (PO)	Xanthine oxidase inhibitor	1st line; adjust starting dose in CKD; titrate ↑ q2–5wk; a/w rash, hypersensitivity syndrome (see below), BM suppression (avoid w/ AZA/6-MP), diarrhea, N/V, hepatitis; monitor CBC, LFT's; *not nephrotoxic* max dose = 800 mg/d
Febuxostat (PO)	Nonpurine xanthine oxidase inhib	2nd line; use if allopurinol intolerant; a/w LFT, rash, arthralgias, N/V; avoid w/ AZA/6-MP (BM suppress); start 40 mg, max dose = 120 mg/d
Pegloticase (IV)	Recombinant uricase	For refractory tophaceous gout; infusion reactions (including anaphylaxis); Ab formation may limit use (*JAMA* 2011;306:711);

		avoid w/ G6PD deficiency
Probenecid (PO)	Uricosuric	Rarely used; risk of urolithiasis

- Allopurinol hypersensitivity syndrome: 10–25% mortality; ↓ risk by *starting* w/ dose 100 mg/d if eGFR >40 or 50 mg/d if eGFR ≤40; titrate up by 100 mg/d (if eGFR >40) or 50 mg/d (if eGFR ≤40) q2–5wk until UrA <6 mg/dL (dose can be >300 mg/d even in CKD). *Associated with HLA-B5801*, esp. Han Chinese, Koreans, Thai; screen in these high-risk populations prior to initiating allopurinol (*Curr Opin Rheumatol* 2014;26:16).

CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE/PSEUDOGOUT

Definition

- Deposition of CPPD crystals w/in tendons, ligaments, articular capsules, synovium, cartilage; frequently asymptomatic

Etiologies (*Rheumatology* 2012;51:2070)

- Most cases *idiopathic*; consider further metabolic eval in young (<50 y) and florid forms
- Metabolic (*3 H's*): hemochromatosis; hyperparathyroidism; hypomagnesemia (esp. in Gitelman's or Bartter's syndromes)
- Joint trauma (incl. previous surgery); intra-articular hyaluronate can precipitate attacks
- Familial chondrocalcinosis (autosomal dominant disorder); early-onset, polyarticular dis.

Clinical manifestations (*Rheum Dis Clin NA* 2014;40:207)

- Chondrocalcinosis: calcification of cartilage, resulting from CPPD deposition in articular cartilage, fibrocartilage or menisci
  ↑ incidence w/ age; 20% >60 y have knee chondrocalcinosis in autopsy studies
- Pseudogout: acute CPPD crystal-induced mono- or asymmetric oligoarticular arthritis, *indistinguishable from gout except through synovial fluid exam for crystals*
  location: knees, wrists and MCP joints
  precipitants: surgery, trauma, or severe illness
- Chronic forms: "pseudo-RA" and pyrophosphate arthropathy (may involve axial skeleton, resembles OA)

Diagnostic studies

- Arthrocentesis is gold standard: rhomboid shaped, weakly *positively* birefringent crystals (yellow *perpendicular* & blue *parallel* to axis on polarizer; see table above)
- Radiographs: see table above

Treatment (*NEJM* 2016;374:2575)

- Asymptomatic chondrocalcinosis requires no treatment
- Acute therapy for pseudogout: no RCTs, extrapolated from practice in gout; ∴ same as for gout, though colchicine not as effective
- If associated metabolic disease, Rx of underlying disorder *may* improve arthritis sx
- Low-dose daily colchicine or NSAID may be effective for prophylaxis or chronic arthropathy

SERONEGATIVE SPONDYLOARTHRITIS

Definition and classification system (*NEJM* 2016;374:2563)

- Spondyloarthritis (SpA): group of inflammatory disorders that share common clinical manifestations: inflammatory spine disease, peripheral arthritis, enthesitis (see below), and extra-articular manifestations (primarily ocular and skin disease)
- Seronegative = absence of autoantibodies
- Subtypes: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), IBD-associated arthritis, juvenille SpA and undifferentiated

Epidemiology & pathogenesis (*Nat Rev Rheumatol* 2015;11:110)

- Prevalence 0.5–2% worldwide; AS and non-radiographic axial SpA most common
- HLA-B27 accounts for ~30% of attributable genetic risk but not required for diagnosis
- Environmental factors likely critical for disease, esp reactive arthritis (ie, infection)

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features		
Disease	Epidemiology	Key Features
AS	♂:♀ = 3:1; onset in teens to mid- 20s (rare after 40 y)	Progressive limitation of spinal motion, "bamboo spine," ⊕ Schober test
Psoriatic arthritis	♂ = ♀; peak incidence 45–54 y; seen in 20–30% of Pts w/ psoriasis	In 13–17% arthritis precedes skin findings by yrs; does not correlate with psoriasis activity; a/w HIV
Reactive arthritis	♂ >> ♀; 20–40 y; 10–30 d after GI or GU infxn* in genetically susceptible host	Previously "Reiter's syndrome": arthritis, urethritis, and conjunctivitis. Most resolve w/in 12 mo.
IBD- associated arthritis	♂ = ♀; seen in 20% of IBD Pts; Crohn's > UC	Type I <5 joints: correlates w/ IBD activ. Type II >5 joints or axial disease: does not correlate w/ IBD activity

*GU: Chlamydia, Ureaplasma urealyticum; GI: Shigella, Salmonella, Yersinia, Campylobacter, C. diff.

Major clinical manifestations (*Lancet* 2017;390:73)

- Inflammatory back pain: SI joints (sacroiliitis), apophyseal joints of spine
  characterized by IPAIN (Insidious onset, Pain at night, Age of onset <40 y, Improves w/ exercise/hot water, No improvement w/ rest), a.m. stiffness, *responsive to NSAIDs*
- Peripheral arthritis: typically asymmetric, oligoarticular, large joints, lower > upper limbs; however, can be symmetric & polyarticular (thus, mimic RA), espec. in psoriatic arthritis
- Enthesitis: inflammation at site of tendon/ligament insertion into bone, esp Achilles, plantar fascia (calcaneal insertion), pre-patellar, elbow epicondyles
- Rigidity of spine: bamboo spine by X-ray, ankylosis due to progressive growth of bony spurs that bridge intervertebral disc
- Dactylitis: "sausage digit," inflammation of entire digit (joint + tenosynovial inflamm)

- Uveitis: anterior uveitis *most common extra-articular manifestation* in seronegative SpA*;* usually unilateral and p/w pain, red eye, blurry vision, photophobia
- Subtypes also distinguished by *axial* vs *peripheral* predominant involvement

Distinguishing Features				
	Axial Predom	**Peripheral Predominant**		
Feature	**Ankylosing Spondylitis**	**Psoriatic**	**Reactive**	**IBD Assoc**
Axial involv.	100%	20–40%	40–60%	5–20%
Sacroiliitis	Symmetric	Asymm	Asymm	Symmetric
Periph involv.	Less common ~50%	Frequent	Frequent	Frequent
Peripheral distribution	Lower > upper	Upper > lower (see below)	Lower > upper	Lower > upper
HLA-B27	80–90%	20%	50–80%	5–30%
Enthesitis	Frequent	Frequent	Frequent	Rare
Dactylitis	Uncommon	Common	Common	Uncommon
Ocular	Uveitis in 25–40%	Conjuncti-vitis, uveitis, episcleritis	**Conjunctivitis** (noninfectious), uveitis, keratitis	Uveitis
Skin	None	**Psoriasis;** nail pitting and onycholysis	Circinate balanitis, keratoderma blennorrhagica	*E. nodosum*, pyoderma-gangrenosum
Imaging	Bamboo spine (symm syndes.)	"Pencil-in-cup" DIP deformity	*Asymmetric* syndesmophytes	Periph dis. rarely erosive

Clinical assessment (*Nat Rev Rheumatol* 2012;8:253)

- Seronegative: notable for *absence* of rheumatoid factor or autoantibodies; ± ↑ESR/CRP
- HLA-B27: nonspecific, b/c common in general population (6–8%); most useful when high clinical suspicion but nl imaging; ⊕ 90% of Pts w/ AS, but only 20–80% in other SpA
- Axial disease physical exam

  The following are not specific PEx findings but useful in monitoring disease during Rx:

  Lumbar flexion deformity assessed by modified Schober's test (⊕ if <5 cm ↑ in distance between a point 5 cm below the lumbosacral jxn and another point 10 cm above, when going from standing to maximum forward flexion)

  T-spine mobility (extension) and kyphosis severity measured by occiput-to-wall distance (although occiput-to-wall distance also increased in osteoporotic kyphosis)
- Infectious evaluation for reactive arthritis (⊖ studies do not r/o)

  GU: U/A, PCR of urine and/or genital swab for *Chlamydia;* urethritis usually due to *Chlamydia* infxn preceding arthritis, but can also see sterile urethritis post dysentery

  GI: ✔ stool Cx, *C. diff* toxin. Consider HIV in workup for reactive or psoriatic

arthritis.

- Radiology
  MRI preferred for *early* detection of inflammation (sacroiliitis)
  Plain films detect late structural changes (SI erosions/sclerosis)
    Calcification of spinal ligaments w/ bridging symm syndesmophytes ("bamboo spine")
    Squaring and generalized demineralization of vertebral bodies ("shiny corners")

Descriptions of skin manifestations

- Psoriasis: erythematous plaques with sharply defined margins often w/ thick silvery scale
- Circinate balanitis: shallow, painless ulcers of glans penis and urethral meatus
- Keratoderma blennorrhagica: hyperkeratotic lesions on soles of feet, scrotum, palms, trunk, scalp
- Erythema nodosum: red tender nodules in subcutan. fat (panniculitis), typically on shins
  Ddx includes idiopathic, infxn, sarcoid, drug rxn, vasculitis, IBD, lymphoma
- Pyoderma gangrenosum: neutrophilic dermatosis → painful ulcers w/ violaceous border
  Ddx incl. idiopathic, IBD, RA, heme and solid malignancies, MGUS, MDS, polycyth. vera

Psoriatic arthritis subtypes (*NEJM* 2017;376:957; 2018;391:2273 & 2285)

- Monoarticular/oligoarticular (eg, large joint, DIP joint, dactylitic digit): most common initial manifestation
- Polyarthritis (small joints of the hands/feet, wrists, ankles, knees, elbows): indistinguishable from RA, but often asymmetric
- Arthritis mutilans: severe destructive arthritis with bone resorption, esp. hands
- Axial disease: unilateral/asymmetric sacroiliitis
- DIP-limited: good correlation with nail pitting and onycholysis

Treatment approach (*Ann Rheum Dis* 2012;71:319; *Arth Rheum* 2016;68:282)

- Untreated disease may lead to irreversible structural damage and associated ↓ function
- Early physiotherapy beneficial
- Tight control of inflammation improves joint outcomes in PsA (*Lancet* 2015;386:2489)
- NSAIDs: 1st line; rapidly ↓ stiffness and pain; prolonged, continuous administration may modify disease course but associated w/ GI and CV toxicity (*Cochrane Database Syst Rev* 2015;17:CD010952); may exacerbate IBD
- Intra-articular corticosteroids in mono- or oligoarthritis; limited role for systemic steroids, esp. for axial disease
- Conventional DMARDs (eg, MTX, SAS, leflunomide): no efficacy for axial disease or enthesitis; may have role in peripheral arthritis, uveitis, and extra-articular manifestations
- Anti-TNFs: effective for both axial and peripheral manifestations, improves function and may slow progression of structural changes (*Curr Rheumatol Rep* 2012;14:422); adalimumab or infliximab preferred if inflammatory eye disease
- Anti-IL17A (secukinumab, ixekizumab): for both axial and peripheral PsA & for ankylosing spondylitis (*NEJM* 2015;373:1329 & 2534; *Lancet* 2015;386:1137)

- Anti-IL12/23 (ustekinumab): for both axial and peripheral PsA (*Ann Rheum Dis* 2014;73:990)
- PDE-4 inhibitor (apremilast): peripheral arthritis in PsA (*Ann Rheum Dis* 2014;73:1020); associated with GI side effects and significant wt loss
- JAK inhibitor: for anti-TNF resistant peripheral PsA (*NEJM* 2017;377:1525)
- Psoriasis (skin) also responds to anti-TNF, anti-IL17A, anti-IL12/23, PDE-4 inhib, JAK inhib
- Other:
  Abx in reactive arthritis if evidence of active infxn; consider prolonged abx for refractory *Chlamydia* ReA (*Arthritis Rheum* 2010;62:1298)
  Involve ophthalmologist for any evidence of inflammatory eye disease (may benefit from steroid eye drops or intravitreal steroid injections)
  Treat underlying IBD when appropriate

INFECTIOUS ARTHRITIS & BURSITIS

ETIOLOGIES & DIAGNOSIS OF INFECTIOUS ARTHRITIS

Etiologies (*Curr Rheumatol Rep* 2013;15:332)

- Bacterial (nongonococcal): early diagnosis and treatment essential
- Gonococcal (*N. gonorrhea*): consider in sexually active young adults
- Viral: parvovirus, HCV, HBV, acute HIV, Chikungunya; mainly polyarticular, may mimic RA
- Mycobacterial: monoarticular or axial (Pott's disease)
- Fungal: *Candida* (esp. prosthetic joints), coccidiomycosis (valley fever), histoplasmosis
- Other: Lyme, *Mycoplasma*, *Salmonella* (2° to anti-TNF Rx), Brucellosis, *T. whipplei*

Diagnosis (*JAMA* 2007;297:1478)

- H&P w/ poor sensitivity and specificity for septic arthritis
- Arthrocentesis in acute onset inflammatory monoarthritis to r/o septic arthritis; if possible obtain fluid sample prior to starting antibiotics
- Do not tap through overlying infected area to prevent introducing infxn into joint space
- ✔ Fluid cell count w/ diff, Gram stain, bacterial culture, crystal analysis; WBC >50k w/ PMN predominance suspicious for bact. infxn; *crystals do not r/o septic arthritis!*

BACTERIAL (NONGONOCOCCAL) ARTHRITIS

Epidemiology & risk factors

- Immunocompromised host: DM, EtOH use, HIV, age >80, SLE, cancer, steroid use, etc.
- Damaged joints: RA, OA, gout, trauma, prior surgery/prosthetic, prior arthrocentesis (rare)
- Bacterial seeding: bacteremia especially secondary to IVDU or endocarditis; direct inoculation or spread from contiguous focus (eg, cellulitis, septic bursitis, osteo)

Clinical manifestations (*JAMA* 2007;297:1478; *Lancet* 2010;375:846)

- Acute onset monoarticular arthritis (>80%) w/ pain (Se 85%), swelling (Se 78%), warmth
- Location: knee (most common), hip, wrist, shoulder, ankle. In IVDU, tends to involve other areas including axial joints (eg, SI, symphysis pubis, sternoclavicular, manubrial joints).
- Constit. sx: fevers (Se 57%), rigors (Se 19%), sweats (Se 27%), malaise, myalgias, pain
- Infection can track from initial site to form fistulae, abscesses, or osteomyelitis
- *Septic bursitis must be differentiated from septic intra-articular effusion*

Additional diagnostic studies (*JAMA* 2007;297:1478)

- Synovial fluid: WBC usually >50k (Se 62%, Sp 92%) but can be <10k, >90% polys; Gram stain ⊕ in ~75% of *Staph*, ~50% of GNR; Cx ⊕ in >90%; synovial bx most sens.

- Leukocytosis (Se 90%, Sp 36%); elevated ESR/CRP (Se >90%)
- Blood cultures ⊕ in >50% of cases, ~80% when more than 1 joint involved
- X-rays of joints should be obtained but usually normal until after ~2 wk of infection when may see bony erosions, joint space narrowing, osteomyelitis, and periostitis
- CT & MRI useful esp. for suspected hip infection or epidural abscess

Treatment for native joints (*Curr Rheumatol Rep* 2013;15:332)

- Prompt empiric antibiotics guided by Gram stain after surgical drainage. If Gram stain ⊖, empiric Rx w/ vancomycin; add anti-pseudomonal agent if elderly, immunocompromised.

Common Microbes (by Gram stain)		Population	Initial Antibiotic Regimen (tailor based on Gram stain, cx, clinical course)
GPC	*S. aureus* (most common)	Normal joints Prosthetic joints Damaged joints	Vancomycin*
	S. epidermidis	Prosthetic joints Postprocedure	Vancomycin*
	Streptococci	Healthy adults Splenic dysfunction	PCN-G or ampicillin
GN	Diplococci: *N. gonorrhea*	Sexually active young adults	Ceftriaxone or cefotaxime
	Rods: *E. coli*, *Pseudomonas*, *Serratia*	IVDU, GI infection immunosupp, trauma elderly	Cefepime or piperacillin/tazobactam + antipseudomonal aminoglycoside in IVDU

* Can later Δ to antistaphylococcal penicillin or cefazolin based on sensitivities

- IV antibiotics × ≥2 wk followed by oral antibiotics; varies by clinical course & microbiology
- Joint must be drained, often serially; arthroscopic drainage for larger joints and as initial treatment but may also be accomplished by arthrocentesis. Serial synovial fluid analyses should demonstrate ↓ in WBC and sterility.
- 10–15% mortality (up to 50% w/ polyarticular); depends on virulence, time to Rx, host

Prosthetic joint infections (*Infect Dis Clin North Am* 2012;26:29; *CID* 2013;56:e1)

- ↑ risk in first 2 y s/p procedure; rate generally low (0.5–2.4%); risk factors include obesity, RA, immunocompromised state, steroids, & superficial surgical site infxn
- Staphylococci (coag negative & *S. aureus*) in >50%; polymicrobial in 10–20%
- Early (<3 mo s/p surgery) or delayed (3–24 mo) onset typically acquired during implantation; early w/ virulent organisms (eg, MRSA) and delayed w/ less virulent organisms (eg, *P. acnes*, coag negative *Staph*) & more indolent presentation
- Late (>24 mo) onset typically related to secondary hematogenous seeding
- Diagnosis requires arthrocentesis by orthopedics; ESR & CRP (CRP Se 73–91%, Sp 81–86%; *NEJM* 2009;361:787) can be helpful

- Treatment typically requires prolonged abx & 2-stage joint replacement (joint retention a/w ~40% failure rate; *CID* 2013;56:182) or life-long suppressive abx. *ID and orthopedics consultation required.*

DISSEMINATED GONOCOCCAL INFECTION (DGI)

Epidemiology (*Infect Dis Clin North Am* 2005;19:853)

- *N. gonorrhea;* most frequent type of infectious arthritis in sexually active young adults
- Normal host as well as Pts w/ deficiencies of terminal components of complement
- ♀:♂ = 4:1; ↑ incidence during menses, pregnancy, & postpartum period, SLE; ↑ incidence in homosexual males; rare after age 40 y

Clinical manifestations

- Preceded by mucosal infection (eg, cervix, urethra, anus, or pharynx) that is often asx
- Two distinct syndromes, although Pts can have both:
  Joint localized: purulent arthritis (40%), usually 1–2 joints (knees > wrists > ankles)
  DGI: triad of polyarthralgias, tenosynovitis, skin lesions
  1) *polyarthralgias*: migratory joint pain, can affect small or large joints
  2) *tenosynovitis*: pain/inflammation of tendon and its sheath in wrists, fingers, ankles, toes
  3) *skin lesions*: gunmetal gray pustules with erythematous base on extremities & trunk
- Rare complications: Fitz-Hugh-Curtis syndrome (perihepatitis), pericarditis, meningitis, myocarditis, osteomyelitis from direct extension of joint-localized infection

Additional diagnostic studies

- Synovial fluid: WBC >50k (but can be <10k), poly predominant
  Gram stain ⊕ in ~25%; culture ⊕ in up to 50% if done w/ Thayer-Martin media
- Blood culture: more likely ⊕ in DGI; rarely in joint localized disease
- Gram stain and culture of skin lesions occasionally ⊕
- Cervical, urethral, pharyngeal, rectal PCR or cx on Thayer-Martin media; ✔ *Chlamydia*

Treatment

- Ceftriaxone × 7–14 d w/ empiric azithromycin 1g x 1 dose for *Chlamydia* (fluoroquinolones no longer recommended due to resistance)
- Joint arthroscopy/lavage may be required for purulent arthritis; rarely >1 time

OLECRANON & PREPATELLAR BURSITIS

Epidemiology & risk factors (*Infect Dis North Am* 2005;19:991)

- >150 bursae in the body; 2 most commonly infected are olecranon and prepatellar
- Most commonly (esp. superficial bursae) due to direct trauma, percutaneous inoculation, or contiguous spread from adjacent infection (eg, cellulitis)
- Other risk factors: recurrent noninfectious inflammation (eg, gout, RA, CPPD), diabetes
- *S. aureus* (80%) most common, followed by streptococci

Diagnosis

- Physical exam: discrete bursal swelling, erythema, maximal tenderness at center of bursa with preserved joint range of motion
- Aspirate bursa if concern for infxn, ✔ cell count, Gram stain, bacterial cx, crystals
  WBC >20k w/ poly predominance suspicious for bacterial infection, but lower counts common (crystals do *not* rule out septic bursitis!)
- Assess for adjacent joint effusion, which can also be septic
- Do not tap through infected skin to avoid introducing infxn into bursa

Initial therapy

- Prompt empiric coverage for staphylococci and streptococci: PO abx acceptable for mild presentation; vancomycin if ill appearing; broaden spectrum based on risk factors
- Modify antibiotics based on Gram stain, culture results, & clinical course. Duration of Rx is 1–4 wks. Serial aspirations every 1–3 d until sterile or no reaccumulation of fluid.
- Surgery if unable to drain bursa through aspiration, evidence of foreign body or necrosis, recurrent/refractory bursitis w/ concern for infxn of adjacent structures

CONNECTIVE TISSUE DISEASES

Approx Prev of Autoantibodies in Rheumatic Diseases

Disease	ANA	dsDNA	Sm	Ro/La	Scl-70	RNA PIII	Centr	Jo-1	U1-RNP	RF
SLE	≥95	75	20	25	⊖	⊖	⊖	⊖	45	35
Sjögren's	≥95	rare	⊖	45	⊖	⊖	⊖	⊖	rare	>75
Diffuse SSc	>90	⊖	⊖	rare	40	20	rare	⊖	rare	30
Limited SSc	>90	⊖	⊖	rare	10	rare	60	⊖	rare	30
IM	75–95	⊖	⊖	⊖	rare	⊖	⊖	25	⊖	15
MCTD	≥95	⊖	⊖	rare	⊖	⊖	⊖	⊖	always	50
RA	40	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	70

Centr, centromere; IM, inflammatory myopathies; RF, rheumatoid factor; Sm, Smith; SSc, systemic sclerosis; (*Primer on the Rheumatic Diseases*, 12th ed., 2001; *Lancet* 2013;382:797)

- Only order auto-Ab testing if clinical suspicion for CTD, the presence of auto-Ab without characteristic clinical findings ≠ diagnosis, and auto-Ab do not define a particular CTD
- Overlap syndromes may be reflected by multiple autoantibodies

see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

SYSTEMIC SCLEROSIS AND SCLERODERMA DISORDERS

Definition & epidemiology (*Best Pract Res Clin Rheumatol* 2010;24:857)

- Scleroderma refers to the presence of tight, thickened skin
- Localized scleroderma: *morphea* (plaques of fibrotic skin), *linear* (fibrotic bands), "*en coup de saber*" (linear scleroderma on one side of scalp and forehead ≈ saber scar)
- Systemic sclerosis (SSc) = scleroderma + internal organ involvement
  SSc w/ *limited cutaneous disease:* formerly CREST syndrome (see below)
  SSc w/ *diffuse cutaneous disease:* often rapidly progressive disorder affecting skin
  SSc *sine scleroderma* (visceral disease without skin involvement, rare)
- Peak onset of SSc between ages 30–50; ♀ > ♂ (7:1); African American > white
- 1–2/100,000 annual incidence of systemic disease in the U.S.
- Pathogenesis: endothelial injury → ROS production → oxidative stress → perivascular inflammation → fibrosis. Cytokines, growth factors, genetics, environ. factors + antibodies (against PDGF receptor, endo. cells, fibroblasts) all contribute (*NEJM* 2009;360:1989).

ACR/EULAR SSc classification criteria (*Ann Rheum Dis* 2013;72:1747)

- Sufficient for dx: skin thickening of fingers of both hands extending proximal to MCPs
- Other items considered in criteria: Raynaud's, SSc-related auto-Ab, pulm hypertension (PHT) and/or ILD, abnormal nailfold capillaries, telangiectasia, fingertip lesions (ulcers, scars), skin thickening limited to fingers (not beyond MCPs)
- Rule out other causes of thickened skin: diabetes (scleredema), scleromyxedema, toxin, hypothyroidism, nephrogenic systemic fibrosis, eosinophilic fasciitis, amyloidosis, GVHD

Clinical Manifestations of Systemic Sclerosis (*Lancet* 2017;390:1685)		
Skin	Tightening and thickening of extremities, face, trunk (bx not req for dx) "Puffy" hands, carpal tunnel syndrome, sclerodactyly Nailfold capillary dilatation & dropout Immobile, pinched, "mouse-like" facies and "purse-string" mouth Calcinosis cutis (subcutaneous calcification), telangiectasias	
Arteries	Raynaud's phenomenon (80%); digital or visceral ischemia	
Renal	Scleroderma renal crisis (SRC) = accelerated development of HTN (*relative ↑ in BP as compared with Pt's baseline BP*), MAHA Urine sed. typically bland; "onion-skin" hypertrophy of capillaries Affects 5–10% of Pts, 66% w/in 1st yr (*Rheum* 2009;48:iii32); >15 mg/d prednisone and RNA Pol III Ab a/w ↑ risk of developing SRC Poor prognosis w/ 50% mortality	
GI (>80% of Pts)	GERD and erosive esophagitis Esophageal dysmotility → dysphagia, odynophagia, aspiration Gastric dysmotility → early satiety and gastric outlet obstruction Small intestinal dysmotility → malabsorption, bact overgrowth, bloating	
Musculoskel	Arthralgias/arthritis; myositis; joint contractures; tendon friction rubs	
Cardiac	Myocardial fibrosis; pericardial effusion; conduction abnormalities; CAD	
Pulmonary	Pulmonary fibrosis (typically develops w/in 4 y); pulmonary arterial hypertension (typically develops after many yrs); #1 cause of mortality	
Endocrine	Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism	
SSc Subgroup Comparison		
	Limited	Diffuse
General		Fatigue, weight loss
Skin	Thickening on extremities *distal* to elbows/knees and *face* only	Thickening of distal *and proximal* ext, face *and trunk*
Pulmonary	PAH (rapidly progressive) > fibrosis	Fibrosis > PAH
GI	Primary biliary cirrhosis	
Renal	SRC later in disease course	SRC earlier & more common
Cardiac		Restrictive cardiomyopathy
Other	CREST syndrome = Calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasias	Raynaud's
Antibodies	Centromere (10–40%)	Scl 70, RNA-Pol III (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

Diagnostic studies & monitoring (*Semin Arthritis Rheum* 2005;35:35)

- Autoantibodies: >95% Pts w/ auto-Ab; generally mutually exclusive
  - ⊕ anti-Scl-70 (anti-topoisomerase 1): a/w diffuse SSc; ↑ risk pulm fibrosis

⊕ anticentromere: a/w limited SSc; ↑ risk of severe digit ischemia and PHT
⊕ anti-RNA-Pol III: a/w diffuse SSc; ↑ risk renal crisis; a/w cancer
⊕ ANA (>90%), ⊕ RF (30%), ⊕ anti-U1-RNP a/w overlap syndrome
Other: anti-Th/To (a/w limited SSc), U3-RNP (a/w ILD), PmScl (polymyositis-SSc overlap)

- CXCL4 levels reported to help diagnose disease and be correlated w/ degree of lung & skin fibrosis and disease progression but awaits validation (*NEJM* 2014;370:433)
- At baseline: ✔ BUN/Cr & UA for proteinuria, PFTs (spirometry, lung volumes, D_LCO), high-res chest CT (if diffuse disease), TTE (RVSP for PHT), RHC if ↑ RVSP or suspect PHT
- Annual PFTs; TTE q1–2y
- Skin bx not routine, but helpful to assess other possible causes for skin thickening
- ↑ risk of malignancy (esp. lung cancer) compared to general population, ∴ must be vigilant
- Frequent (eg, daily) BP ✔ to monitor for HTN suggestive of scleroderma renal crisis

Treatment (*Arthritis Rheumatol* 2018;70:1820)

- *Minimize steroid exposure to reduce risk of renal crisis*
- *Pulmonary* fibrosis: MMF (*Lancet Respir Med* 2016;4:708) vs. cyclophosphamide (NEJM 2006;354:2655); MMF + perfinidone under evaluation (*Rheum Dis Clin NA* 2015;41:237)
  PAH: pulmonary vasodilators (see "Pulm Hypertension"), early Rx a/w better outcomes
- Renal crisis: ACEI (not ARB) for Rx, not prophylaxis (*Semin Arthritis Rheum* 2015;44:687)
- GI: PPI and/or H2-blockers for GERD; antibiotics for malabsorption
  hypomotility: metoclopramide or erythromycin; nonoperative Rx of pseudo-obstruction
- Cardiac: NSAIDs ± colchicine superior to steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, hydroxychloroquine, MTX
- Myositis: MTX, AZA, steroids
- Skin: PUVA for morphea. Pruritus: emollients, topical or oral steroids (↓ dose). Fibrosis: MTX or MMF ? efficacy (*Ann Rheum Dis* 2017;76:1207; *Int J Rheum Dis* 2017;20:481)
- Auto-HSCT promising for severe disease (*NEJM* 2018;378:35)

INFLAMMATORY MYOPATHIES

Definition & epidemiology (*JAMA* 2013;305:183; *NEJM* 2015;372:1734)

- All lead to skeletal muscle inflammation & weakness, variable extramuscular involvement
- Polymyositis (PM): idiopathic diffuse polymyopathy, onset typically 40s–50s; ♀ > ♂
- Dermatomyositis (DM): similar to PM; also occurs in childhood, but differentiated from other myopathies by skin manifestations; malignancy a/w PM (10%) and DM (24%)
- Necrotizing autoimmune myositis (NM): usually in adults; risk factors include statin exposure ⊕ anti-HMGCR), CTD, malignancy, and rarely viral infection
- Inclusion body myositis (IBM): onset after age 50; ♂ > ♀; often *misdiagnosed as PM*
- DDx: drug-induced toxic myopathy (statins, cocaine, steroids, colchicine); infxn (HIV, EBV, CMV); metabolic (hypothyroid, hypo-K, hypo-Ca); neuromuscular dis. (eg,

myasthenia gravis); glycogen storage disease; mitochondrial cytopathy; muscular dystrophy

Clinical manifestations (*NEJM* 2015;372:1734)

- Muscle weakness: gradual (wks → mos) except in NM, progressive and painless
  - DM/PM/NM: proximal and symmetric*;* difficulty climbing stairs, arising from chairs, brushing hair; fine motor skills (eg, buttoning) lost late
  - IBM may be *asymmetric and distal*
- Skin findings in dermatomyositis: may precede myositis by mos to yrs
  - *Gottron's papules*: seen in >80% of Pts & pathognomonic; violaceous, often scaly, areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli
  - *Heliotrope rash*: purplish discoloration over upper eyelids ± periorbital edema
  - *Poikiloderma*: red or purple rash w/ areas of hyper and hypopigmentation mostly on sun-exposed areas; upper back (shawl sign), neck & chest (V sign), and hips (Holster sign)
  - *Mechanic's hands*: cracking, fissuring radial side of digits and can include pigmentation along palmar crease; a/w antisynthetase syndrome; also seen in PM
- Pulmonary: acute alveolitis, interstitial lung disease; resp muscle weakness; aspiration
  - *Antisynthetase syndrome*: acute onset DM or PM w/ rapidly progressive ILD, fever, weight loss, Raynaud's, mechanic's hands, arthritis; most commonly anti-Jo-1 ⊕
- Cardiac: (33%): often asx; conduction abnl; myo/pericarditis; HF uncommon; ↑ CK-MB/Tn
- GI: dysphagia, aspiration
- Polyarthralgias or polyarthritis: usually early, nonerosive; small joints > large joints
- Raynaud's (30%, DM and overlap CTD) w/ dilatation & dropout of nail bed capillaries

Diagnostic studies

- ↑ CK (rarely >100,000 U/L, can be ↑↑↑ in NM), aldolase, SGOT, LDH; ± ↑ ESR & CRP
- Autoantibodies: ⊕ ANA (>75%) (*Curr Rheumatol Rep* 2013;15:335)
  - ⊕ anti-Jo-1 (25%): most common specific Ab; a/w antisynthetase syndrome
  - ⊕ anti-Mi-2 (DM > PM 15-20%) is a/w disease that responds well to steroids
  - ⊕ anti-SRP is a/w NM, poor Rx response; ⊕ anti-HMGCR in NM a/w statin exposure
- Consider EMG (↑ spontaneous activity, ↓ amplitude, polyphasic potentials w/ contraction) or MRI (muscle edema, inflammation, atrophy) for evaluation; may guide biopsy
- Pathology and muscle biopsy: all with interstitial mononuclear infiltrates, muscle fiber necrosis, degeneration & regeneration (required for definitive diagnosis)
  - PM: *T cell–mediated muscle injury;* endomysial inflam. surrounds non-necrotic fibers
  - DM: *immune complex deposition in blood vessels with complement* activation; perimysial, perivascular inflam (B & CD4 T cells), complement in vessels.
  - NM: *necrotic fibers w/ macrophages*
  - IBM: *T cell–mediated muscle injury, vacuole formation;* same as PM with eosinophilic inclusions and rimmed vacuoles (EM)

Treatment (PM & DM, no effective treatment for IBM) (*Autoimmun Rev* 2011;11:6)

- Steroids (prednisone 1 mg/kg); MTX or AZA early if mod/severe or taper fails (2–3 mo)
- For resistant (30–40%) or severe disease: AZA/MTX combo, IVIg (DM ± PM), rituximab (*Arthritis Rheum* 2013;65:314), MMF, cyclophosphamide (esp. if ILD or vasculitis)
- IVIg w/ pulse steroids acutely for life-threatening esophageal or resp muscle involvement
- ✔ for occult malignancy (esp. if DM); monitor respiratory muscle strength with spirometry
- NM: discontinue statin if taking; steroids + MTX or IVIG if needed (MUSCLE NERVE 2010;41:185)

Myositides, Myopathies, and Myalgias

Disease	Weakness	Pain	↑ CK	↑ ESR	Biopsy
DM/PM/NM	⊕	⊖	⊕	±	as above
IBM	⊕	⊖	⊕	⊖	as above
Hypothyroidism	⊕	±	⊕	⊖	mild necrosis inflam, atrophy
Steroid-induced	⊕	⊖	⊖	⊖	atrophy
PMR	⊖	⊕	⊖	⊕	normal
Fibromyalgia (*JAMA* 2014;311:1547)	⊖	⊕ (tender points)	⊖	⊖	normal

SJÖGREN'S SYNDROME (*NEJM* 2018;378:931)

Definition & epidemiology

- Chronic dysfxn of exocrine glands (eg, salivary/lacrimal) due to lymphoplasmacytic infiltration, extraglandular manifestations common in primary form
- Can be primary or secondary (a/w RA, scleroderma, SLE, PM, hypothyroidism, HIV)
- More prevalent in ♀ than ♂; typically presents between 40 & 60 y of age

Clinical manifestations

- Dry eyes (keratoconjunctivitis sicca): ↓ tear production; burning, scratchy sensation
- Dry mouth (xerostomia): difficulty speaking/swallowing, dental caries, xerotrachea, thrush
- Parotid gland enlargement: intermittent, painless, typically bilateral
- Vaginal dryness and dyspareunia
- Recurrent nonallergic rhinitis/sinusitis due to upper airway gland involvement
- Extraglandular manifestations: arthritis, interstitial nephritis (40%), type I RTA (20%), cutaneous vasculitis (25%), neuropathies (10%), PNS or CNS disease, ILD, PBC
- ↑ risk of lymphoproliferative disorders (~50× ↑ risk of lymphoma and WM in 1° Sjögren's)

Diagnostic studies

- Autoantibodies: ⊕ ANA (95%), ⊕ RF (75%)
  Primary Sjögren's: ⊕ anti-Ro (anti-SS-A, 56%) and/or ⊕ anti-La (anti-SS-B, 30%)

- Schirmer test: filter paper in palpebral fissures to assess tear production
- Rose-Bengal staining: dye that reveals devitalized epithelium of cornea/conjunctiva
- Ocular staining score: substitute for Rose-Bengal staining to determine degree of keratoconjunctivitis sicca using fluorescein and lissamine green
- Biopsy (minor salivary, labial, lacrimal, or parotid gland): lymphocytic infiltration

Classification criteria (≥4 points 96% Se & 95% Sp; *Arthritis Rheum* 2016;69:35)

- 3 points: ⊕ anti-Ro; labial saliv. gland bx w/ lymphocytic sialadenitis & score ≥1 foci/4mm^2
- 1 point: abnormal ocular staining score ≥5; Schirmer's test ≤5 mm/5 min; unstimulated salivary flow rate of ≤0.1 mL/min

Treatment (*Arth Res Ther* 2013;15:R172)

- Ocular: artificial tears, cyclosporine eyedrops, autologous tears
- Oral: sugar-free gum, lemon drops, saliva substitute, hydration, pilocarpine, cevimeline
- Systemic: depends on extraglandular manifest.; NSAIDs, steroids, DMARDs, rituximab

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Definition (*Best Pract Res Clin Rheumatol* 2012;26:61)

- Features of SLE, systemic sclerosis, and/or polymyositis that appear gradually over years and often evolve to a dominant phenotype of SLE or systemic sclerosis
- Different from undifferentiated CTD (UCTD): non-specific symptoms that fail to meet criteria for any CTD; 30% go on to develop CTD over 3–5 y (usually SLE)

Clinical & laboratory manifestations (variable clinical course)

- Raynaud's phenomenon typical presenting symptom (75–90%); see below
- Hand edema ("puffy hands"), sclerodactyly, RA-like arthritis w/o erosions, polyarthralgias
- Pulmonary involvement (85%) with pulmonary hypertension, fibrosis
- Pericarditis most frequent cardiovascular manifestation; GI: dysmotility (70%)
- Membranous & mesangial GN common (25%); low risk for renal HTN crisis or severe GN
- ⊕ ANA (>95%); ⊕ RF (50%); requires ⊕ anti-U1-RNP but *not* specific (seen in ~50% SLE)

Treatment: As per specific rheumatic diseases detailed above

RAYNAUD'S PHENOMENON

Clinical manifestations & diagnosis (*NEJM* 2016;375:556)

- Episodic, reversible digital ischemia, triggered by cold temp, or stress, classically: blanching (white, ischemia) → cyanosis (blue, hypoxia) → rubor (red, reperfusion); color Δ usually well demarcated; affects fingers, toes, ears, nose

Primary vs. Secondary Raynaud's Phenomenon		
	Primary (80–90%)	Secondary (10–20%)

Vessel wall	*Functionally* abnl	*Structurally* abnl
Etiologies	Idiopathic; however, can be exacerbated by comorbid conditions, including HTN, athero, CAD, DM	SSc, SLE, PM-DM, MCTD, Sjögren's, RA Arterial dis (athero, Buerger's), trauma Heme (cyro, Waldenström's, APLAS) Drugs (ergopeptides, estrogens, cocaine)
Epidem.	20–40 y; ♀ > ♂ (5:1)	>35 y
Clinical	Mild, *symm.* episodic attacks *No tissue injury*, PVD, or systemic sx*; spares thumb*	Severe, *asymm*. attacks; tissue ischemia & injury (eg, digital ulcers); can be assoc w/ systemic sx; may affect thumb or prox limbs
Auto Ab	CTD antibodies	Depends on etiology, CTD Ab often ⊕
Nailfold	Normal capillaroscopy	Dropout and enlarged or distorted loops

Treatment (*Curr Opin Rheumatol* 2011;23:555; *BMJ* 2012;344:e289)

- All: avoid cold, maintain warmth of digits & body; avoid cigarettes, sympathomimetics, caffeine & trauma; abx for infected ulceration
- Mild–mod: long-acting CCB, topical nitrates, SSRI, ARB, α-blockers, ASA/clopidogrel
- Severe: PDE inhibitors, anti-ET-1 receptor (if ulcers esp. w/ PHT), digital sympathectomy
- Digit-threatening: IV prostaglandins, digital sympathectomy, ± anticoagulation

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production

Epidemiology (*Lancet* 2014;384:1878)

- Prevalence 15–50/100,000; predominantly affects women 2nd to 4th decade
- ♀:♂ ratio = 8:1; African American:Caucasian ratio = 4:1
- Complex genetics; some HLA association; rarely C1q & C2 deficiency

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria		
Clinical Criteria	SLICC Classification Criteria*	Other Clinical Features
Constit (84%)		Fever, malaise, anorexia, ↓ wt
Cutaneous/Oral/ Ophthalmologic (81%)	1. Acute or subacute cutaneous changes 2. Chronic cutaneous changes 3. Oral or nasal ulcers 4. Nonscarring alopecia	Malar rash (spares nasolabial folds), discoid rash (papules w/ keratosis & plugging), bullous SLE, urticaria, TEN Photosens. (n/v, rash, fever) Vasculitis, panniculitis (lupus profundus) Raynaud's, nailfold cap Δs, Sicca syndrome Conjunctivitis, episcleritis
Musculoskeletal (85–95%)	5. Joint disease: synovitis or tenderness & morning stiffness involving ≥2 joints	Arthralgias and myalgias Avascular necrosis of bone
Cardiopulmonary (33%)	6. Serositis: pleuritis (37%) or pleural effusion, pericarditis (29%) or pericardial effusion	Pneumonitis, IPF, shrinking lung, PAH, DAH Myocarditis, CAD Libman-Sacks endocarditis
Renal (77%)	7. Proteinuria (>0.5 g/dL) or RBC casts	Nephrotic syndrome Lupus nephritis (qv)
Neurologic (54%)	8. Seizures or psychosis w/o other cause	Cognitive dysfxn, stroke, cranial or periph neuropathies, transverse myelitis, mononeuritis multiplex
GI (~30%)		Serositis (peritonitis, ascites) Vasculitis (bleeding, perf.) Hepatitis, pancreatitis
Hematologic	9. Hemolytic anemia 10. Leukopenia (<4000/mm^3) *or* lymphopenia (<1000/mm^3) 11. Thrombocytopenia (<100,000/mm^3)	Anemia of chronic disease Antiphospholipid synd (VTE w/ ⊕ ACL Ab, lupus anticoag, and/or B2GPI Ab) Splenomegaly, LAN
Immunologic	12. ⊕ ANA; 13. ⊕ anti-ds-DNA 14. ⊕ anti-Sm; 15. ⊕ APLA 16. ↓ Complement: C3, C4, CH50 17. ⊕ Direct Coombs' (w/o #9)	↑ ESR/CRP, ⊕ anti-Ro/La, ⊕ anti-RNP, ⊕ RF, ⊕ anti-CCP

*Expert opinion, not dx criteria for SLE: ≥4/17 SLICC criteria, including ≥1 clinical & ≥1 immunologic, *or* bx proven SLE

nephritis w/ ⊕ ANA or anti-ds-DNA (*Arth Rheum* 2012;64:2677)

Autoantibodies in SLE (*NEJM* 2008;358:929)			
Auto-Ab	**Frequency (approx)**	**Clinical Associations**	**Timeline**
ANA	95–99% if active disease 90% if in remission Homogeneous or speckled	Any or all of broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro **La**	15–35% ⊕ anti-Ro may be seen w/ ⊖ or low titer ANA	Sjögren's/SLE overlap Neonatal lupus; photosens.; subacute cutaneous lupus	
ds-DNA	70%; ~95% Sp; titers may parallel dis. activity, esp. renal	Lupus nephritis Vasculitis	Appears mos before or at dx, but may become ⊕ after dx
Sm	30%; very specific for SLE	Lupus nephritis	
U1-RNP	40%	MCTD; Raynaud's Tend *not* to have nephritis	
Histone	90% in DLE; 60–80% in SLE	Mild arthritis and serositis	At diagnosis

Workup

- Autoantibodies: ANA, if ⊕ → ✔ anti-ds-DNA, anti-Sm, anti-Ro, anti-La, anti-U1-RNP
- CBC, APLA (⊕ in 20–40%; ACL, B2GP1, lupus anticoagulant), total complement, C3 & C4
- Lytes, BUN, Cr, U/A, urine sed, spot microalb:Cr ratio or 24-h urine for CrCl and protein
- If ↓ GFR, active sediment, hematuria, or proteinuria (>0.5 g/dL) → renal bx to guide Rx

Treatment of SLE (*Curr Rheumatol Rep* 2011;13:308; *Arthritis Care Res* 2015;67:1237)		
Drug	Indication	Adverse Effects
Hydroxychloroquine (HCQ)	All Pts b/c ↓ flares (*NEJM* 1991;324:150); monoRx for arthritis, serositis, skin disease	Retinal damage (<1%) Stevens-Johnson; myopathy *Not immunosuppressive*
NSAIDs	Arthritis, myalgias, serositis	Gastritis, UGIB, renal failure
Corticosteroids	Low dose (10–15 mg) for arthritis, serositis; high-dose (1 mg/kg) ± pulse (1 g × 3 d) for major dis (eg, renal, CNS, heme)	Adrenal suppression, DM, cataracts, osteopenia, avascular necrosis of bone, myopathy
Mycophenolate (MMF)	Nephritis (induction/maint) Nonrenal refractory to HCQ	Cytopenias, ↑ LFTs, diarrhea, teratogen
Cyclophosphamide (CYC)	Nephritis CNS disease (induction, minimize exposure)	Cytopenias, infertility, teratogen, myeloproliferative disorders, hemorrhagic cystitis, bladder cancer
Azathioprine (AZA)	Nephritis (maintenance) Non-renal disease refractory to HCQ	Myelosuppression (✔TPMT), hepatotoxicity, teratogen lymphoproliferative disorders
Methotrexate (MTX)	Arthritis (preferred over MMF/AZA) Skin disease & serositis	Myelosuppression, alopecia, hepatotoxicity, stomatitis, pneumonitis, teratogen

Cyclosporine (CsA)	Renal disease	Hyperplastic gums, HTN hirsutism, CKD, anemia
Belimumab (*NEJM* 2013;368:1528)	Arthritis, serositis, skin disease (esp. if ⊕ ds-DNA or ↓ C3/C4)	B-cell depletion (< RTX, different mechanism)
Rituximab (RTX)	Refractory SLE, ITP, AIHA	Infusion reaction; serum sickness; PML
Baricitinib (*Lancet* 2018;392:222)	Prelim data: 4 mg w/ efficacy in arthritis, skin disease	Infections (zoster), ↑ LFTs, cytopenias, dyslipidemia

Lupus Nephritis (*Arthritis Care Res* 2012;64:797)		
Class	Presentation	Treatment (all benefit from HCQ)
I: Min. mesangial	Normal U/A & creatinine	No specific treatment
II: Mesangial prolif	Micro hematuria/proteinuria	No specific treatment ± ACEI
III: Focal prolif	Hematuria/proteinuria, ± HTN, ↓ GFR, ± nephrotic	Induce: MMF *or* CYC + steroids Maintenance: ? MMF > AZA
IV: Diffuse prolif	Hematuria/proteinuria and HTN, ↓ GFR, ± nephrotic	
V: Membranous (can coexist with class III or IV)	Proteinuria, nephrotic	ACEI If nephrotic-range proteinuria, induce w/ MMF + steroids Maintenance: MMF superior to AZA
VI: Adv. sclerotic	ESRD	Renal replacement therapy

(*Ann Rheum Dis* 2010;69:2083; *NEJM* 2004;350:971 & 2005;353:2219 & 2011;365:1886)

Prognosis (*Arth Rheum* 2006;54:2550; *Rheum [Oxford]* 2016;55:252)

- 5-y survival rate >90%, 10-y survival rate >80%
- Leading causes of morbidity and mortality: infection, renal failure, neurologic and cardiovascular events; thrombotic complications (*Medicine* 2003;82:299)

Drug-induced lupus (DLE) (*Drug Saf* 2011;34:357; *Curr Opin Rheumatol* 2012;24:182)

- Many drugs: procainamide, hydralazine, penicillamine, minocycline, INH, methyldopa, quinidine, chlorpromazine, diltiazem, anti-TNF (esp. infliximab), interferons
- Abrupt onset; generally mild disease with arthritis, serositis, skin disease; renal dx, malar and discoid rash rare; prevalence ♀:♂ = 1:1
- ⊕ Anti-histone (95%) (may be ⊖ in anti-TNF); ⊖ anti-ds-DNA (often ⊕ in anti-TNF cases, even w/o manifestations of DLE) & ⊖ anti-Sm; normal complement levels
- Usually reversible w/in 4–6 wk after stopping medication

VASCULITIS

OVERVIEW

- Inflammation w/in blood vessel walls causing end-organ damage often a/w systemic sx; may be primary or secondary (eg, infection, malignancy) in etiology
- Classified by size of *predominant* vessel affected (*Arthritis Rheum* 2013;65:1); overlap of vessel size affected is common
- Clinical manifestations based on size of vessels involved; constitutional sx (low-grade fever, fatigue, weight loss, myalgias, anorexia) common to all

Distinguishing Characteristics of Vasculitis Subtypes

	Large Vessel		*Medium Vessel*	*Small Vessel*	
	TAK	**GCA**	**PAN**	**ANCA-Assoc.**	**IC**
Epidem	Young, ♀ > ♂	Elderly, ♀ > ♂	Middle-aged to older	Variable	Variable
Renal	Arteries	None	Microaneurysms	GN	GN
Pulm	Rare	None	Rare	Frequent	Cryo > HSP
Periph Neurop	No		Yes	Yes	Yes
GI	Uncommon		Yes	Yes	HSP > Cryo
Skin	Rare	None	Common	Common	Common
Granul.	Yes		No	Yes, except MPA	No
Other			Mesenteric aneurysms, testicular involv.	GPA: upper airway EGPA: asthma	HSP: IgA-dep Cryo: HCV

TAK, Takayasu's arteritis; GCA, giant cell arteritis; PAN, polyarteritis nodosa; ANCA-assoc. is GPA, EGPA, & MPA; IC, immune complex small-vessel vasculitis (eg, HSP, cryoglobulinemia); GN, glomerulonephritis.

LARGE-VESSEL VASCULITIS

Takayasu's arteritis ("pulseless disease")

- Arteritis of aorta and its branches → stenosis/aneurysm → claudication; onset <50 y
- Pattern of involvement: aorta and branches; most often subclavian and innominate arteries (>90%), as well as carotid, coronary, renal, pulmonary (~50%)
- Epidemiology: most common in Asia; ♀:♂ ~9:1; age <50 y
- Clinical manifestations and physical findings (*Circ* 2015;132:1701)
  Systemic inflamm with fever, arthralgias, wt loss

Vessel inflamm w/ pain & tenderness, ↓ & unequal pulses/BPs in extremities, bruits, limb claudication, renovascular HTN (>50%), neurogenic syncope; Ao aneurysm ± AI

"Burnt out" or fibrotic period (eg, vascular stenosis)

- Dx studies: ↑ ESR (75%), CRP; arteriography (MRA, CTA) → occlusion, stenosis, irregularity, and aneurysms; carotid U/S Doppler studies; PET-CT; pathology → focal panarteritis, cellular infiltrate with *granulomas* and giant cells (bx not required for dx)
- Rx: steroids ± MTX or AZA; anti-TNF (2nd line, *Autoimmun Rev* 2012;11:678); anti-IL-6 ? effective (*J Autoimmun* 2018;91:55); ASA; surgical/endovascular revasc (*Circ* 2008;69:70)
- Monitoring: MRA or PET-CT (*Arth Rheum* 2012;64:866); ESR/CRP (*Ann Rheum Dis* 2009;68:318)

Giant cell arteritis (GCA) (*JAMA* 2016;315:2442)

- Granulomatous arteritis of aorta/branches w/ predilection for temporal artery
- Pattern of involvement: extracranial branches of carotid artery, esp. temporal artery (thus also called temporal arteritis); aorta and/or its branches in 10–80%
- 90% of Pts w/ GCA are >60 y, peak incidence at 70–80 y, extremely rare <50 y; ♀:♂ = 3:1
- Clinical manifestations (*NEJM* 2014;371:50)

  Constitutional sx: fevers, fatigue, wt loss

  Temporal artery (TA) → headache, tender TAs and scalp, absent TA pulse

  Ophthalmic artery (20%) → optic neuropathy, diplopia, amaurosis fugax, blindness

  Facial arteries → jaw claudication

  Large vessel vasculitis → intermittent claudication of extremities; thoracic aorta aneurysm

  Strong association w/ PMR; ~50% of Pts w/ GCA ultimately received PMR diagnosis
- Dx studies: ↑ ESR (Se 84%, Sp 30%), ↑ CRP (Se 86%, Sp 30%), anemia

  temporal artery bx *whenever GCA suspected* (Se ≤85%); 1–2 cm ± bilat to ↑ yield (3–7% discordance) (*Ann Rheum Dis* 2009;68:318) → vasculitis & *granulomas*

  if suspect aortitis or lg-vessel involvement (BP Δ or bruits) → MRI/MRA or PET-CT
- Rx: steroids: *do not await bx/path results to begin!* Have at least 2 wk to bx w/o Δ results. Prednisone 40–60 mg/d w/ *slow* taper, ASA daily; consider IV steroid pulse if vision threatened. Adding tocilizumab helps achieve sustained remission (*NEJM* 2017;377:317).
- Polymyalgia rheumatica (*JAMA* 2016;315:2442; *Lancet* 2017;390:1700)

  Seen in 50% of GCA Pts; 15% of Pts w/ PMR develop GCA

  Age ≥50 y; ESR >40 mm/h (and/or ↑ CRP); *bilateral pain & morning stiffness* (>30 min), involving 2 of 3 areas: neck or torso, shoulders or prox. arms, hips or prox. thighs; nighttime pain; ± subdeltoid bursitis on U/S; exclude other causes of sx (eg, RA); nl CK

  Rx: pred 12.5–25 mg/d; if clinical improvement, initiate slow taper. If no improvement, ↑ dose. Consider MTX if at high risk for steroid side effects (*Ann Rheum Dis* 2015;74:1799).
- Follow clinical status & ESR/CRP (*Ann Rheum Dis* 2009;68:318); ~1/3 relapse over 2 y (*J Rheum* 2015;42:1213)

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa ("classic" PAN) (*Arth Rheum* 2010;62:616)

- Necrotizing nongranulomatous vasculitis of medium and small arteries (w/ muscular media) w/o glomerulonephritis or capillary involvement (ie, no DAH), not a/w ANCA
- Epidemiology: ♂ > ♀; average age of onset ~50 y; 1° vs. 2° (HBV > HCV; ~10%)
- Clinical manifestations
  - Constitutional sx (80%): wt loss, fever, fatigue
  - Neuro (79%): mononeuritis multiplex, peripheral neuropathies, stroke
  - Musculoskeletal (64%): extremity pain, myalgias, arthralgias, arthritis
  - Renal (51%): HTN, hematuria, proteinuria, renal failure, *glomerulonephritis unusual*
  - GI (38%): abd pain, GIB/infarction, cholecystitis; GU (25%): ovarian or testicular pain
  - Skin (50%): livedo reticularis, purpura, nodules, ulcers, Raynaud's
  - Ophthalmic (9%): retinal vasculitis, retinal exudates, conjunctivitis, uveitis
  - Cardiac (22%): coronary arteritis, cardiomyopathy, pericarditis
  - Pulmonary: rare; if lung involvement, suspect other vasculitis
- Dx studies: ↑ ESR/CRP, ANCA, HBV testing, ↓ C3/C4 if HBV-associated
  - Angiogram (mesenteric or renal vessels) → microaneurysms & focal vessel narrowing
  - CTA may be adequate to make dx, but conventional angiogram is most sensitive
  - Biopsy (sural nerve, skin, or affected organ) → vasculitis of small- and medium-vessel arteries with fibrinoid necrosis *without granulomas*
- Rx: based on severity; steroids ± DMARD (eg, MTX or CYC); antivirals if a/w HBV

ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS

Microvascular vasculitis (eg, capillaries, postcapillary venules, & arterioles)

Disease	Gran	Renal	Pulm	Asthma	ANCA Type[a]	ANCA ⊕
Granulomatosis with polyangiitis[b]	⊕	80%	90% (+ ENT)	—	anti-PR3 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic granulomatosis with polyangiitis[b]	⊕	45%	70%	⊕	anti-MPO (p-ANCA)	50%

[a]Predominant ANCA type; either p- or c-ANCA can be seen in all three diseases (*NEJM* 2012;367:214).

[b]GPA is formerly Wegener's granulomatosis and EGPA is formerly Churg-Strauss.

Differential diagnosis of ANCA (*Lancet* 2006;368:404)

- anti-PR3 (c-ANCA): GPA, EGPA, microscopic polyangiitis (rarely), levamisole (contaminant in cocaine) both c- & p-ANCA ⊕
- anti-MPO (p-ANCA): microscopic polyangiitis, EGPA, GPA, drug-induced vasculitis, nonvasculitic rheumatic dis., levamisole (contaminant in cocaine) both c- & p-ANCA ⊕
- Atypical ANCA patterns: drug-induced vasculitis, nonvasculitic rheumatic diseases, ulcerative colitis, primary sclerosing cholangitis, endocarditis, cystic fibrosis

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis)

- Necrotizing granulomatous systemic vasculitis frequently affecting nose, sinuses and/or upper respiratory tract in addition to kidneys, lungs, etc.
- Epidemiology: any age, but ↑ incidence in young and middle-aged adults; ♂=♀
- Clinical manifestations
  - Constitutional: fever, fatigue, malaise, anorexia, unexplained wt loss
  - Respiratory (90%): Upper: recurrent sinusitis, rhinitis, oral/nasal ulcers, nasal crusting, saddle-nose deformity, otitis, hearing loss, subglottic stenosis; Lower: pulm. infiltrates, nodules, pulm. hemorrhage, hemoptysis, pleurisy
  - Renal (80%): RPGN (pauci-immune), RBC casts, dysmorphic RBCs, hematuria
  - Ocular (50%): episcleritis, scleritis, uveitis, orbital granulomas → proptosis, corneal ulcer
  - Neurologic: cranial and peripheral neuropathies, mononeuritis multiplex
  - Skin (50%): palpable purpura, livedo reticularis
  - Hematologic: ↑ incidence DVT/PE (20×) when disease active (*Ann Intern Med* 2005;142:620)
- Dx studies: 90% ⊕ ANCA (80% PR3, 20% MPO), less Se in limited upper-airway disease
  - CXR or CT → nodules, infiltrates, cavities; sinus CT → sinusitis ± bone erosions
  - ↑ BUN & Cr, proteinuria, hematuria; sediment w/ RBC casts, dysmorphic RBCs
  - Biopsy → necrotizing granulomatous inflammation of arterioles, capillaries, veins
- Treatment: assess disease severity with BVAS/WG score (*Arth Rheum* 2001;44:912)
  - Mild disease (no end-organ dysfxn; BVAS 0-3): MTX + steroids (*Arth Rheum* 2012;64:3472)
  - Severe disease (end-organ damage incl. pulm hemorrhage, RPGN etc.; BVAS >3):
    - *Induction:* [RTX 375 MG/m^2/wk × 4 wk *or* CYC 2 mg/kg/d × 3–6 mo or pulse 15 mg/kg q2–3wk] + steroids 1 g IV × 3 d → 1–2 mg/kg/d (*NEJM* 2005;352:351, 2010;363:211, & 2013;369:417; *Annals* 2009;150:670; *Ann Rheum Dis* 2015;74:1178)
    - If RPGN: ± plasma exchange to ? ↓ risk of ESRD (*Am J Kidney Dis* 2011;57:566)
    - *Maintenance:* RTX q6mo superior to AZA or watchful waiting (*Arth Rheum* 2012;64:3760; *NEJM* 2014;371:1771)
  - Relapse: mild → steroids ± MTX or AZA; severe → reinduce w/ steroids + RTX or CYC
  - ↑ ANCA w/o clinical evidence of flare should *not* prompt Δ Rx (*Annals* 2007;147:611)

Microscopic polyangiitis (MPA) (*Rheum Dis Clin North Am* 2010;36:545)

- Similar to GPA, but w/o ENT/airway involvement & nongranulomatous
- Epidemiology: ♂ > ♀; avg onset 50–60 y
- Clinical manifestations: similar to GPA *w/o upper respiratory involvement;* Renal (80–100%): glomerulonephritis Pulmonary (25–50%): pulmonary capillary alveolitis, pulmonary fibrosis Constitutional and neuro sx similar to GPA; skin lesions (eg, palpable purpura) in 30–60%
- Dx studies: 70% ⊕ ANCA (almost all anti-MPO)
  - biopsy → necrotizing, nongranulomatous inflammation of small vessels, pauci-immune (minimal deposition of complement or Ig; contrast w/ HSP, cryoglobulinemia, etc.)
  - urine sediment and CXR findings similar to those seen in GPA

- Treatment: as for GPA; ↓ relapse rate compared to GPA

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)

- Similar to GPA w/ more frequent cardiac involvement, a/w asthma and eosinophilia
- Epidemiology: rare; can present at any age (typically 30–40 y); a/w HLA-DRB4
- Clinical manifestations (*Curr Rheumatol Rep* 2011;13:489)
  - Initial sx: asthma, sinusitis, allergic rhinitis (new asthma in adult raises suspicion)
  - Eosinophilic infiltrative disease: transient pulm infiltrates, gastroenteritis, or esophagitis
  - Systemic small-vessel vasculitis: neuropathy (mononeuritis multiplex), renal (glomerulonephritis), skin (palpable purpura, petechial, nodules)
  - Cardiac: coronary arteritis, myocarditis, CHF, valvular insufficiency (*Medicine* 2009;88:236)
- Dx studies: 50% ⊕ ANCA (MPO > PR3), eosinophilia (5–10 k/μL, 80–100%), biopsy → microgranulomas, fibrinoid necrosis, and thrombosis of small arteries and veins with eosinophilic infiltrates
- Treatment: high-dose steroids + CYC (if severe); anti-IL5 (mepolizumab) for refractory/relapsing (*NEJM* 2017;376:1921)

Renal-limited vasculitis

- Small vessel pauci-immune vasculitis causing RPGN w/o other organ involvement
- Dx studies: 80% ⊕ ANCA (MPO > PR3); biopsy with pauci-immune GN ± granulomas
- Treatment identical to that for GPA/MPA

IMMUNE COMPLEX (IC)–ASSOCIATED SMALL-VESSEL VASCULITIS

Henoch-Schönlein purpura (HSP)

- IgA-mediated vasculitis w/ predilection for skin, GI tract, and kidneys
- Epidemiology: ♂ > ♀, children > adults, onset in winter > summer
- May develop after upper respiratory tract infection (esp. *Strep*) or drug exposure
- Clinical manifestations
  - Palpable purpura on extensor surfaces (lower extremity first) & buttocks
  - Polyarthralgias (nondeforming) esp. involving hips, knees, & ankles
  - Colicky abdominal pain ± GIB or intussusception
  - Nephritis ranging from microscopic hematuria & proteinuria to ESRD
- Dx studies: skin bx w/ immunofluorescence → leukocytoclastic vasculitis w/ IgA and C3 deposition in vessel wall; renal bx → mesangial IgA deposition
- Treatment: often self-limiting over 4 wk; steroids ± DMARDs for renal or severe disease

Connective tissue disease–associated vasculitis

- Small-vessel vasculitis a/w RA, SLE or Sjögren's syndrome
- Clinical manifestations
  - Distal arteritis: digital ischemia, livedo reticularis, palpable purpura, cutaneous ulceration
  - Visceral arteritis: pericarditis and mesenteric ischemia
  - Peripheral neuropathy

- Dx studies: skin/sural nerve bx, EMG, angiography; ↓ C′ in SLE; ⊕ RF or anti-CCP in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs)

Cutaneous leukocytoclastic angiitis

- Most common type of vasculitis; heterogeneous group of clinical syndromes due to IC deposition in capillaries, venules, and arterioles; includes *hypersensitivity vasculitis*
- Etiologies
  - Drugs: PCN, ASA, amphetamines, levamisole, thiazides, chemicals, immunizations, etc.
  - Infections: *Strep*, *Staph*, endocarditis, TB, hepatitis
  - Malignancy (paraneoplastic)
- Clinical manifestations: abrupt onset of palpable purpura and transient arthralgias after exposure to the offending agent; visceral involvement rare but can be severe
- Dx studies: ↑ ESR, ↓ complement levels, eosinophilia; ✔ U/A; skin biopsy → leukocytoclastic vasculitis *w/o IgA deposition* in skin (to distinguish from HSP)*;* if etiology not clear, consider ANCA, cryoglobulins, hepatitis serologies, ANA, RF
- Treatment: withdrawal of offending agent ± rapid prednisone taper

Behçet's syndrome (*Curr Rheum Opin* 2010;12:429)

- Systemic vasculitis affecting all vessel sizes, a/w painful oral and/or genital ulcers
- Epidemiology: usually young adults (25–35 y); a/w HLA-B51 in areas of highest prevalence on the old Silk Road (Turkey, Middle East, and other Asian countries)
- Classification criteria (#1 + ≥2 others is 91% Se & 96% Sp; *Lancet* 1990;335:1078)
  1. Recurrent oral aphthous ulceration (≥3× in 1 y, usually 1st manifestation)
  2. Recurrent genital ulceration (labia in females, scrotum in males)
  3. Eye lesions: uveitis, scleritis, retinal vasculitis, optic neuritis; *may threaten vision*
  4. Skin lesions: pustules, papules, folliculitis, erythema nodosum (scarring)
  5. ⊕ pathergy test (prick forearm w/ sterile needle → pustule) (not sensitive in Caucasians)
- Other clinical manifestations: most recur but are not chronic
  - Arthritis: mild, ± symmetric, nondestructive, involving knees and ankles
  - Neurologic: usually involvement of midbrain parenchyma; peripheral neuropathy rare
  - Vascular: superficial or deep vein thrombosis (25%); arterial stenosis, occlusion, and aneurysm can also occur; low incidence of thromboembolism
- Dx studies: ↑ ESR/CRP; ulcer swab to r/o HSV; ulcer bx nonspecific; ophtho eval if sx
- Treatment (*Rheumatology* 2007;46:736; *Ann Rheum Dis* 2008;67:1656 & 2009;68:1528)
  - Mucocutaneous:
    - Mild: topical steroids, colchicine (esp. for erythema nodosum), dapsone, apremilast (PDE-4 inhib) for oral ulcers and ? genital ulcers (*NEJM* 2015;372:1510),
    - Severe: oral steroids, steroid-sparing agents
  - Arthritis: NSAIDs, colchicine, steroids, steroid-sparing agents
  - Ocular: topical and/or systemic steroids ± steroid-sparing agents
  - Steroid-sparing: AZA, anti-TNF, CYC (large vessel and CNS ds), CsA, MTX, IFNα-2A,

Venous thrombosis: steroids and anticoagulation (careful if aneurysm present)

IGG4-RELATED DISEASE

Definition & etiology (*NEJM* 2012;366:539; *Ann Rev Pathol* 2014;9:315)

- Characterized by tumor-like inflammatory lesions that can affect nearly any organ
- Etiology unclear: ? autoimmune; unclear role of IgG4 Ab; Pt may have h/o atopy

Clinical manifestations (*Lancet* 2015;385:1460; *Arth Rheum* 2015;67:2466)

- Commonly pancreatitis, aortitis, cholangitis, sialadenitis, thyroiditis, orbital myositis ± pseudotumor, retroperitoneal fibrosis
- Multiple lesions may be present synchronously or metachronously

Diagnosis (*Ann Rheum Dis* 2015;74:1 & 14)

- Biopsy w/ specific histopathology & immunohistochemistry findings: lymphoplasmacytic infiltrate w/ significant IgG4+ plasma cell infiltrate, fibrosis, obliterative phlebitis
- ↑ serum IgG4 (Se 90%, Sp 60%); *not specific* seen in GPA, bronchiectasis (*Ann Rheum Dis* 2014;74:14)

Treatment (*Arth Rheum* 2015;67:1688)

- Prednisone vs. rituximab (*Ann Rheum Dis* 2015;74:1171)

CRYOGLOBULINEMIA

Definition & types (*Lancet* 2012;379:348; *Oncology* 2013;37:1098)

- Cryoglobulins: proteins that precipitate from *serum or plasma* on exposure to cold and redissolve on rewarming, characterized by their composition; a/w chronic immune stimulation and/or lymphoproliferation
- Distinguish from *cryofibrinogenemia* = proteins (eg, fibrin, fibrinogen) that precipitate only from *plasma;* found in autoimmune dis, malignancies, infxns; unclear clinical significance

Types of Cryoglobulinemia

Feature	Type I (monoclonal)	Type II (mixed)	Type III (mixed)
Frequency	10–15%	50–60%	25–30%
Cryoglobulin composition	*Monoclonal* Ig (usually IgM or IgG)	*Monoclonal* IgM w/ RF activity + *polyclonal* IgG	*Polyclonal* IgG and IgM
Common etiologies	**Plasma cell dyscrasias**	**Infection, malignancy,** autoimmune syndromes	**Autoimmune synd.,** infxn
Primary manifestations	**Hyperviscosity** ± thrombosis → ischemia	**IC-mediated vasculitis,** w/ multiorgan involvement. Can be asx.	

Etiologies

- Hematologic diseases
  Type I: multiple myeloma, MGUS, Waldenström's, chronic lymphocytic leukemia
  Type II: B-cell lymphomas, solid-organ malignancies
- Infections (types II & III): viral (HCV [>80% RNA ⊕], HBV, HIV, HAV, EBV, CMV), bacterial (endocarditis, strep, etc.), fungal (coccidiomycosis, etc.), parasitic (malaria, amoebiasis)
- Autoimmune syndromes (type III > II): Sjögren's syndrome, SLE, RA, PAN
- Renal transplant recipients (*Clin Nephrol* 2008;69:239)
- Essential (idiopathic) in 10% of cases

Pathophysiology

- Type I: cryo precipitation in microcirculation → hyperviscosity & vascular occlusion
- Types II/III: defective/insufficient immune complex (IC) clearance → IC-mediated inflammation of blood vessels w/ complement activation → vasculitis

Clinical manifestations

- Most patients with circulating cryoglobulins are asx

- Type I: hyperviscosity (cold worsens sx) → H/A, visual disturbance, livedo, digital ischemia
- Type II/III: vasculitis (sx not affected by cold exposure)
  - "Meltzer's triad" (purpura, arthralgias, weakness) seen in 25–30% of Pts
  - General: weakness, low-grade fever
  - Dermatologic (54–80%): lower extremity purpura, livedo reticularis, leg ulcers
  - Joint (44–70%): symmetric, migratory arthralgias of small or medium joints
  - Renal (50%): glomerulonephritis (proteinuria, hematuria, ARF, HTN, edema)
  - Neurologic (17–60%): peripheral neuropathy (polyneuropathy > mononeuritis multiplex)
  - Hematologic: anemia, thrombocytopenia, ↑ risk of B-cell lymphoma
  - GI (5%): abdominal pain, hepatosplenomegaly, abnormal LFTs

Diagnostic studies

- ✔ Cryoglobulins; must keep blood *warmed to 37°C at all times* en route to lab; early cooling causes false ⊖ cryoglobulin, loss of RF and ↓↓ complement
- *Cryocrit* is quantification of cryoprotein, does not always correlate w/ disease activity
- False ↑ in WBC or plt on automated CBC, due to cryoprecipitation
- Type I: ✔ serum viscosity, symptomatic if ≥4.0 centipoise; complement levels normal
- Type II: ↓ C4 levels, variable C3 levels, ↑ ESR, ⊕ rheumatoid factor (RF)
  - ✔ HCV, HBV, & HIV serologies in all Pts w/ mixed cryoglobulinemia
  - Bx of affected tissue: hyaline thrombi; vasculitis w/ mixed inflammatory infiltrates of small vessels; leukocytoclastic vasculitis in purpuric lesions

Treatment (*Blood* 2012;119:5996; *Medicine* 2013;92:61)

- Treat underlying disorder:
  - Lymphoproliferative disease: chemotherapy and/or radiation
  - HCV: antivirals ± immunosuppression for severe disease (*NEJM* 2013;369:1035)
  - Connective tissue–related disease: DMARD/steroids ± rituximab
- Type I: plasma exchange if hyperviscosity; steroids, alkylating agents, rituximab, chemo
- Type II: NSAIDs for control of mild symptoms for Pts w/ normal renal function.
  - Rituximab or cyclophosphamide for major organ involvement. For mixed cryo, plasmapheresis or plasma exchange only in severe, life-threatening disease.

AMYLOIDOSIS

Deposition of misfolded and insoluble fibrous proteins in normal organs and tissues

Classification of Amyloidosis			
Type	**Precursor**	**Causative diseases**	**Main organs affected**
AL (Primary) Most common ~2000 cases/y	Monoclonal Ig light chain	MM Light chain disease ($\lambda > \kappa$) MGUS, WM	**Renal, cardiac, GI, neuro, cutaneous,** hepatic, pulmonary
AA (Secondary)	Serum amyloid A (SAA)	Inflam: RA, IBD, FMF Chronic infxns: osteo, TB	**Renal, GI, hepatic,** neuro, cutaneous
Hereditary ↑ incid Afr Am	Mutant TTR, etc.	*Mutant* proteins	**Neurologic, cardiac**
Senile	Normal TTR	*Normal* proteins; 2° aging	**Cardiac**, aorta, GI
Aβ_2M	β_2-microglobulin	Dialysis-associated β_2m (normally renally excreted)	Musculoskeletal
Localized	β-amyloid protein Peptide hormones	Localized production and processing	Neurologic Endocrine

TTR, transthyretin (prealbumin). Adapted from *NEJM* 1997;337:898; 2003;349:583; & 2007;356:2361.

Clinical Manifestations of Amyloidosis (*Lancet* 2016;387:2641)		
System	Manifestations	Amyloid
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	CMP (either restrictive or dilated); orthostatic hypoTN ↓ QRS amplitude, conduction abnormalities, AF	AL, hereditary, senile
GI	Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction Macroglossia → dysphonia and dysphagia	All systemic
Neurologic	Peripheral neuropathy with painful paresthesias Autonomic neuro → impotence, dysmotility, ↓ BP Carpal tunnel syndrome	Hereditary, AL, organ-specific, Aβ_2M
Cutaneous	Waxy, nonpruritic papules; periorbital ecchymoses "Pinch purpura" = skin bleeds with minimal trauma	AL
Hepatic & splenic	Hepatomegaly, usually *without* dysfunction Splenomegaly, usually *without* leukopenia or anemia	All systemic
Endocrine	Deposition with rare hormonal insufficiency	Organ-specific
Musculoskel	Arthralgias and arthritis (especially shoulder)	AL, Aβ_2M
Pulmonary	Airway obstruction; pleural effusions	AL, AA
Hematologic	Factor X deficiency	AL

Diagnostic studies

- Biopsy (abdominal SC fat pad, rectal, or affected tissue) → apple-green birefringence on Congo red stain; fat pad bx Se 60–85%, Sp 90–100%
- If suspect AL → ✔ SIEP & UIEP (↑ Se vs. SPEP & UPEP) & free light chains, ± BM bx
- If suspect renal involvement ✔ U/A for proteinuria
- If suspect cardiac involvement ✔ ECG (↓ voltage, conduction abnl), TTE (biventricular valve leaflet & interatrial septum thickening), ↑ wall w/o ↑ volt has 75% Se, 95% Sp; MRI
- Genetic testing for hereditary forms

Treatment of Amyloidosis	
AL	Limited involvement: high-dose melphalan → auto HSCT (*NEJM* 2007;357:1083) Not HSCT candidate: [low-dose melphalan + dexamethasone] or [cyclophosphamide + bortezomib + dexamethasone] (*Blood* 2015;126:612) Relapsed: lenalidomide, thalidomide, or bortezomib (*Blood* 2010;116:1990 & 2014;124:2498)
AA	Rx underlying disease. Colchicine for FMF, esp. to prevent renal disease. ? Anti-cytokine Rx (anakinra or tocilizumab) (*Clin Exp Rheumatol* 2015;33:46)
ATTR	Liver Tx prevents further protein deposition (*Muscle Nerve* 2013;47:157) ↓ hepatic TTR production: siRNA (patisiran) or anti-sense oligo (inotersen) improve neuropathy (*NEJM* 2018;379:11 & 22) Stabilize TTR tetramers (also useful for senile amyloidosis): tafamidis ↑ QoL & ↓ CV hosp & mortality (*NEJM* 2018;379:1007)

- Clearance of amyloid by Ab against serum amyloid P under study (*NEJM* 2015;373:1106)
- Cardiac involvement: diuretics; avoid dig, CCB, and vasodilators; ? ICD for 1° prevention
- Heart, kidney, and liver Tx may be considered in those w/ advanced disease
- Median survival: 12–18 mo for AL (~6 if cardiac); 11 y for AA; variable for others

CHANGE IN MENTAL STATUS

Consciousness/Arousal (description of patient & timing is most helpful)

- Arousal: spectrum from awake/alert → drowsy → stupor → coma. Terms vague & subjective, so most useful to describe response to increasing stimulation (eg, voice → noxious).
- Coma: lack of response to external stimuli. Degree formalized in Glasgow Coma Scale. Caused by focal lesions in brainstem (reticular activating system), thalamus, or diffuse dysfxn of both cerebral hemispheres. Mimics: locked-in synd., akinetic mutism, catatonia.
- Delirium/acute confusional state: altered attention & awareness, develops over hrs to days, often fluctuating, accompanied by cognitive Δs (eg, disorientation, memory loss, perceptual Δs); sometimes w/ sleep–wake dysregulation, autonomic Δs, emotionality
- Dementia: progressive cognitive impairment developing over mos to yrs; often affects memory, language, visuospatial and executive function; attention often spared

Etiologies of Decreased Responsiveness	
1° Neurologic (*usually with focal signs*)	Systemic *(esp. in elderly or prior CNS injury)*
Vasc: ischemic stroke/TIA, ICH, VST, PRES, vasculitis, pituitary apoplexy Seizure: postictal, status, nonconvulsive Infxn: meningitis, encephalitis, abscess Trauma: TBI, concussion, diffuse axonal injury ↑ intracranial pressure: mass, edema, hydrocephalus, herniation Autoimmune/paraneoplastic enceph. Neurodeg: late-stage (eg, Alzheimer's) or rapidly progressive (eg, CJD)	Cardiac: global ischemia, HoTN, HTN enceph Pulmonary: ↓ PaO2, ↑ PaCO2 GI: liver failure, ↑ NH3 Renal: uremia, dialysis, ↓ or ↑ Na, ↓ or ↑ Ca Heme: TTP/HUS, DIC, hyperviscosity Endo: ↓ glc, DKA/HHNS, hypothyr., Addisonian ID: pneumonia, UTI, endocarditis, sepsis Hypothermia & hyperthermia Meds: anticholin., anti-hist., psychotrop., digoxin Toxins/withdrawal: EtOH, sedative, opiate, CO Psychiatric: catatonia, serotonin synd., NMS

Initial evaluation

- History (witness & background *crucial*): tempo, premorbid sx (eg, focal neuro deficits, HA, infxn, pain, falls), medical conditions (eg, dementia, epilepsy, onc, cardiac, psych, infection/immune status), accompanied by head trauma, current meds (eg, sedatives, opioids, anticoag, anticonvulsants, immunosuppressants), drug/alcohol use
- General exam: *VS*, breathing pattern (eg, Cheyne-Stokes), tongue bite (seizure), *nuchal rigidity* (meningitis, SAH; *do not test* if c/f trauma/cervical spine fx), ecchymoses, rash, signs of head trauma (eg, Battle sign, raccoon eyes, hemotympanum, CSF rhinorrhea), asterixis, liver disease stigmata, embolic phenomena/endocarditis, s/s drug use
- Neuro exam (see below): perform off sedatives/paralytics if possible, look for focal deficits suggesting structural cause (eg, stroke, herniation), s/s of ↑ ICP (eg, HA, vomiting, papilledema, abducens nerve palsy, unilateral dilated pupil, ↑ BP/↓ HR, fixed downgaze)

Neuro Exam in Patients with Decreased Responsiveness	
Mental status	Arousal (behavioral response to ↑ intensity of stimulation, GCS)
Cranial nerves	Pupils: *pinpoint* → opiates, pontine lesion; *midposition & fixed* → midbrain lesion; *fixed & dilated* → severe anoxic injury, herniation, anti-cholin. Extraocular movements / vestibulo-ocular reflex tests: Oculocephalic maneuver ("doll's eyes"): nl = eyes move opposite head movement (do not test if possible cervical spine trauma) Vestibular (cold) caloric stimulation: in coma, nl = eyes move slowly to lavaged ear, then quickly away (*do not test w tymp memb perf)* Corneal reflex, facial grimace to nasal tickle Gag & cough reflexes (with ET tube manipulation if necessary)
Motor	Tone, spont movements, flexor/extensor posturing of arms/legs, strength
Sensory	Response to painful stimuli: purposeful vs. reflexive/posturing
Reflexes	Deep tendon reflexes, Babinski, "triple" flexion (ankle, knee, & hip flexion to noxious stimulation → not suggestive of intact cortical function)

Glasgow Coma Scale (sum points from each of 3 categories to calculate score)			
Eye Opening	**Best Verbal Response**	**Best Motor Response**	**Points**
		Follows commands	6
	Oriented	Localizes pain	5
Spontaneous	Confused	Withdraws from pain	4
To voice	Inappropriate words	Flexor posturing	3
To painful stimuli	Unintelligible sounds	Extensor posturing	2
None	None (intubated = 1T)	None	1

Initial treatment

- Empiric antibiotics if c/f CNS infection: vancomycin/CTX, consider acyclovir and ampicillin
- Immobilization of C-spine if concern for cervical trauma
- Thiamine 100 mg IV → dextrose 50 g IVP (this order to prevent exacerbation of Wernicke's)
- If opiates suspected: naloxone 0.01 mg/kg; if BDZ suspected, consider flumazenil 0.2mg IV
- If concern for ↑ ICP ± herniation: ↑ head of bed; osmotherapy w/ mannitol or hypertonic saline; ↑ ventilation; dexamethasone for tumor edema; c/s neurosurgery (? decompress)

Diagnostic studies (*Lancet* 2014;384:2064)

- All patients: check fingerstick glucose, electrolytes, BUN/Cr, LFTs, CBC, tox screen, U/A
- *Based on clinical suspicion:*
  - Labs: NH_3, TSH, cort stim, B_{12}, ABG, HIV, ESR, ANA, TPO/anti-TG, BCx, drug levels
  - Imaging: head CT, then MRI; CTA if c/f stroke/SAH; radiographs to r/o C-spine fracture
  - Lumbar puncture to r/o meningitis, SAH, or noninfectious inflammation (eg, autoimmune)

EEG to evaluate for nonconvulsive seizures, toxic/metabolic encephalopathy

Further treatment of delirium (*NEJM* 2017;377:1456)

- Treat underlying acute illness, eliminate precipitating factors, & provide supportive care
- Address sensory & cognitive impairments (frequent reorientation, glasses/hearing aids, etc.)
- Decrease/prevent infection/restraints if possible, remove lines/catheters if unnecessary
- Promote good sleep: reduce noise & nighttime interventions; sedative med if necessary
- Meds: consider antipsychotics (but neither haloperidol nor ziprasidone ↓ delirium duration in ICU Pts; *NEJM* 2018;379:2506); avoid benzos except in EtOH withdrawal or seizures

---

ANOXIC BRAIN INJURY (at risk if ≥5 min cerebral hypoxia)

Initial evaluation (*Circulation* 2010:S768)

- Neuro exam: arousal/verbal, eyes & other cranial nerves, motor response to pain
- Imaging: CT usually not informative w/in first day after arrest, but should be done prior to initiating hypothermia if patient found down or has had head trauma

Targeted temperature management (*Circulation* 2015;132:2448)

- Indications: comatose (GCS <8) w/in 6h after cardiac arrest (not isolated resp. arrest). Studied only in VT/VF, but consider after asystole or PEA, or 6–12h post-arrest.
- Exclusions: pregnancy, CV instability despite pressors/assist devices, other cause of coma, persistent ↓ O_2. Relative contraindications: major head trauma, coagulopathy/bleeding, major surgery <14d, systemic infection/sepsis.
- Target temp: 32–36°C × ≥24h. Initial studies showing benefit targeted 32–34°C, but subsequent study showed ≈ outcomes for 36°C vs. 33°C (*NEJM* 2013;369:2197). Some still target 32–34°C and reserve 36°C for Pts w/ contraindic to more aggressive cooling.
- Method: ice packs to head/neck/torso; cooling blankets; cooling vest or endovascular catheter. Goal to achieve target temp <6h (but no benefit to prehosp cooling; *JAMA* 2014;311:45). Pts should be sedated/paralyzed while cooled. MAP goal >70. Start rewarming 24h after cooling is initiated (rewarm ≤0.5°C per h).
- In Pts not cooled or after rewarming Pts who were cooled: prevent fever (goal <36°C) for ≥48h post arrest
- Complications
  - Dysrhythmias (brady most common): if significant or hemodynamic instability → rewarm
  - Coagulopathy (can receive lytics, GP IIb/IIIa inhibitors, etc.); monitor PT & PTT
  - Infection: monitor surveillance blood cultures during cooling
  - Hyperglycemia during cooling, hypoglycemia w/ rewarming; stop insulin if glc <200 mg/dL
  - Hypokalemia during cooling, hyperkalemia w/ rewarming; keep K 4–5 mEq/L

Ongoing evaluation

- Neuro exam: daily focus on coma exam. No exam finding is reliable <24 h or on sedation.

Should be off sedation for adequate time (depends on dose, duration, Pt's metabolism).

- Labs: daily CBC, PT/PTT, electrolytes. Serum neuron-specific enolase (NSE) on days 1–3.
- Imaging: noncontrast CT 24 h after arrest; if unrevealing, consider MRI around days 3–5
- EEG: consider in all to exclude seizures; greatest risk during rewarming
- Somatosensory evoked potentials (SSEP): helpful for prediction of poor outcome if cortical responses are absent bilaterally; perform 48 h after arrest (72 h if cooled)

Prognosis (*Nat Rev Neuro* 2014;10:190)

- Prior to cooling era, poor prognosis at 72 h if absent pupillary & corneal reflexes and no motor response to pain; or absent SSEPs at 48 h. With cooling, unclear if prior measures as reliable. Overall ~12% survive to hosp. d/c; VT/VF 25-40%, PEA ~10%, asystole ~2%.
- Prognosis requires multifactorial assessment based on age, exam, comorbidities, ancillary data. Poor signs: absent brainstem reflexes, Rx-resistant myoclonus, EEG w/ absent background/reactivity, NSE >33, diffuse hypoxic injury on MRI. If doubt, err on more time.

SEIZURES

Definitions & clinical manifestations (*Epilepsia* 2017;58:522)

- Seizure: transient neurologic symptoms due to excessive synchronous neuronal activity; may be *provoked* by a reversible factor lowering the seizure threshold, or *unprovoked*
- Epilepsy: ≥2 unprovoked seizures occurring >24 h apart *or* 1 unprovoked seizure w/ ≥60% probability of further seizures over the next 10 y (see below for prognostication)
- Generalized seizures (involves brain diffusely)
  - *Tonic-clonic* (grand mal):
    - Aura (sec to mins): premonition with paresthesias, focal motor contractions, abnormal smells/tastes, fear, depersonalization, déjà vu, autonomic changes, automatisms
    - Ictal period (sec to mins): lateral gaze and head deviation, tonic contraction of muscles → intermittent relaxing and tensing of muscles, tongue biting, urinary incontinence, pooling of secretions, incontinence
    - Postictal period (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd's paralysis).
  - *Absence* (petit mal): transient lapse of consciousness w/o loss of postural tone, usu pedi
  - *Myoclonic* (infantile spasms & juvenile myoclonic epilepsy): sudden, brief contraction
- Focal seizures (involves discrete brain area, often associated with a structural lesion)
  - *w/o impaired awareness:* focal motor/autonomic sx (formerly "simple partial seizure") or focal sensory/psychic symptoms (eg, aura)
  - *w/ impaired awareness:* dyscognitive features (formerly "complex partial seizure")
  - *evolving to bilateral, convulsive seizure* (formerly "secondarily generalized seizure")
- Status epilepticus: continuous convulsive seizure ≥5 min or >2 seizures w/o resolution of postictal encephalopathy; *life threatening*
- Nonconvulsive status epilepticus: alteration of awareness (ranging from confusion to coma) w/o motor manifestations of seizure; dx with EEG

Differential diagnosis

- Syncope (*Lancet Neurol* 2006;5:171)

Feature	Seizure	Syncope
Aura	Unusual behavior/automatisms	Diaphoresis, nausea, tunnel vision
Convulsions	Variable duration	Usually <10 sec
Postictal state	Yes; can be ≥30 min	None or short
Other clues	Tongue biting, incontinence	Skin pallor, clamminess

- Nonepileptic seizure (aka "psychogenic"): may see side-to-side head turning, asymmetric large-amplitude limb movements, hip thrusting, diffuse shaking w/o LOC,

crying/talking during event; diagnosis requires spell capture on EEG with no EEG correlate

- Other: metabolic disorders (eg, alcoholic blackouts, hypoglycemia), migraine, TIA, transient global amnesia, narcolepsy (cataplexy), nonepileptic myoclonus, tics, asterixis

Etiologies of seizures (vary strongly by age)

- Without focal lesion: genetic predisposition to seizures or epilepsy syndrome; alcohol withdrawal, illicit drugs; meds (eg, β-lactams, bupropion, fluoroquinolones, tramadol, MNZ, meperidine, CsA); electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia); autoimmune encephalitis, idiopathic (~60%)
- With focal lesion: tumor, trauma, stroke, subdural hematomas, posterior reversible encephalopathy syndrome, mesial temporal sclerosis, abscess, focal cortical dysplasia

Clinical evaluation (*JAMA* 2016;316:2657)

- *History key in differentiating seizure from other causes of transient loss of consciousness.* Must talk to witnesses. Ask about prodrome, unusual behavior before spell, type & pattern of abnl movements incl. head turning & eye deviation (gaze preference usually *away* from seizure focus), loss of responsiveness.
- Recent events: illnesses/fevers, head trauma, sleep deprivation, stressors
- PMH: prior seizures or ⊕ FHx; prior CNS infection, stroke or head trauma; dementia
- Medications (new or noncompliance), alcohol and illicit drug use
- General physical exam should include the skin, looking for neuroectodermal disorders (eg, neurofibromatosis, tuberous sclerosis) that are a/w seizures
- Neurologic exam should look for focal abnormalities → underlying structural abnormality

Diagnostic studies (*Neurology* 2007;69:1996)

- Lab: full lytes, BUN, Cr, glc, LFTs, tox screen, AED levels (valproic acid and phenytoin have therapeutic range; levetiracetam level rarely useful unless ? noncompliance), illicit drug screen
- Routine EEG (~30 min): may help determine risk of seizure recurrence after 1st-time unprovoked seizure. Caveat: interictal EEG nl in 50% of Pts w/ epilepsy, and interictal epileptiform activity (spikes or sharp waves) seen in up to 2% of nl population; EEG w/in 24h, sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): if suspicion for non-convulsive status or non-epileptic seizures; video monitoring may help w/ nonepileptic seizures
- MRI to r/o structural abnormalities; ↑ Se w/ fine coronal imaging of frontal & temporal lobes
- LP (if no space-occupying lesion on imaging): if suspect meningoencephalitis (eg, fever, ↑ WBC, nuchal rigidity) or autoimmune encephalitis and in *all* HIV ⊕ Pts

Treatment (*Neurology* 2015;84:1705; *Lancet* 2015;385:884)

- Treat any underlying precipitants, including CNS infections, intoxication, withdrawal, etc.
- Antiepileptic drug (AED) Rx usually reserved for Pts w/ ≥2 *unprovoked* seizures, single seizure w/ high risk of recurrence (see below), or underlying structural abnormality. *Provoked* seizures generally treated by addressing underlying cause; consider AED if status epilepticus on presentation, focal neuro exam, postictal Todd's paralysis.

- After 1st unprovoked sz, weigh risks of recurrence vs AED. ↑ risk of recurrence if abnl EEG, MRI, or nocturnal sz. If EEG & MRI nl → 65% sz-free at 5 y (*Lancet Neurol* 2006;5:317).
- Immediate treatment w/ AED after 1st unprovoked seizure ↓ risk of recurrence over 2 y, but does not Δ long-term prognosis
- If AED Rx indicated, choice dependent on type of seizure, side effects, cost, mechanism of elimination (if hepatic or renal insufficiency), teratogenesis, and drug interactions
- Introduce gradually, monitor carefully
- May consider withdrawal of meds if seizure free (typically for at least 1 y) and normal EEG
- Individual state laws mandate seizure-free duration before being allowed to drive

Antiepileptic Drugs and Side Effects

Medication	Avg daily dose	Common side effects	
		Systemic	*Neurologic (all: sedation)*
Carbamazepine	400–1600 mg	Aplastic anemia, ↓WBC, rash, hepatotoxicity, ↓ Na	Diplopia, confusion, ataxia
Ethosuximide	500–1500 mg	Rash, BM suppression	Behavioral Δs
Gabapentin	900–3600 mg	GI upset, wt gain	Nystagmus, ataxia
Lacosamide	200–400 mg	Prolonged PR interval	Dizziness, diplopia
Lamotrigine	100–300 mg	Rash (Stevens-Johnson)	Tremor, HA, blurred vision, insomnia
Levetiracetam	1000–3000 mg	GI upset (rare)	Emotional lability
Oxcarbazepine	600–2400 mg	Hyponatremia, rash	Diplopia, dizziness
Phenobarbital	50–200 mg	Rash	Cognitive slowing
Phenytoin	200–400 mg	Gum hyperplasia	Dizziness, ataxia
Topiramate	100–400 mg	↓ wt, hypohidrosis, kidney stones, glaucoma, met acid	Cognitive slowing
Valproic acid	500–2500 mg	Hepatotox, ↑ NH_3, ↑ wt, ↓ hair	Tremor
Zonisamide	200–600 mg	↓ wt, hypohidrosis, nephrolith	Cog slowing, fatigue

(*NEJM* 2008;359:166; *Lancet Neurol* 2011;10:446)

Status epilepticus (*Epilepsy Curr* 2016;16:48)

- ABCs: vital signs, oral airway or endotracheal intubation. Place Pt in semiprone position to ↓ risk of aspiration. Obtain IV access. Give thiamine, dextrose, IV normal saline.
- STAT glc, metabolic panel, CBC, tox screen, lactate, AED levels, consider head CT, LP
- Start standing AED after loading dose.

Treatment of Status Epilepticus			
Time (min)	**Antiepileptic**	**Dosing regimen**	**Typical adult dose**
<5	**Lorazepam** or **Midazolam** or **Diazepam***	0.1 mg/kg IV>IM 0.2 mg/kg IM 0.2 mg/kg IV or 0.2-0.5 mg/kg PR	2–4 mg IV pushes, up to 10 mg Up to 10 mg x1 Up to 10 mg IV; up to 20 mg PR
<10	**Phenytoin** or **Fosphenytoin** or **Valproate** or **Levetiracetam**	20 mg/kg 20 mg PE/kg 40 mg/kg 20–40 mg/kg	1.0–1.5 g IV (max 1.5 g) over 20 min 1.0–1.5 g PE IV over 5–10 min 1.0– 1.5 g IV (max 3 g) over 5–10 min 2g IV (max 4.5 g) over 10–15 min
	Subsequent steps mandate intubation, EEG monitoring, and ICU admission		
<30–60	General anesthesia with continuous midazolam, pentobarbital, or propofol		

PE, phenytoin equivalents. *Consider PR diazepam if no IV access and IM midazolam is contraindicated.

ALCOHOL WITHDRAWAL

Clinical manifestations

- Minor withdrawal sx (6–48 h after last drink): mild anxiety, tremulousness, HA
- Withdrawal seizures: typically w/in 48 h after last drink; if unRx'd, 1/3 → delirium tremens
- Alcoholic hallucinosis: isolated hallucinations (typically visual) 12–48 h after last drink
- Delirium tremens (DT): disorientation, agitation, hallucinations, ↑ HR & BP, fever, diaphoresis; begins 48–96 h after last drink, lasts 5–7 d
- Consider other dx: CNS infxn or bleed, sz, drug O/D, coingestions, acute liver failure, GIB
- Ten-item scale (CIWA-Ar) used to assess and manage alcohol withdrawal (see Appendix)

Treatment (*NEJM* 2003;348:1786)

- Benzodiazepines (BDZ)
  - Drug: diazepam (long-acting w/ active metab; ↓ risk of recurrent withdrawal), lorazepam (short half-life), chlordiazepoxide, oxazepam (no active metab; good if cirrhosis)
  - Dosing: typically start w/ diazepam 10–15 mg IV q10–15min (or lorazepam 2–4 mg IV q15–20min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1h until score <8 × 8 h, then q2h × 8 h, and if stable, then q4h (*JAMA* 1994;272:519)
- If refractory to BDZ prn → BDZ gtt, phenobarb, dexmedetomidine, or propofol (& intubation)
- *Avoid* βB (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; thiamine *then* glc to prevent *Wernicke's encephalopathy* (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO_4
- Prophylaxis: if min sx or asx (ie, CIWA score <8) but prolonged heavy EtOH consumption or h/o withdrawal seizures or DTs → chlordiazepoxide 25–100 mg (based on severity of EtOH use) q6h × 24 h, then 25–50 mg q6h × 2 d

DIZZINESS

Differential diagnosis

- Includes a variety of sx. Disequilibrium: sense of imbalance, gait disturbance; vertigo: perception of spinning; near syncope: lightheadedness due to cerebral hypoperfusion.
- Vertigo Ddx:
  - *Peripheral*
    - BPPV: dislodged canaliths in semicircular canal; episodic rotatory vertigo (<1 min episodes), triggered by changes in position; Rx: Epley/BBQ roll maneuver
    - Meniere's disease: ↑ endolymphatic pressure in inner ear; episodic rotatory vertigo (min-hrs), N/V, aural fullness, hearing loss, tinnitus; Rx: diuretics, ↓ salt
    - Vestibular neuritis: sudden-onset w/ gait ataxia; if w/ hearing loss = labyrinthitis
  - *Central*
    - Posterior circulation stroke/TIA: "5 Ds" of dizziness, diplopia, dysarthria, dysphagia, dystaxia; sudden onset (resolves after mins in TIA, persists in stroke)
    - Other: migraine, Chiari, epilepsy, MS, tumors, drugs/meds, concussion

Initial evaluation

- Hx: ask open-ended questions (description by Pt may be unreliable), pace of illness, episodic vs. chronic, meds, other sx of posterior circ including diplopia, dysarthria, ataxia

Exam	Peripheral Causes	Central Causes
Orthostatics	⊕ in orthostatic syncope	Typically absent
Eye movements	Nystagmus unidirectional if present, never vertical, suppressed w/ fixation	Nystagmus bidirectional, often vertical, not suppressed w/ fixation
Hearing	May be impaired in some peripheral causes of vertigo	Normal (rarely unilat. hearing loss in AICA-territory stroke)
Coord./gait	Normal	May reveal limb, trunk, gait ataxia

- HINTS testing (*Stroke* 2009;40:3504)
  - Head impulse test: Pt fixates on examiner's nose during rapid passive head turn; presence of "catch-up saccade" supports peripheral dysfunction to side of turn
  - Nystagmus (see table above)
  - Test of skew: vertical refixation saccade on alternating eye cover supports central cause
- Dix-Hallpike test: Pt sitting → lying back w/ 45° head tilt; elicits rotatory nystagmus after delay of secs; fatigues if repeated; ⊕ suggests BPPV w/ affected ear down
- Supine Roll test: nystagmus elicited by head turn while patient supine; when ⊕ suggests BPPV w/ affected ear down (lateral canal, 8% of cases)
- Studies: ECG, basic labs, if concerning s/s on HINTS → MRI brain
- Treatment: reposition maneuv. for BPPV, vestib. PT; anti-hist., sedatives or anti-emetics

STROKE

ISCHEMIC STROKE

Etiologies

- Embolic: artery → artery, cardioembolic (~30% due to AF; *NEJM* 2014;370:2478), paradoxical
- Thrombotic: large vessel (atherosclerosis) vs. small vessel ("lacunar," lipohyalinosis of small arteries, often related to smoking, HTN, hyperlipidemia, & DM)
- Other: dissection, vasculitis, vasospasm, hypercoag, hypoperfusion, endocarditis, venous

Clinical manifestations

- Timing: embolic → sudden onset; thrombotic → may have stuttering course

Stroke Syndromes by Vascular Territory	
Artery	Deficits
ICA → Ophth	Amaurosis fugax (transient monocular blindness)
ACA	Hemiplegia (leg > arm), abulia, urinary incontinence, primitive reflexes
MCA	Hemiplegia (face & arm > leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. div → receptive Apraxia & neglect if nondom. hemisphere.
PCA	Macular-sparing homonymous hemianopia; alexia w/o agraphia Thalamic syndromes with contralateral hemisensory disturbance
Vertebral, PICA	Wallenberg syndrome = numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, dysphagia, ipsilateral Horner's, hiccups
Basilar	Pupillary Δs (midbrain=dilated, pons=pinpoint), long tract signs (quadriplegia, sensory loss), CN abnl, cerebellar dysfxn. Top of basilar → "locked in" synd.
Cerebellar	Vertigo, N/V, diplopia, dysarthria, nystagmus, ipsilateral limb ataxia
Lacunar (arterioles)	5 major syndromes: pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, dysarthria + clumsy hand, mixed sensorimotor

Transient ischemic attack (TIA)

- Sudden deficit due to cerebral ischemia; no stroke on imaging; most resolve in <1 h
- Ddx: seizure, migraine, hypoglycemia, amyloid spells, TGA, anxiety
- Risk of subsequent stroke ~2% by 1 wk (*NEJM* 2016;374:1533). Can stratify based on $ABCD^2$: Age ≥60 y (+1); BP ≥140/90 (+1); Clin features: unilat. weak. (+2), speech impair. w/o weakness (+1); Duration ≥60 (+2) or 10–59 min (+1); DM (+1)

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis stigmata
- Neurologic exam, NIH stroke scale (http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf)

Acute workup

- Electrolytes, Cr (relevant for contrast); glc, CBC, coags (see exclusion criteria for lysis)
- Cardiac biomarkers, 12-lead ECG, tox screen
- STAT CT to r/o ICH prior to lysis. (Se ICH ≈ MRI, CT faster). Early signs of stroke: hyperdense artery, loss of gray-white differentiation, edema, insular ribbon. CT can be nl initially, and not Se for small & brainstem. CTA if considering endovascular intervention.

Acute treatment of ischemic stroke (*Lancet* 2017;389:641; *Stroke* 2018;49:e46)

- Thrombolysis (IV): tPA 0.9 mg/kg (max 90 mg), w/ 10% as bolus over 1 min, rest over 1 h
  consider if onset w/in 4.5 h, ∅ ICH, ∅ contraindic. (incl. current/prior ICH; head trauma or stroke w/in 3 mo; intracranial neoplasm, AVM or aneurysm; recent intracranial/intraspinal surgery; active internal bleeding; noncompressible arterial puncture; ↑ BP; multilobar infarct; plt <100k, INR >1.7, on Xa inhib, PTT >40, glc <50)
  0–3 h: 12% absolute ↑ in good neuro outcome (min/no disability), 5.8% absolute ↑ in ICH, trend toward 4% absolute ↓ mortality
  3–4.5 h: 7.4% absolute ↑ in good neuro outcome, 1.8% absolute ↑ in ICH, ∅ mortality benefit (nb, trial excluded patients with previous strokes + DM)
  Data for TNK, Rx up to 9 h, and for MRI imaging to guide Rx (*NEJM* 2018;378:1573 & 379:611; 2019;380:1795)
- BP: lower to <185/110 to consider lysis; if lyse keep <180/105 × 24 h (consider labetalol or nicardipine), o/w permissive HTN unless >220/120 or sx; if sx HoTN consider vasopressors
- Initiate ASA w/in 24–48 h; avoid anticoagulation w/in 24 h of lysis; see below for long-term Rx
- Cerebral edema → herniation: 1–5 d post large MCA or cerebellar strokes, ↑ risk in young. Elevate HOB >30°; mannitol ± 23% NaCl. Hemicraniectomy ↓ mortality (*NEJM* 2014;370:1091). Neurosurgery consult in select MCA and all large cerebellar strokes.
- Endovascular thrombectomy indicated if w/in 6 h of sx onset, pre mRS 0-1, occlusion in ICA or MCA, NIHSS ≥6 (clinical severity), ASPECTS ≥6 (CT based likelihood of recovery) (*NEJM* 2015;372:11, 1009, 1019, 2285 & 2296; *Lancet* 2016;387:1723). May extend to 6–24 h if mismatch between infarct size and clinical deficits or stroke penumbra (*NEJM* 2018;378:11 & 708).

Workup to assess for etiology/modifiable risk factors

- Cardiac: prolonged Holter for AF (eg, 10 d at presentation, 3 & 6 mo detects in 14%); TTE to r/o thrombus/veg, w/ bubble study to r/o PFO/atrial septal aneurysm if suspect embolic
- Vessel imaging: CTA or MRA head/neck; carotid U/S w/ Doppler if contraindic to CTA/MRA
- Labs: lipids, HbA1c, TSH, homocysteine, Lp(a), hypercoag w/u (if <65 y or cryptogenic stroke; ideally drawn before starting anticoag), ESR/CRP, blood cx if s/s systemic infection
- MRI helpful if dx of stroke unclear (esp. post circ) or to define stroke subtype, age, exact

size
DWI bright/*ADC* dark = earliest finding in acute ischemia (~w/in mins, up to days)
T2-FLAIR: hyperintense w/in hrs, persists for wks; *PWI* differentiates irreversibly infarcted core vs. viable penumbra; *T1 fat-sat* (neck vessels) if suspicious for dissection

Secondary stroke prevention (*NEJM* 2012;366:1914)

- Antiplatelet therapy: different agents likely have similar efficacy
  ASA ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (*NEJM* 2001;345:1444)
  clopidogrel: marginally superior to ASA, slightly ↑ ICH (*Lancet* 1996;348:1329)
  clopidogrel + ASA (vs. ASA alone): Rx for 21 d in minor strokes/TIA → ↓ risk of stroke, ? ↑ ICH; longer Rx not better & ↑ ICH (*NEJM* 2013;369:11 & 2018;379:215; *BMJ* 2018;363:k5108) Rx for 90 d if stroke due to intracranial athero (*NEJM* 2011;365:993)
- Anticoagulation (AC): consider for AF (qv), cardiac/paradoxical emboli (except bacterial endocard); large extra-dural dissections; hypercoag; bridge to CEA in sx carotid stenosis
  Hold off on AC in large strokes for ~2–4 wk given risk of hemorrhagic conversion
- Long-term SBP target 120–139 mmHg (*JAMA* 2011;306:2137)
- ↓ LDL-C (<< 70 mg/dL): ↓ recurrence w/ statin PCSk9i added to statin (*NEJM* 2017;376:1713)
- Fluoxetine: improved motor recovery after 3 mo (*Lancet Neurol* 2011;10:123)
- Carotid revascularization (*NEJM* 2013;369:1143)
  CEA (*if* surgical morbidity & mortality ≤6%) indicated for:
  sx stenosis 70–99% (benefit ↑ for males, >75 y, ≤2 wk from stroke) → 65% ↓ RR of repeat stroke, slight benefit for 50–69% stenosis (*NEJM* 1991;325:445; *Lancet* 2004;363:915)
  asx stenosis 70–90%, <79 y: 50% ↓ RR of repeat stroke (*Lancet* 2010;376:1074)
  Stenting: c/w CEA, periprocedural stroke ↑ (esp. in elderly) & MI ↓ (but many asx), subseq. stroke rate ≈ (*NEJM* 2016;374:1011 & 1021; *Lancet* 2016;387:1305; *Lancet Neuro* 2019;18:348)

Patent foramen ovale (PFO; in ~27% of population) (*NEJM* 2005;353:2361)

- ↑ stroke risk: ≥4 mm separation, R→L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- If PFO & stroke/TIA: no benefit of warfarin over ASA (*Circ* 2002;105:2625), but consider if at high risk for or has DVT/PE. Closure ↓ recurrence by ≥50% if ↑ risk features (see above) and absence of factors suggesting alternate etiology (*NEJM* 2017;377:1011, 1022, 1033). RoPE score: age (+1 for each decade <70); cortical stroke on imaging (+1); HTN, DM, h/o stroke/TIA, smoker (+1 for each *absent* risk factor). Consider closure if >7 (*JAHA* 2018;7:1).

INTRACRANIAL HEMORRHAGE (ICH)

Classification by location

- Hemorrhagic strokes: intraparenchymal hemorrhage (IPH) & subarachnoid hemorrhage (SAH)
- Other ICH: epidural hematoma (EDH) & subdural hematoma (SDH)

Etiologies

- AVM, aneurysm, cerebral venous sinus thrombosis → IPH or SAH
- HTN (basal ganglia, cerebellum, brainstem), cerebral amyloid (lobar), tumor (esp. w/ melanoma, renal cell CA, chorio-CA, thyroid CA) → IPH
- Trauma → all locations (nb, IPH or SAH caused by trauma technically not a stroke)

Clinical manifestations (*Lancet* 2017;389:655 & *NEJM* 2017;377:257)

- ↓ consciousness, N/V, HA, progressive focal neurologic deficits
- *SAH:* thunderclap HA, onset w/ exertion; nuchal pain/rigidity; LOC. *EDH:* initial lucid interval.

Workup (*Acad Emerg Med* 2016;23:963)

- STAT CT brain, angio (CT-A or conventional) if suspicious for vascular source
- ? LP for xanthochromia if no evid of ICH on CT (although ⊖ LR 0.01) & suspicious for SAH
- Coags (PT, PTT, INR)

Management (*Crit Care Med* 2016;44:2251; *JAMA* 2019;321:1295)

- Reverse coagulopathy, INR <1.4. Plt >100k, no need for plt tx if on antiplt Rx (? if ↑ ICH), DDAVP if uremic. 2-3 mo after recovers, can restart antiplt mono Rx (*Lancet* 2019;393:2013).
- BP control w/ art line, nicardipine or labetalol gtt. SBP goal <140 for 1st 24 h, then <160 (*NEJM* 2013;368:2355 & 2016;375:1033), though BP goals controversial (*NEJM* 2016;375:1033)
- SAH: endovasc coiling vs. surg clipping (depends on location, comorbid.; *Lancet* 2015;385:691) of aneurysm/AVM; nimodipine to ↓ risk of vasospasm (monitor w/ TCDs), seizure Ppx
- Surg evac: EDH; SDH if >1 cm or rapid ↑; IPH: no obvious benefit (*Lancet* 2013;382:397)
- Venous sinus thrombosis: start anticoagulation, manage ↑ ICP and seizures as needed

WEAKNESS & NEUROMUSCULAR DYSFUNCTION

Feature	Upper Motor Neuron	Lower Motor Neuron	Neuromuscular Junction	Myopathy
Distribution of weakness	UE Ext, LE Flex, hip abductors	Distal, segmental	Ocular, bulbar, proximal limb	Proximal, symmetric
Atrophy	None	Severe	None	Mild
Fasciculations	None	Common	None	None
Tone	↑	↓	Normal	Normal or ↓
Reflexes (DTRs)	↑	↓	Normal	Normal or ↓
Toes (Babinski)	Upgoing	Downgoing	Downgoing	Downgoing

PERIPHERAL NEUROPATHIES

Etiologies based on presentation

- Mononeuropathy (1 nerve): *acute* → trauma; *chronic* → entrapment, compression, DM, Lyme. Common: median n. (carpal tunnel); ulnar n. (elbow or wrist); radial n. (spiral groove); com. peroneal n. (fibular head w/ leg crossing); lat. femoral cutan. n. (inguinal lig)
- Mononeuropathy multiplex (axonal loss of multiple, noncontig. nerves): vasculitic synd. (eg, PAN, Churg–Strauss, Wegener's, SLE, RA, Sjögren's, cryo, HCV), DM, Lyme, HIV, leprosy, hereditary neurop. w/ pressure palsies, infiltrative (sarcoid, lymphoma, leukemia)
- Polyneuropathy (multiple symmetric nerves, generally length dependent): 30% idiopathic;
  W/ autonomic features: DM, EtOH, paraneoplastic, B_{12} def, amyloid, chemo, 1° dysauto
  Painful (small fiber nerves): DM, EtOH, amyloid, chemo, sarcoid, heavy metals, porphyria
  Demyelinating. Acute: AIDP (Guillain-Barré), diphtheria. Subacute: meds (taxanes), paraneoplastic. Chronic: idiopathic, DM, CIDP, anti-MAG, HIV, hypothyroidism, toxins, paraproteinemia, hereditary (eg, CMT).
  Axonal. Acute: acute motor axonal neuropathy, porphyria, vasculitis, uremia, critical illness. Subacute: EtOH, sepsis, paraneoplastic, meds (cisplatin, paclitaxel, vincristine, INH, ddI, amio). Chronic: DM, uremia, lead, arsenic, HIV, paraproteinemia, B_{12} defic.

Clinical manifestations

- Weakness, fasciculations, cramps, numbness, dysesthesias (burning/tingling), allodynia
- ± Autonomic dysfxn (orthostasis, constipation, urinary retention, impotence, abnl

sweating)
- Depressed or absent DTRs (may be normal in small fiber neuropathy)

Diagnostic studies
- Distal symmetric polyneuropathy: CBC, lytes, BUN/Cr, Hb_{A1C}, B_{12}, TSH, ESR, SPEP + IF
- EMG/NCS (often no change in 1st 10–14 d or in small-fiber neuropathy)
- Based on H&P: LFTs, ANA, anti-Ro/La, HIV, Cu, Lyme, RPR, UA, UPEP+IF, ACE, ANCA, heavy metals, LP (AIDP/CIDP), cryo, paraneoplastic Abs, genetic testing. Autonomic testing/skin bx (small fiber), nerve bx (mononeuropathy multiplex), fat pad bx (amyloid).
- MRI if possible radiculopathy or plexopathy (after EMG)

Pharmacologic treatment of neuropathic pain (*Lancet Neurol* 2015;14:162)
- Gabapentin, pregabalin, TCAs (nortriptyline, amitriptyline), SNRIs (duloxetine, venlafaxine)
- 2nd line: tramadol, topicals (lido, capsaicin); 3rd line: nerve block, botulinum toxin A

GUILLAIN-BARRÉ SYNDROME (GBS)

Definition & epidemiology (*Nat Rev Neurol* 2014;10:469)
- AIDP (60–80%); acute motor axonal neuropathy (AMAN; 7–30%; a/w anti-GM1, anti-GD1a Abs; worse prognosis); Miller Fisher synd. (ophthalmoplegia & ataxia; a/w anti-GQ1b Ab)
- Incidence 1–2 per 100,000; most common acute/subacute paralysis
- Precipitants in 60%: viral illness (influenza, CMV, EBV, HIV, Zika), URI (*Mycoplasma*), gastroenteritis (*Campylobacter*), Lyme, immunizations (no proven risk w/ current), surgery

Clinical manifestations (*Lancet* 2016;388:717)
- Pain (55–90%), distal sensory dysesthesias & numbness often 1st sx, back pain common
- Progressive symmetric paralysis in legs and arms over hrs to days; plateau in 1–4 wk
- Hypoactive then absent reflexes. <10% w/ reflexes on presentation, but all develop hypo/areflexia during course. Minority of AMAN w/ preserved reflexes throughout.
- Resp failure requiring mech vent occurs in 25%; autonomic instability & arrhythmias in 60%

Diagnostic studies (results may be normal in first several days)
- LP: albuminocytologic dissociation = ↑ protein w/o pleocytosis (<10 WBCs) seen in up to 64% of Pts. ↑ protein in ½ in 1st wk, ¾ by 3rd wk of sx. Unlikely to be GBS if WBC >50
- EMG/NCS: ↓ conduction velocity, conduction block, abnl F-waves; can be nl in 1st 2 wk
- FVC & NIF: to assess for risk of resp. failure (cannot rely on P_aO_2 or S_aO_2 alone)

Treatment
- Plasma exchange or IVIg of equal efficacy (*Neuro* 2012;78:1009); steroids not beneficial
- Supportive care with monitoring in ICU setting if rapid progression or resp. failure

- Watch for autonomic dysfunction: labile BP, dysrhythmias (telemetry)
- Erasmus GBS outcome score can help w/ prognostication (*Lancet Neurol* 2007;6:589). Most recover near baseline in 1 y; 3–5% mortality. Residual deficits: pain, fatigue.

MYASTHENIA GRAVIS (MG)

Definition & epidemiology (*Lancet Neurol* 2015;14:1023; *NEJM* 2016;375:2570)

- Autoimmune disorder with Ab against acetylcholine receptor (AChR, 80%), muscle-specific kinase (MusK, 4%), lipoprotein-related protein 4 (LRP4, 2%), or other NMJ proteins
- Prevalence: 1 in 7500; affects all ages, peak incidence 20s–30s (women), 60s–70s (men)
- 15% of AchR MG a/w thymoma; 30% of pts w/ thymoma develop AchR MG

Clinical manifestations

- Fluctuating weakness w/ *fatigability* (worse w/ repetitive use, relieved by rest)
- Cranial muscles involved early → 60% present initially w/ ocular sx (ptosis, diplopia); 20% will only have ocular sx; 15% w/ bulbar (difficulty chewing, dysarthria, dysphagia)
- Limb weakness proximal > distal; DTRs preserved; minimal/no atrophy
- MusK MG (F >> M): mostly cranial/bulbar, neck, and resp weakness
- Exacerb. triggered by stressors: URI, surgery, preg/postpartum, meds (eg, Mg, AG, macro-lides, FQ, procainamide, phenytoin, D-penicillamine). Prednisone can *worsen* sx acutely.
- Myasthenic crisis = sx exacerbation, risk of respiratory compromise
- Cholinergic crisis = weakness due to *overtreatment* with anticholinesterase meds; may have excessive salivation, abdominal cramping and diarrhea; rare at normal doses

Diagnostic studies

- Bedside: ptosis at baseline or after >45 sec of sustained upgaze; improved ptosis with ice pack over eyes for 2–5 min (Se 77%, Sp 98%)
- Neostigmine test: temporary ↑ strength; false ⊕ & ⊖ occur; premedicate w/ atropine
- EMG: ↓ response with repetitive nerve stimulation (vs. ↑ response in Lambert-Eaton)
- Anti-AChR Ab (Se 80%, 50% if ocular disease only, Sp >90%); muscle specific receptor tyrosine kinase (MuSK) Ab; AchR modulating Ab
- CT or MRI of thorax to evaluate thymus (65% hyperplasia, 10% thymoma)

Treatment

- Thymectomy if thymoma and in Ab ⊕ Pts w/o thymoma (*NEJM* 2016;375:511)
- Cholinesterase inhibitor (eg, pyridostigmine) is most rapid acting (benefit in 30–60 min). Less effective for MusK MG. Side effects: cholinergic stim (brady, diarrhea, drooling).
- Immunosuppression: prednisone (benefit in wks; don't start during crisis) + AZA (benefit in 6–15 mo). If no response: mycophenolate, rituximab, MTZ, CsA. Goal to taper off steroids
- Myasthenic crisis: treat precipitant; consider d/c cholinesterase inhibitor if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (in

monitored setting b/c risk for initial worsening). ICU if rapid or severe (follow FVC, NIF).

MYOPATHIES

Etiologies

- Hereditary: Duchenne, Becker, limb-girdle, myotonic, metabolic, mitochondrial
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing syndrome
- Toxic: statins, fibrates, glucocorticoids, zidovudine, alcohol, cocaine, antimalarials, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis
- Inflammatory: polymyositis, dermatomyositis, inclusion body myositis, anti-HMGCR

Clinical manifestations

- Progressive or episodic weakness (not fatigue)
- Weakness most often symmetric, proximal > distal (stairs, rising from sitting, etc.)
- ± Myalgias (though not prominent or frequent), cramps, myotonia (impaired relaxation)
- May develop either pseudohypertrophy (dystrophies) or mild muscle atrophy
- Assoc. organ dysfxn: cardiac (arrhythmia, CHF), pulmonary (ILD), dysmorphic features

Diagnostic studies

- CK, aldolase, LDH, electrolytes, ALT/AST, PTH, TSH, ESR, HIV
- Autoantibodies: ANA, RF, anti-Jo1, antisynthetase, anti-Mi-2, anti-SRP, anti-HMGCR (if statin use), 5TN1CA (in inclusion body myositis)
- EMG/NCS: low-amplitude, polyphasic units w/ early recruitment, ± fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)
- Age-appropriate cancer screening if polymyositis or dermatomyositis suspected

HEADACHE

Primary headache syndromes (International Headache Society Classification)

- Tension-type: bilateral, pressure-like pain of mild–mod intensity, not throbbing or aggravated by physical activity. A/w photophobia or phonophobia, not N/V. Freq a/w myofascial sensitivity in neck/head. Triggers: stress, sleep deprivation, dehydration, hunger. Episodic HA Rx: NSAIDs, acetaminophen (risk of med overuse HA); chronic HA Rx: TCAs.
- Cluster HA and other trigeminal autonomic cephalalgias (TACs) (*Continuum* 2018;24:1137)
  Characterized by unilateral headache a/w ipsilateral autonomic sx (rhinorrhea, red/tearing eye, miosis, ptosis, lid edema, sweating), subtypes differentiated by timing.
  Cluster: ♂ > ♀, unilateral pain w/ autonomic sx & restlessness; attacks 15 min–3 h, up to 8/d (circadian). Ppx: CCB (verapamil). Rx: high-flow O_2 (12–15 L/min), sumatriptan.
  Paroxysmal hemicrania: similar to cluster, but ♀ > ♂, attacks 2–30 min. Rx: indomethacin.
  Hemicrania continua: ♀ > ♂, ice pick–like pain lasting >3 mo. Rx: indomethacin.
  Short-lasting unilateral neuralgiform HA (SUNA/SUNCT)*:* ♂ > ♀, excruciating, stabbing, electrical pain, 5 sec–4 min, up to 200×/d. Rx: lamotrigine, gabapentin, topiramate.
- Migraine: *see below*

Secondary causes of headaches

- Traumatic: post-concussion, SAH, SDH, postcraniotomy
- ↑ ICP: mass (tumor, abscess, vascular malformations, ICH), hydrocephalus, idiopathic intracranial hypertension (pseudotumor cerebri), altitude-associated cerebral edema
- ↓ ICP: post-LP headache, CSF leak/dural tear, overshunting
- Vascular: stroke (esp. posterior circ), dissection, vasculitis (incl. temporal arteritis), reversible cerebral vasoconstriction syndrome (RCVS), ICH, venous sinus thrombosis
- Meningeal irritation: meningitis, SAH
- Extracranial: sinusitis, TMJ syndrome, glaucoma
- Systemic: hypoxia (OSA), hypercapnia, dialysis, HTN, cardiac cephalalgia, hypoglycemia, ↓ TSH, pheo, medication overuse (analgesics), withdrawal (caffeine, opioids, estrogen)

Clinical evaluation (*JAMA* 2006;296:1274 & 2013;310:1248)

- History: onset (sudden vs. gradual), quality, severity, location, duration, triggers, alleviating factors, positional component, hormonal triggers (menstruation), preceding trauma, associated sx (visual Δs, "floaters," N/V, photophobia, focal neurologic sx), medications (analgesics), substance abuse (opioids, caffeine), personal/family hx of HA

- General and neurologic exam (including funduscopic exam, visual fields)
- Warning signs (should prompt neuroimaging)
  Explosive onset (vasc); "worst HA of my life" (SAH, RCVS); *meningismus* (SAH, infxn)
  Positional: lying > standing (↑ ICP); *N/V* (↑ ICP; migraines)
  Visual sx: diplopia, blurring, ↓ acuity (GCA, glaucoma, ↑ ICP); *eye pain* (glaucoma, trigeminal autonomic cephalalgia, optic neuritis)
  Abnl neuro exam (struct. lesion, poss. in migraine); ↓ *consciousness* (± fever): infxn, ICH
  Age >50 y; immunosuppression (CNS infections, PRES)
- Imaging: CT or MRI; consider CTA (beading in vasculitis/RCVS/vasospasm), CTV/MRV
- LP if ? SAH (✔ for xanthochromia), idiopathic intracranial HTN (✔opening press); image first!

MIGRAINE (*NEJM* 2017;377:553)

Definition & clinical manifestations (*Lancet* 2018;391:1315)

- Epidemiology: affects 15% of women and 6% of men; onset usually by 30 y
- Migraine w/o aura (most common): ≥5 attacks lasting 4–72 h with both (a) N/V *or* photophobia & phonophobia, and (b) ≥2 of following: unilateral, pulsating, mod–severe intensity, or aggravated by routine activity
- Migraine w/ aura: ≥2 attacks w/: (a) aura defined as ≥1 fully reversible sx: visual Δs (flickering spots, visual loss), sensory sx (paresthesias, numbness), speech disturbance; *and* (b) unilateral progression of sx(s) over ≥5 but ≤60 min; *and* (c) HA w/in 60 min of aura
- Aura may occur w/o HA ("acephalgic migraine"), must r/o TIA/stroke (typically rapid onset)
- If motor weakness, consider sporadic or familial hemiplegic migraine: aura of reversible motor weakness (up to 24 h), a/w CACNA1A, ATP1A2, or SCN1A mutations
- Precipitants: stress, foods (cheese, chocolate, MSG), fatigue, EtOH, menses, exercise

Treatment

- Abortive Rx: 5-HT_1 agonists (triptans) effective if given early in migraine attack; contraindicated if motor aura, CAD, prior stroke. Also consider acetaminophen, caffeine, NSAIDs (ketorolac), steroids, Mg, metoclopramide, prochlorperazine, valproate, dihydroergotamine (caution if CAD, recent triptan use). *Avoid butalbital, opioids.*
- Prophylaxis: valproic acid, topiramate, β-blockers (propranolol first-line), TCAs, Mg, B2, botox, anti-CGRP & receptor mAbs (femanezumab, erenumab; *NEJM* 2017;377:2113 & 2123)

BACK AND SPINAL CORD DISEASE

Differential diagnosis of back pain

- Musculoskeletal: involving spine (vertebra, facet joints), paraspinal muscles and ligaments, sacroiliac joint, or hip joint. Spondylolisthesis, vertebral fx, OA, inflam. spondyloarthritis (RA, ankylosing spondylitis, reactive, psoriatic), musculoligamentous "strain," myofascial pain syndrome, trochanteric bursitis.
- Spinal cord (myelopathy)/nerve root (radiculopathy):
  Degenerative/traumatic: disc herniation, foraminal or lumbar stenosis, spondylolisthesis
  Neoplastic: lung, breast, prostate, RCC, thyroid, colon, multiple myeloma, lymphoma
  Infectious: osteomyelitis/discitis, epidural abscess, zoster, Lyme, CMV, HIV, spinal TB
- Referred pain from visceral disease:
  GI: PUD, cholelithiasis, pancreatitis, pancreatic cancer
  GU: pyelonephritis, nephrolithiasis, uterine or ovarian cancer, salpingitis
  Vascular: aortic dissection, leaking aortic aneurysm

Initial evaluation (*Lancet* 2017;389:736)

- History: location, radiation, trauma, wt loss, cancer hx, fever, immunocompromised, IV drug use, neurologic sx, saddle anesthesia, bowel/bladder sx (retention, incont.)
- General physical exam: local tenderness, ROM, signs of infection or malignancy; paraspinal tenderness or spasm in musculoskeletal strain
- Signs of radiculopathy (sharp/lancinating pain radiating into limb):
  Spurling sign (cervical radiculopathy): radicular pain w/ downward force to extended & ipsilaterally rotated head; 30% Se, 93% Sp
  Straight leg raise (sciatica or lumbosacral radiculopathy): radicular pain at 30–70°; ipsilateral: 92% Se, 28% Sp; crossed (contralateral leg raised): 28% Se, 90% Sp
  Patrick/FABER test (sacroiliac joint syndrome): severe pain on hip external rotation; 70% Se, 100% Sp
  Neurogenic claudication in lumbar stenosis (see table on next page)
- Neurologic exam: full motor (including sphincter tone), sensory (including perineal region; note dermatomal patterns), and reflexes including bulbocavernous, anal wink (S4), and cremasteric (L2)
- Red flags: upper motor neuron signs (hyperreflexia, upgoing toes), cauda equina or conus medullaris syndromes (saddle anesthesia, bowel or bladder dysfunction, reduced rectal tone, loss of sacral reflexes), pain at rest or at night
- Laboratory (depending on suspicion): CBC w/ diff, ESR/CRP, Ca, PO_4, CSF, BCx
- Neuroimaging: low yield if nonradiating pain, high false ⊕ rate (incidental spondylosis); depending on suspicion: X-rays, CT or CT myelography, MRI, bone scan
- EMG/NCS: may be useful to distinguish root/plexopathies from peripheral neuropathies

SPINAL CORD COMPRESSION

Clinical features

- Etiologies: tumor (vertebral mets, intradural meningioma/neurofibroma), epidural abscess or hematoma, vascular malformation (dural AV fistula), degenerative dis. (spondylosis)
- Acute: flaccid paraparesis and absent reflexes ("spinal shock")
- Subacute–chronic: spastic paraparesis and hyperreflexia (upgoing toes ± ankle clonus)
- Posterior column dysfunction in legs (loss of vibratory and/or proprioceptive sense)
- Sensory loss below level of lesion (truncal level ± bilateral leg sx is clue for cord process)

Evaluation & treatment

- Empiric spine immobilization (collar, board) for all trauma patients
- STAT MRI (at and above clinical spinal level, with gadolinium) or CT myelogram
- Emergent neurosurgical and/or neurology consultation. Urgent radiation therapy ± surgery for compression if due to metastatic disease (*Lancet Oncol* 2017;18:e720).
- Empiric broad-spectrum antibiotics ± surgery if c/f epidural abscess
- High-dose steroids depending on cause:
  Tumor: dexamethasone 16 mg/d IV (usually 4 mg q6h) with slow taper over wks
  Trauma: methylprednisolone 30 mg/kg IV over 15 min then 5.4 mg/kg/h × 24 h (if started w/in 3 h of injury) or × 48 h (if started 3–8 h after injury) (*Cochrane* 2012:CD001046)

NERVE ROOT COMPRESSION

Clinical features (*NEJM* 2015;372:1240)

- Radicular pain aggravated by activity (esp. bending, straining, coughing), relieved by lying
- Sciatica = radicular pain radiating from buttocks down lateral aspect of leg, often to knee or lateral calf ± numbness and paresthesias radiating to lateral foot. Caused by compression of nerve roots, plexus, or sciatic nerve.

Pathophysiology

- <65 y: 90% from disc herniation. ≥65 y also w/ more degenerative contributors: ligamentous hypertrophy, osteophyte formation, facet arthropathy, neural foraminal narrowing
- Spinal stenosis: central canal narrowing → root compression via direct impingement, CSF flow obstruction, vascular compromise

Disc Herniation: Cervical and Lumbar Radiculopathy					
Disc	**Root**	**Pain/paresthesias**	**Sensory Loss**	**Motor Loss**	**Reflex Loss**
C4–C5	C5	Neck, shoulder, upper arm	Shoulder, lateral arm	Deltoid, biceps, infraspinatus	Biceps
C5–C6	C6	Neck, shoulder, lat. arm, radial forearm, thumb & index finger	Radial forearm, thumb & index finger	Biceps brachioradialis	Biceps, brachio-radialis, supinator
C6–C7	C7	Neck, lat. arm, ring & index fingers	Index & middle fingers	Triceps, extensor carpi ulnaris	Triceps, supinator
C7–T1	C8	Ulnar forearm and hand	Ulnar half of ring finger, little finger	Intrinsic hand muscles, flexor dig profundus	Finger flexion
L3–L4	L4	Anterior thigh, inner shin	Anteromedial lower leg, inner foot	Quadriceps	Patella
L4–L5	L5	Lat. thigh & calf, dorsum of foot, great toe	Lat. calf & great toe	Foot dorsiflex., invers. & evers., toe extension	Medial hamstring
L5–S1	S1	Back of thigh, lateral posterior calf, lat. foot	Lateral foot & toes, sole of foot	Gastrocnemius	Achilles

Nb, lumbar disc protrusion tends to compress the nerve root that exits 1 vertebral level below the protrusion.

Neurogenic vs. Vascular Claudication		
Features	Neurogenic Claudication	Vascular Claudication
Cause	Lumbar spinal stenosis (with nerve root compression)	Peripheral artery disease (with limb ischemia)
Pain	Radicular back/buttock pain Radiating down legs	Cramping leg pain Mostly in calves; radiating up legs
Worse with	Walking & standing Hyperextension/lying prone	Walking Biking
Better with	Bending forward, sitting	Rest (standing or sitting)
Other sx	Numbness/paresthesias	Pale, cool extremity
Exam	± Focal weakness, ↓ reflexes ↓ Lumbar extension Preserved pulses	Diminished/absent pulses (dorsalis pedis/posterior tibialis) Pallor
Diagnostic studies	MRI lumbar spine CT myelogram (if no MRI) EMG/NCS	Arterial Doppler studies Ankle-brachial index (ABI) Arteriography
Treatment	PT (flexion exercise), NSAIDs, epidural steroid injections (ESI)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

	Surgery (if other Rx fails)	

Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. (*NEJM* 2007;356:1241 & 2008;358:818)

Evaluation & treatment of nerve root compression (*NEJM* 2016;374:1763)

- MRI if sx not improved after 6 wk of conservative tx; if non-diagnostic, consider EMG/NCS
- Conservative: avoid bending/lifting; soft collar (cervical radiculopathy); NSAIDs; muscle relaxants; lidocaine patch/ointment; Rx neuropathic pain (see "Peripheral Neuropathies"); physical therapy. Insufficient evidence to recommend oral steroids.
- Avoid opiates when possible; risks outweigh benefits in noncancerous back pain
- Spinal epidural steroid injections (ESI): limited short-term relief of refractory radicular pain
- Surgery: cord compression or cauda equina syndrome; progressive motor dysfunction; bowel/bladder dysfunction; failure to respond to conservative Rx after 3 mo

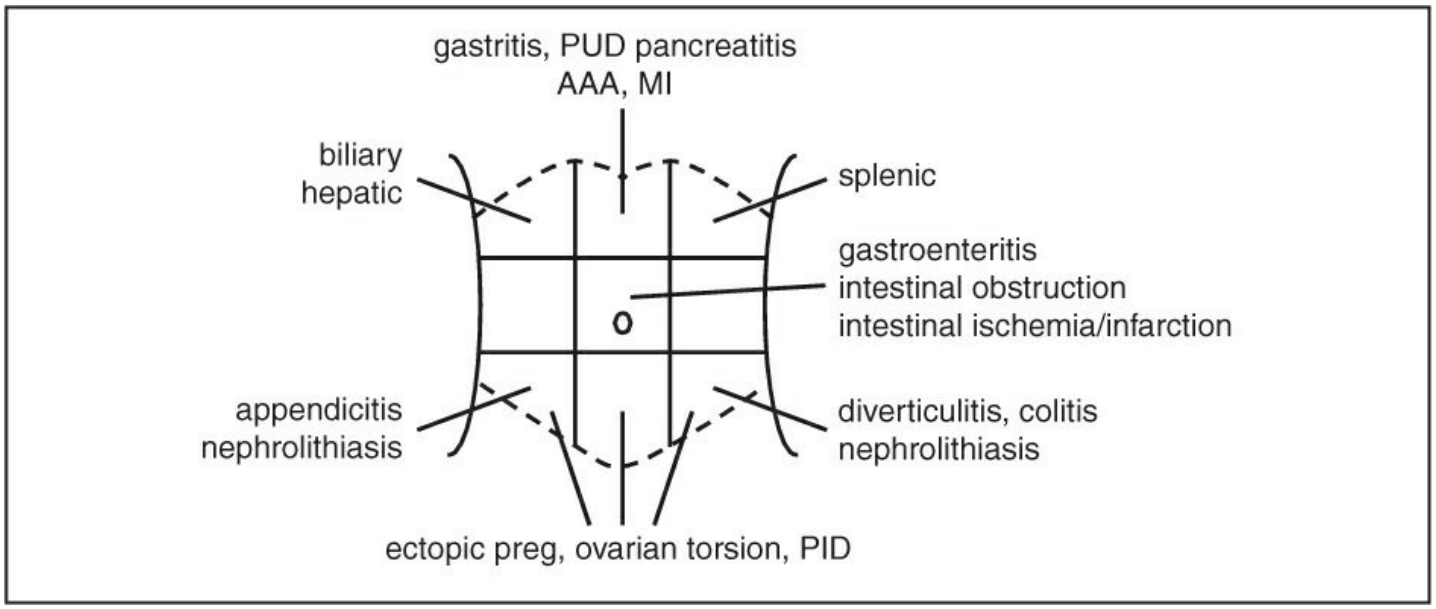
SURGICAL ISSUES

ABDOMINAL PAIN

Visceral Pain		
Anatomic Division	Viscera	Area to Which Pain Referred
Foregut	Esophagus & duodenum	Epigastrium
Midgut	Jejunum to mid-transverse colon	Umbilicus
Hindgut	Mid-transverse colon to rectum	Hypogastrium

Pain due to pancreatitis and nephrolithiasis commonly radiates to the back

Figure 10-1 Etiologies of abdominal pain based on location



Initial evaluation

- History: onset of pain, location, exacerbating/relieving factors
- Assoc. sx: fevers/chills, N/V, Δ in bowel habits (diarrhea/constipation, stool diam. or color, hematochezia, melena), jaundice, Δ in urine color, Δ in wt, menstrual hx in women
- PMHx: previous incisions or abdominal surgeries; Ob/Gyn hx
- Exam: VS; general posture of Pt; comprehensive abdominal exam looking for signs of peritonitis, which include rebound tenderness and involuntary guarding, abdominal wall rigidity, pain w/ percussion/minimal palpation; presence of hernias; rectal/pelvic
- Labs: CBC, electrolytes, LFTs, amylase/lipase, pregnancy test
- Imaging: depends on suspected etiology, may include RUQ U/S for biliary/hepatic disease, KUB for intestinal obstruction, CT for pancreatitis or intestinal disease. Do not delay resuscitation or surgical consultation for ill Pt while waiting for imaging.

ACUTE ABDOMEN

Definition
- Acute onset abdominal pain that portends need for urgent surgery

Etiologies
- Perforated viscus → peritonitis (perforated ulcer, complicated diverticulitis, trauma)
- Intraperitoneal or retroperitoneal bleed (also see "Acute Aortic Syndromes")
- Bowel obstruction (adhesions from previous surgeries, malignancies, hernias)
- Acute mesenteric ischemia (esp if afib, "pain out of proportion to exam")
- Mimics: severe pancreatitis can resemble peritonitis; renal colic causes severe abdominal pain but not abdominal rigidity

Initial evaluation
- H&P as above
- Labs as above plus: PT/INR, PTT, lactate, type & screen (crossmatch if active bleeding)
- Imaging: KUB (upright) or if stable, CT abd/pelvis w/ IV contrast (IV/PO if suspect obstruction)

Initial management
- Immediate surgical consultation for suspected acute abdomen
- NPO, start IV fluids (NS or LR), Foley, NGT placement if obstruction suspected
- Broad spectrum abx if perforation suspected

EXTREMITY EMERGENCIES

Acute limb ischemia (see "Peripheral Artery Disease" for details)
- Definition: sudden ↓ in perfusion causing threat to limb viability
- Eval: detailed vascular exam (incl. pulses & Doppler signals, motor/sensory function); CTA
- Initial management: anticoag for embolism/thrombosis (heparin dose 80 U/kg bolus, then 18 U/kg drip); immediate surgical consultation

Compartment syndrome (*Clin Orthop Relat Res* 2010;468:940)
- Definition: ↑ intracompartmental pressure w/ compressive closure of venules → ↑ hydrostatic force resulting in further increases in compartment pressure
- Etiologies: orthopedic (fracture), vascular (ischemia-reperfusion), iatrogenic (eg, vascular injury in anticoagulated Pt), soft tissue injury (eg, prolonged limb compression)
- Clinical manifestations: pain esp. on passive movement, swollen/tense compartment, paraesthesia, pallor, pulselessness, paralysis (late)
- Evaluation: surgical evaluation of compartment pressures; intracompartment pressure >30 or difference between diastolic & intracompartment pressure of >10–30 is diagnostic
- Treatment: fasciotomy

SURGICAL TUBES, DRAINS, WOUNDS

Tracheostomy (*Otolaryngol Head Neck Surg* 2013;148:6)

- Typically a cuffed tube, which creates a tight seal to facilitate ventilation throughout tube
- Speaking valve (eg, Passy-Muir): 1-way valve that allows inhalation through tube, but exhalation around tube through vocal cords (nb, cuff should not be inflated)
- 1st routine tube Δ for *percutaneously* placed tubes should be ~10 d postop; *surgically* placed tubes can be Δ'd >5 d postop; first Δ should be overseen by experienced person
- Accidental dislodgement: intubate from above (if airway/vent nec & anatomically possible)
  w/in 7 d of placement: emergent surgical consultation
  >7 d after placement: replace with a similar size tube or smaller

Chest tubes (*Eur J Cardiothorac Surg* 2011;40:291)

- Inserted for PTX, chest trauma or after thoracic surg for drainage of air/ fluid from thoracic cavity. Range from small (8-10 Fr for spont PTX) to large (28-32 Fr after pulm resections)
- Connected to 3-chamber chest drainage system:
  1st: collection chamber for pleural fluid
  2nd: water seal chamber used to allow air to exit pleural space on exhalation and prevent air from entering on inhalation
  3rd: suction control chamber which regulates suction transmitted to pleural space
- Monitor for output and presence of air leak (indicated by bubbling in *water seal chamber*)
- Removal determined by overall daily outputs and presence of air leak
- If accidentally removed or dislodged, tube should be completely removed and an occlusive dressing (eg, 4 × 4 covered w/ Tegaderm or silk tape) should be placed *rapidly* over site. CXR STAT; new tube should be placed if persistent PTX.

Gastrostomy/jejunostomy tubes (*Paediatr Child Health* 2011;16:281)

- Placed for tube feedings, hydration, and delivery of medications
- Should not be removed for ≥6–8 wk to allow establishment of mature gastrocutaneous tract
- Obstructed tubes can be cleared by flushing with agents such as carbonated water, meat tenderizer, & pancreatic enzymes. ↓ obstruction by flushing before & after meds and flushing q4–6h when receiving continuous feeds.
- Inadvertent removal: place Foley catheter of similar size or smaller into tract *immediately* to prevent stoma from closing. Tube then replaced and confirmed via fluoro study.

Suture/staple removal

- Should be done in consultation w/ surgical team; timing depends on location of wound
- *Should not be removed if there is evidence of wound separation during removal!*
- After removal, wound should be reapproximated w/ Steri-Strips

Decubitus ulcers (*J Wound Ostomy Continence Nurs* 2012;39:3)

- Sores in dependent areas exposed to repeated pressure (commonly sacrum, heels)
- Risk factors: immobility, poor nutritional status
- Stage I (non-blanchable erythema); Stage II (partial thickness); Stage III (full-thickness skin loss); Stage IV (full-thickness tissue loss)

- Treatment: offload area, air mattress, pillows and/or support boots, nutritional support
- Surgical consultation for debridement of ulcers with necrotic or infected tissue, may require plastic surgical reconstruction for advanced ulcers once clean

---

MAXIMIZING A SURGICAL CONSULT

- For ill Pt, call surgical consult early, do not wait for labs & imaging results
- If potential surgical emergency, make Pt NPO, start IVF, ✔ coags, type, & screen
- Have appropriate-level MD who knows & has examined Pt call consult

OB/GYN ISSUES

VAGINAL BLEEDING

Bleeding from lower (vulva, vagina, cervix) or upper genital tract (uterus)

Etiologies

- Premenopausal
  - Not pregnant: menses, lower tract (trauma, STI, cervical dysplasia/cancer), & abnormal uterine bleeding (polyp, adenomyosis, leiomyoma, hyperplasia/cancer, coagulopathy, ovulatory dysfunction, endometrial, & iatrogenic)
  - Pregnant
    - 1st trimester: threatened abortion, spont. abortion (missed, incomplete, or complete), ectopic preg, molar preg (partial/complete hydatidiform mole)
    - 2nd or 3rd trimester: preterm labor/labor, placenta previa, placental abruption
- Postmenopausal: atrophy, polyp, leiomyoma, endometrial hyperplasia/cancer

History & exam

- Age, menopausal status, gestational age if preg, volume & duration of current bleeding
- If premenopausal: menstrual hx including age of onset, interval between & duration of menses, any assoc. sx & LMP to assess timing of menstrual cycle
- Past Ob/Gyn hx: incl. any structural abnl, STI, & contraception
- Health maint.: Pap smear, HPV screening, domestic violence, anticoag/antiplt meds
- General physical & abdominal exam (incl. tenderness, masses)
- Pelvic exam: external (quantity of bleeding seen on vulva, any lesions, any trauma), speculum exam (quantity of bleeding, cervical os open/close; & if open, dilation, any polyps), & bimanual exam (cervical dilation, uterine size/tenderness, adnexal mass/tenderness)

Laboratory evaluation & imaging

- Urine (rapid test) & serum preg test (βhCG), Hct/hemoglobin
- Pelvic U/S: visualize leiomyoma & if preg, intrauterine preg & placental position to r/o placenta previa/abruption
- If preg & intrauterine preg not seen, *must r/o ectopic as life-threatening dx* (βHCG > discrim. zone → ? ectopic; if βHCG < discrim. zone → follow βHCG) (*JAMA* 2013;309:1722)

VAGINAL DISCHARGE

Fluid or mucus from vagina, cervix, or uterus

Etiologies

- Infectious: bacterial vaginosis, candida vulvovaginitis, trichomoniasis

- Noninfectious: physiologic (in preg/non-preg), rupture of membranes, foreign-body rxn

Initial evaluation

- Age, LMP, gestational age if preg or menopausal status
- Discharge quantity, color, consistency, odor, assoc. sx (itchiness, redness, abd/pelvic pain)
- Past Gyn hx: incl. STI and contraception usage (condoms ↓ STI risk)
- Tampon or condom use as risk factors for retained foreign body
- Pelvic exam: external (quantity & quality of discharge on vulva, any lesions), speculum (discharge, appearance of cervix), bimanual (cervical motion tenderness)
- Laboratory: pH of discharge, microscopy (saline & KOH wet mounts), urine preg test

Treatment

- Bacterial vaginosis: oral/vaginal metronidazole or clindamycin
- Candida vulvovaginitis: oral/topical antimycotic medications
- Trichomoniasis: oral metronidazole

ADNEXAL MASS IN NON-PREGNANT WOMAN

Mass arising from ovary, fallopian tube, or surrounding connective tissue

Etiologies

- Ovarian: functional cyst (follicular/corpus luteum), hemorrhagic cyst, endometriomas, ovarian torsion, tubo-ovarian abscess, benign & malignant ovarian tumors
- Fallopian tube: paratubal cyst, hydrosalpinx, ovarian torsion, tubo-ovarian abscess

Initial evaluation

- LMP/menopausal status, assoc. sx of abd/pelvic pain, FHx of gyn cancers
- Abd exam (distension, tenderness, masses), bimanual (uterine or adnexal masses)
- Preg test if premenopausal (if ⊕, then mass likely preg), CA-125 if postmenopausal
- Pelvic U/S (even if mass 1st identified on CT, because U/S is best modality), U/S appearance of mass important factor to determine risk of malignancy

OPHTHALMIC ISSUES

INITIAL EVALUATION

- Ocular symptom: onset (sudden or progressive) & duration of sx; unilateral vs. bilateral; pain; photophobia; discharge; Δ in near (eg, book) or far (eg, TV across room) vision
- Pre-existing ocular conditions, eye meds (incl any Δs), recent h/o ocular surgery, trauma
- Ocular exam: vision (✔ with Pt's correction [glasses/contacts]) w/ each eye; pupillary exam; EOM; confrontation visual fields (important if suspect CNS problem)
- Overall: VS, immunocomp., s/s of infxn, h/o malig, CNS issues, Δ in meds, CBC, coags

COMMON VISUAL SYMPTOMS

- Fluctuation in vision (ie, blurry): med-induced refractive error (eg, systemic steroids, chemoRx), hyperglycemia, dry eye (common). Visual defect may p/w "blurred vision." Bilateral: glaucoma (common), homonymous contral. CNS lesion; bitemporal: pituitary, toxic/nutritional. Unilateral: ipsilateral orbital, retinal, or optic nerve lesion.
- Red eye:
  Bilateral: viral conjunct., (starts in 1 eye; also w/ lid swelling, discharge); chronic inflammation (dry eyes, rosacea, autoimmune disease)
  Unilateral: subconj. hemorrhage, infxn, or inflam (eg, episcleritis, iritis, uveitis, scleritis); acute angle closure (qv). Scleritis & acute angle closure p/w severe pain, H/A, nausea.
- Double vision (diplopia): fixed double vision w/ ophthalmoplegia from orbital process or cranial nerve palsy (III, IV, VI). Transient "diplopia" due to fatigue or sedation.
- Flashing lights/floaters: vitreous detach. (common, benign); retinal detach. (unilateral visual field defect; urgent ophthalmology consult); hemorrhage; intraocular lymphoma

ACUTE VISUAL CHANGES

Etiologies of Acute Vision Loss (italics indicates a/w pain)		
	Unilateral	Bilateral
Transient (<24 h, often <1 h)	Ret. art. embolism, impending retinal artery or vein occlusion (amaurosis fugax), vasospasm, carotid disease	Ocular surface dis. (dry eye), bilat. carotid dis., TIA, migraine, high ICP (papilledema)
Prolonged (>24 h)	Retinal art/vein occl, retinal detach., retina/vitreous heme, retinitis, ant. optic neurop./*corneal ulcer, GCA, acute angle closure glaucoma*	Visual cortex stroke, post. ischemic neuropathy (profound hypotension during surgery), post. reversible enceph. synd., *GCA*

COMMON OCULAR CONDITIONS (FRONT TO BACK)

- Orbit: orbital cellulitis (fever, proptosis, ↓ EOM; *emergent abx, scan & referral*)
- Lids: hordeolum or chalazion (stye); preseptal cellulitis; ptosis (age; Horner's; CN III palsy: EOM restricted in all directions except laterally [eye is "down & out"], a/w ptosis & mydriasis, seen w/ uncal herniation, aneurysm of post com art., GCA, HTN, DM); incomplete lid closure (CN 7th palsy)
- Conjunctiva: conjunctivitis (red eye); subconj. hemorrhage (HTN, blood thinner); ocular surface disease (dry eyes); episcleritis/scleritis (deep vessels of sclera)
- Cornea: contact lens–related ulcer; herpetic keratitis/scarring/neurotropic ulcers (CN V paresis); pterygium; keratoconus; corneal dystrophy
- Ant. chamber: iritis (inflam. cells); hyphema (blood, post trauma); hypopyon (inflam./infxn)
- Pupil: Anisocoria (physiologic asymmetry); Horner's, CN III
- Lens: cataract (age, trauma, medication, radiation, congenital); post cataract surgery infxn
- Vitreous/Retina/Macula: diabetic retinopathy; macular degen; retinal detachment; retinal ± vitreous hemorrhage; retinitis (infectious)
- Optic nerve (CN II): ischemic neuropathy p/w acute unilat. visual loss, altitudinal field defect; a/w GCA; nonarteritic a/w HTN, hyperchol., DM, thrombophilia. Optic neuritis: often p/w unilat. central scotoma, pain w/ EOM, ↑ visual loss over days; a/w demyelinating disease (eg, MS), also seen w/ sarcoidosis & CTD. Optic neuropathy (glaucoma common).

OCULAR EMERGENCIES

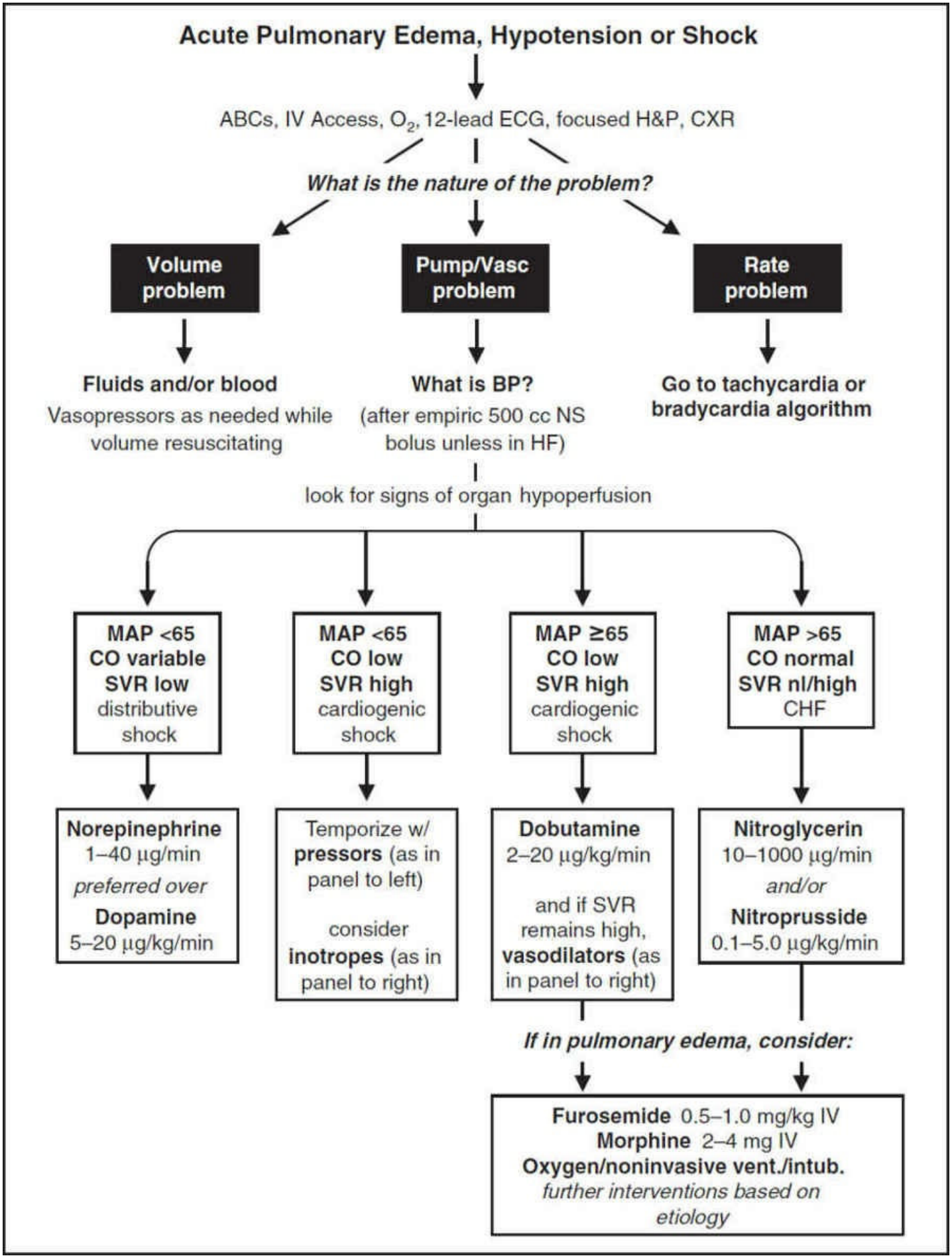
- Chemical splash: alkali worse than acid; immediate eye flush; pH 7.3–7.4 normal
- Acute angle closure glaucoma: fixed mid-dilated pupil, corneal edema, high intraocular pressure (typically >50; normal 8–21). Rx w/ topical drops; may require AC tap/laser.
- Penetrating eye injury: protect eye (no patching), IV abx, tetanus, NPO, surgical prep

ICU MEDICATIONS

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes, and Chronotropes			
Phenylephrine	α_1	10–300 μg/min	
Norepinephrine	$\alpha_1 > \beta_1$	1–40 μg/min	
Vasopressin	V_1	0.01–0.1 U/min (usually <0.04)	
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$	2–20 μg/min	
Isoproterenol	β_1, β_2	0.1–10 μg/min	
Dopamine	D β, D α, β, D	0.5–2 μg/kg/min 2–10 μg/kg/min >10 μg/kg/min	50–200 μg/min 200–500 μg/min 500–1000 μg/min
Dobutamine	$\beta_1 > \beta_2$	2–20 μg/kg/min	50–1000 μg/min
Milrinone	PDE	± 50 μg/kg over 10 min then 0.25–0.75 μg/kg/min	3–4 mg over 10 min then 20–50 μg/min
Vasodilators			
Nitroglycerin	NO	5–500 μg/min	
Nitroprusside	NO	0.25–10 μg/kg/min	10–800 μg/min
Labetalol	α_1, β_1 and β_2 blocker	20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 μg/kg/min	10–120 μg/min
Clevidipine	CCB	1–32 mg/h	
Epoprostenol	vasodilator	2–20 ng/kg/min	
Antiarrhythmics			
Amiodarone	K *et al.* (Class III)	150 mg over 10 min, then 1 mg/min × 6 h, then 0.5 mg/min × 18 h	
Lidocaine	Na channel (Class IB)	1–1.5 mg/kg then 1–4 mg/min	100 mg then 1–4 mg/min
Procainamide	Na channel (Class IA)	17 mg/kg over 60 min then 1–4 mg/min	1 g over 60 min then 1–4 mg/min
Ibutilide	K channel (Class III)	1 mg over 10 min, may repeat × 1	
Propranolol	β blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	$\beta_1 > \beta_2$ blocker	500–1000 μg/kg then 50–200 μg/kg/min	20–40 mg over 1 min then 2–20 mg/min
Verapamil	CCB	2.5–5 mg over 1–2′, repeat 5–10 mg in 15–30′ prn 5–20 mg/h	
Diltiazem	CCB	0.25 mg/kg over 2 min reload 0.35 mg/kg × 1 prn then 5–15 mg/h	20 mg over 2 min reload 25 mg × 1 prn then 5–15 mg/h
Adenosine	purinergic	6 mg rapid push; if no response: 12 mg → 12–18 mg	
Sedation			
Morphine	opioid	1–30 (in theory, unlimited) mg/h	
Fentanyl	opioid	50–100 μg then 50–800 (? unlimited) μg/h	
Propofol	anesthetic	1–3 mg/kg then 0.3–5 mg/kg/h	50–200 mg then 20–400 mg/h
Dexmedetomidine	α_2 agonist	1 μg/kg over 10 min → 0.2–0.7 μg/kg/h	
Diazepam	BDZ	1–5 mg q1–2h then q6h prn	
Midazolam	BDZ	0.5–2 mg q5min prn; 0.02–0.1 mg/kg/h or 1–10 mg/h	
Lorazepam	BDZ	0.01–0.1 mg/kg/h	
Naloxone	opioid antag.	0.4–2 mg q2–3min to total of 10 mg	
Flumazenil	BDZ antag.	0.2 mg over 30 sec then 0.3 mg over 30 sec prn may repeat 0.5 mg over 30 sec to total of 3 mg	

Miscellaneous			
Aminophylline	PDE	5.5 mg/kg over 20 min then 0.5–1 mg/kg/h	250–500 mg then 10–80 mg/h
Octreotide	somatostatin analog	50 μg then 50 μg/h	
Glucagon	hormone	3–10 mg IV slowly over 3–5 min then 3–5 mg/h	
Mannitol	osmole	1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320	

Figure 11-1 ACLS pulmonary edema, hypotension or shock algorithm



(Adapted from ACLS 2005 Guidelines)

ANTIBIOTICS

The following tables of spectra of activity for different antibiotics are generalizations. Sensitivity data at your own institution should be used to guide therapy.

Penicillins		
Generation	Properties	Spectrum
Natural (eg, penicillin)	Some GPC, GPR, GNC, many anaerobes (not *Bacteroides*)	Group A strep, Enterococci, *Listeria, Pasteurella, Actinomyces*, Syphilis
Anti-staph (eg, nafcillin)	Active vs. PCNase-producing Staph Little activity vs. Gram ⊖	Staphylococci (except MRSA) Streptococci
Amino (eg, ampicillin)	Penetrate porin channel of Gram ⊖ Not stable against PCNases	*E. coli, Proteus, Listeria, H. influenzae Salmonella, Shigella, Enterococci*
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. *Enterobacter, Pseudomonas, Serratia*
Carbapenems (eg, imipenem)	Resistant to most β-lactamases	Most Gram ⊕ & ⊖, incl. anaerobes; *not* MRSA or VRE
Monobactams (aztreonam)	Active vs. Gram ⊖ but not Gram ⊕	Gram ⊖ bacterial infxn in Pt w/ PCN or Ceph allergy
β-lact. inhib. (eg, sulbactam, clavulanate)	Inhibit plasma-mediated β-lactamases	Adds staph, *B. fragilis*, & some GNR (*H. flu, M. cat*, some *E. coli*); intrinsic activity against *Acinetobacter*

Cephalosporins		
Resistant to most β-lactamases. No activity vs. enterococci.		
Gen.	Spectrum	Indications
1st (eg, cefazolin)	Most GPC (incl. staph & strep, not MRSA); some GNR (incl. *E. coli, Proteus, Klebsiella*)	Used for surgical Ppx & skin infxns
2nd (eg, cefuroxime, cefotetan)	↓ activity vs. GPC, ↑ vs. GNR. 2 subgroups: Resp: *H. influenzae* & *M. catarrhalis* GI/GU: ↑ activity vs. *B. fragilis*	 PNA/COPD flare Abdominal infxns
3rd (eg, ceftriaxone, ceftazidime)	Broad activity vs. GNR & some anaerobes. Ceftazidime active vs. *Pseudomonas*.	PNA, sepsis, meningitis
4th (eg, cefepime)	↑ resistance to β-lactamases (incl. of staph and *Enterobacter*)	Similar to 3rd gen. MonoRx for nonlocalizing febrile neutropenia
5th (eg, ceftaroline)	Only class of cephalosporin with MRSA activity. NOT active vs. *Pseudomonas*.	MRSA. Not 1st line for MRSA bacteremia.
Combination (eg, ceftolozane-tazobactam, ceftazidime-avibactam)	MDR GNRs, incl. *Pseudomonas*. Ceftaz-avi has activity vs. some carbapenemases.	Complicated UTIs, complicated intra-abdominal infections.

Other Antibiotics	
Antibiotic	Spectrum

Vancomycin	Gram ⊕ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
Linezolid	GPC incl. MRSA & VRE (check susceptibility for VRE)
Daptomycin	
Quinolones	Enteric GNR & atypicals. 3rd & 4th gen. ↑ activity vs. Gram ⊕.
Aminoglycosides	GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.
Macrolides	GPC, some respiratory Gram, atypicals
TMP/SMX	Some enteric GNR, *Stenotrophomonas*, PCP, *Nocardia, Toxo*, most community-acquired MRSA
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (↑ resis. to *B. fragilis*)
Metronidazole	Almost all anaerobic Gram, most anaerobic Gram ⊕
Doxycycline	*Rickettsia, Ehrlichia, Anaplasma, Chlamydia, Mycoplasma, Nocardia*, Lyme
Tigecycline	Many GPC incl. MRSA & VRE; some GNR incl. ESBL but not *Pseudomonas* or *Proteus.*

Treatment for Common Fungi
("x" indicates activity, shaded boxes indicate 1st-line treatment)

Antifungal	*C.albicans*	*C. glabrata & krusei*	Crypto	Endemic Histo, Blasto, Coccidio	Aspergillus	Mucor
Fluconazole	x		x			
Itraconazole	x		x	x		
Voriconazole	x	x	x	x	x	
Posaconazole	x	x	x	x	x	x
Isavuconazole	x		x		x	x
Micafungin	x	x			x	
Ampho B	x	x	x	x	x	x

FORMULAE AND QUICK REFERENCE

CARDIOLOGY

Hemodynamic Parameters	Normal Value
Mean arterial pressure (MAP) = $\frac{SBP + (DBP \times 2)}{3}$	70–100 mmHg
Heart rate (HR)	60–100 bpm
Right atrial pressure (RA)	≤6 mmHg
Right ventricular (RV)	systolic 15–30 mmHg diastolic 1–8 mmHg
Pulmonary artery (PA)	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
Pulmonary capillary wedge pressure (PCWP)	≤12 mmHg
Cardiac output (CO)	4–8 L/min
Cardiac index (CI) = $\frac{CO}{BSA}$	2.6–4.2 L/min/m^2
Stroke volume (SV) = $\frac{CO}{HR}$	60–120 mL/contraction
Stroke volume index (SVI) = $\frac{CI}{HR}$	40–50 mL/contraction/m^2
Systemic vascular resistance (SVR) = $\frac{MAP - \text{mean RA}}{CO} \times 80$	800–1200 dynes × sec/cm^5
Pulmonary vascular resistance (PVR) = $\frac{\text{mean PA} - \text{mean PCWP}}{CO} \times 80$	120–250 dynes × sec/cm^5

"Rule of 6s" for PAC: RA ≤6, RV ≤30/6, PA ≤30/12, WP ≤12. Nb 1 mmHg = 1.36 cm water or blood.

Fick cardiac output

Oxygen consumption (L/min) = CO (L/min) × arteriovenous (AV) oxygen difference

CO = oxygen consumption/AV oxygen difference

Oxygen consumption must be measured (can estimate w/ 125 mL/min/m^2, but inaccurate)
AV oxygen difference = Hb (g/dL) × 10 (dL/L) × 1.36 (mL O_2/g of Hb) × (S_aO_2–$S_{MV}O_2$)

S_aO_2 is measured in any arterial sample (usually 93–98%)

$S_{MV}O_2$ (mixed venous O_2) is measured in RA, RV, or PA (assuming no shunt) (nl ~75%)

$$\therefore \textbf{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6\ (S_aO_2 - S_vO_2)}$$

Assessment of RV function (*Circ* 2017;136:314)

PAPi = Pulmonary artery pulsatility index = [PA systolic – PA diastolic] / RA pressure >1.0 predicts RV failure in acute MI; <1.85 predicts RV failure after LVAD

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein } O_2 \text{ sat} - \text{Pulm. artery } O_2 \text{ sat}} \quad (\text{if no R} \rightarrow \text{L shunt, PV } O_2 \text{ sat} \approx S_aO_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{S_aO_2 - \text{mixed venous } O_2 \text{ sat}} \quad (MVO_2 \text{ drawn proximal to potential L} \rightarrow \text{R shunt})$$

$$\frac{Q_p}{Q_s} = \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{\text{PV } O_2 \text{ sat} - \text{PA } O_2 \text{ sat}} \approx \frac{S_aO_2 - \text{MV } O_2 \text{ sat}}{S_aO_2 - \text{PA } O_2 \text{ sat}} \quad (\text{if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt})$$

Valve equations

Simplified Bernoulli: Pressure gradient (∇P) = $4 \times v^2$ (where v = peak flow velocity)

Continuity (conservation of flow): $\text{Area}_1 \times \text{Velocity}_1 = A_2 \times V_2$ (where 1 & 2 different points)

$$\text{or: AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{LVOT}}{V_{AoV}}\right) \quad (\text{all of which can be measured on echo})$$

$$\text{Gorlin equation: Valve area} = \frac{\text{CO}/(\text{DEP or SEP}) \times \text{HR}}{44.3 \times \text{constant} \times \sqrt{\nabla P}} \quad (\text{constant} = 1 \text{ for AS, } 0.85 \text{ for MS})$$

$$\text{Hakki equation: Valve area} \approx \frac{\text{CO}}{\sqrt{\nabla P}}$$

PULMONARY

Chest Imaging (CXR & CT) Patterns		
Pattern	Pathophysiology	Ddx
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	*Acute:* water (pulm edema), pus (PNA), blood *Chronic:* neoplasm (BAC, lymphoma), aspiration, inflammatory (COP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels	*Acute:* pulm edema, infxn (PCP, viral, resolving bact. PNA) *Chronic:* ILD

	visible)	w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
Septal lines Kerley A & B	Radiopaque material in septae	Cardiogenic pulm edema, interstitial PNA viral, mycoplasma, lymphangitic tumor
Reticular	Lace-like net (ILD)	ILD (esp. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	*Cavitary:* Primary or metastatic cancer, TB (react. or miliary), fungus, Wegener's, RA septic emboli, PNA *Noncavitary:* any of above + sarcoid, hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	PE, cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	Bronchopneumonia, endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, COP
Hilar fullness	↑ LN or pulm arteries	Neoplasm (lung, mets, lymphoma) Infxn (AIDS); Granuloma (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	TB, fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	Aspiration, bronchiect., IPF, RA, SLE, asbestos
Peripheral	n/a	COP, IPF & DIP, eos PNA, asbestosis

CXR in heart failure

- ↑ cardiac silhouette (in systolic dysfxn, not in diastolic)
- Pulmonary venous hypertension: cephalization of vessels (vessels size > bronchi in upper lobes), peribronchial cuffing (fluid around bronchi seen on end → small circles), Kerley B lines (horizontal 1–2-cm lines at bases), ↑ vascular pedicle width, loss of sharp vascular margins, pleural effusions (~75% bilateral)
- Pulmonary edema: ranges from ground glass to consolidation; often dependent and central, sparing outer third ("bat wing" appearance)

Dead space = lung units that are ventilated but not perfused

Intrapulmonary shunt = lung units that are perfused but not ventilated

Alveolar gas equation: $P_AO_2 = [F_IO_2 \times (760 - 47)] - \frac{P_aCO_2}{R}$ (where $R \approx 0.8$)

$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8} \text{ (on room air)}$$

A-a gradient = $P_AO_2 - P_aO_2$ [normal A-a gradient ≈ 4 + (age/4)]

Minute ventilation (V_E) = tidal volume (V_T) × respiratory rate (RR)(nl 4–6 L/min)

Tidal volume (V_T) = alveolar space (V_A) + dead space (V_D)

Fraction of tidal volume that is dead space $\left(\frac{V_D}{V_T}\right) = \frac{P_aCO_2 - P_{expired}CO_2}{P_aCO_2}$

$$P_aCO_2 = k \times \frac{CO_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T}\right)}$$

GASTROENTEROLOGY

Modified Child-Turcotte-Pugh (CPS) Scoring System			
	Points Scored		
	1	**2**	**3**
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (sec > control) or INR	<4 <1.7	4–6 1.8–2.3	>6 >2.3
	Classification		
	A	**B**	**C**
Total points	5–6	7–9	10–15
1-y survival	100%	80%	45%

NEPHROLOGY

Anion gap (AG) = Na – (Cl + HCO_3) (normal = [alb] × 2.5; typically 12 ± 2 mEq)
Delta-delta (ΔΔ) = [Δ AG (ie, calc. AG – expected) / Δ HCO_3 (ie, 24 – measured HCO_3)]
Urine anion gap (UAG) = (UN_a + U_K) – U_{Cl}

Calculated osmoles $= (2 \times \text{Na}) + \left(\frac{\text{glc}}{18}\right) + \left(\frac{\text{BUN}}{2.8}\right) + \left(\frac{\text{EtOH}}{4.6}\right)$

Osmolal gap (OG) = measured osmoles – calculated osmoles (normal <10)

Estimated creatinine clearance $= \frac{[140 - \text{age (yr)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dL)} \times 72}$ (× 0.85 in women)

Fractional excretion of Na $(FE_{Na}, \%) = \left[\frac{\frac{U_{Na}(\text{mEq/L})}{P_{Na}(\text{mEq/L})} \times 100\%}{\frac{U_{Cr}(\text{mg/mL})}{P_{Cr}(\text{mg/dL})} \times 100\ (\text{mL/dL})}\right] = \frac{\frac{U_{Na}}{P_{Na}}}{\frac{U_{Cr}}{P_{Cr}}}$

Corrected Na in hyperglycemia

Estimate in all Pts: corrected Na = measured Na + $\left[2.4 \times \frac{(\text{measured glc} - 100)}{100}\right]$

However, Δ in Na depends on glc (*Am J Med* 1999;106:399)
Δ is 1.6 mEq per each 100 mg/dL ↑ in glc ranging from 100–440
Δ is 4 mEq per each 100 mg/dL ↑ in glc beyond 440

Total body water (TBW) = 0.60 × IBW (× 0.85 if female and × 0.85 if elderly)

$$\text{Free } H_2O \text{ deficit} = TBW \times \left(\frac{[Na]_{serum} - 140}{140}\right) \approx \left(\frac{[Na]_{serum} - 140}{3}\right) \text{(in 70-kg Pt)}$$

Trans-tubular potassium gradient (TTKG) = $[U_K / P_K] / [U_{Osm} / P_{Osm}]$

HEMATOLOGY

Peripheral Smear Findings (also see Photo Inserts)	
Feature	Abnormalities and Diagnoses
Size	normocytic vs. microcytic vs. macrocytic → see below
Shape	Anisocytosis → unequal RBC size; poikilocytosis → irregular RBC shape acanthocytes = spur cells (irregular sharp projections) → liver disease Bite cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = burr cells (even, regular projections) → uremia, artifact Pencil cell → long, thin, hypochromic - very common in adv. iron deficiency Rouleaux → hyperglobulinemia (eg, multiple myeloma) Schistocytes, helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve Spherocytes → HS, AIHA; sickle cells → sickle cell anemia Stomatocyte → central pallor appears as curved slit → liver disease, EtOH Target cells → liver disease, hemoglobinopathies, splenectomy Tear drop cells = dacryocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia
Intra- RBC findings	Basophilic stippling (ribosomes) → abnl Hb, sideroblastic, megaloblastic Heinz bodies (denatured Hb) → G6PD deficiency, thalassemia Howell-Jolly bodies (nuclear fragments) → splenectomy or functional asplenia (eg, advanced sickle cell) Nucleated RBCs → hemolysis, extramedullary hematopoiesis
WBC findings	Blasts → leukemia, lymphoma; Auer rods → acute myelogenous leukemia Hypersegmented (>5 lobes) PMNs: megaloblastic anemia (B_{12}/folate def.) Pseudo-Pelger-Huët anomaly (bilobed nucleus, "pince-nez") → MDS Toxic granules (coarse, dark blue) and Döhle bodies (blue patches of dilated endoplasmic reticulum) → (sepsis, severe inflammation)
Platelet	Clumping → artifact, repeat plt count # → periph blood plt count ~10,000 plt for every 1 plt seen at hpf (100×) Size → MPV (mean platelet volume) enlarged in ITP

(*NEJM* 2005;353:498)

Heparin for Thromboembolism	
80 U/kg bolus 18 U/kg/h	
PTT	Adjustment
<40	bolus 5000 U, ↑ rate 300 U/h
40–49	bolus 3000 U, ↑ rate 200 U/h
50–59	↑ rate 150 U/h
60–85	no Δ
86–95	↓ rate 100 U/h
96–120	hold 30 min, ↓ rate 100 U/h
>120	hold 60 min, ↓ rate 150 U/h

(Modified from *Chest* 2008;133:141S)

Heparin for ACS	
60 U/kg bolus (max 4000 U) 12 U/kg/h (max 1000 U/h)	
PTT	Adjustment
<40	bolus 3000 U, ↑ rate 100 U/h
40–49	↑ rate 100 U/h
50–75	no Δ
76–85	↓ rate 100 U/h
86–100	hold 30 min, ↓ rate 100 U/h
>100	hold 60 min, ↓ rate 200 U/h

(Modified from *Circ* 2007;116:e148 & *Chest* 2008;133:670)

✔ PTT q6h after every Δ ($t_{½}$ of heparin ~90 min) and then qd or bid once PTT is therapeutic
✔ CBC qd (to ensure Hct and plt counts are stable)

Warfarin Loading Nomogram					
Day	INR				
	<1.5	1.5–1.9	2–2.5	2.6–3	>3
1–3	5 mg (7.5 mg if >80 kg)		2.5–5 mg	0–2.5 mg	0 mg
4–5	10 mg	5–10 mg	0–5 mg		0–2.5 mg
6	Dose based on requirements over preceding 5 d				

(*Annals* 1997;126:133; *Archives* 1999;159:46) or, go to www.warfarindosing.org

Warfarin-heparin overlap therapy

- Indications: when failure to anticoagulate carries ↑ risk of morbidity or mortality (eg, DVT/PE, intracardiac thrombus)
- Rationale: (1) Half-life of factor VII (3–6 h) is shorter than half-life of factor II (60–72 h);
  ∴ warfarin can elevate PT *before achieving a true antithrombotic state*
  (2) Protein C also has half-life less than that of factor II;
  ∴ theoretical concern of *hypercoagulable state* before antithrombotic state
- Method: (1) Therapeutic PTT is achieved using heparin
  (2) Warfarin therapy is initiated
  (3) Heparin continued until INR therapeutic for ≥2 d and ≥4–5 d of warfarin (roughly corresponds to ~2 half-lives of factor II or a reduction to ~25%)

Common Warfarin-Drug Interactions	
Drugs that ↑ PT	Drugs that ↓ PT
Amiodarone Antimicrobials: erythromycin, ? clarithro, ciprofloxacin, MNZ, sulfonamides Antifungals: azoles Acetaminophen, cimetidine, levothyroxine	Antimicrobials: rifampin CNS: barbiturates, carbamazepine, phenytoin (initial transient ↑ PT) Cholestyramine

ENDOCRINOLOGY

Examples of Various Cosyntropin Stimulation Test Results			
0'	**30'**	**60'**	**Interpretation**
5.3	15.5	23.2	Normal stimulation test
1.5	13.3	21.1	Acute central AI (eg, apoplexy or CNS bleed). Can look normal.
1.2	1.5	2.0	1° AI (eg, Addisons or adrenal bleed). Flat or minimal stim.
0.8	10.0	19.7	Acute effect of glucocorticoids: low initial value but stims > threshold
5.3	7.2	8.9	Chronic 2° AI: some cortisol production and stim, but evidence of adrenal atrophy
6.7	19.5	17.2	"Early peak" (fast metab): ~5% of Pts peak at 30 rather than 60'
6.3	11.5	16.2	Equivocal test. Can occur due to mild AI, acute illness, liver disease, low cortisol binding protein, renal disease, etc.

NEUROLOGY

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)					
Assign points for each of the 10 criteria; each criteria is scored 0–7, except orientation, which is scored 0–4; add points to calculate score.					
Points	**Anxiety**	**Agitation**	**Tremor**	**HA**	**Orientation**
0	None	None	None	None	Oriented
1		Somewhat	Not visible, but felt at fingertips	Very mild	Cannot do serial additions
2				Mild	Disorient. by ≤2 d
3				Moderate	Disorient. by >2 d
4	Guarded	Restless	Moderate w/ hands extended	Mod severe	Disoriented to person or place
5				Severe	n/a
6				Very severe	n/a
7	Panic	Pacing or thrashing	Severe	Extremely severe	n/a
Points	**N/V**	**Sweats**	**Auditory Hallucinations**	**Visual Halluc.**	**Tactile Disturb**
0	None	None	None	None	None
1		Moist palms	Very mild	Very mild photosens.	Very mild paresthesias
2			Mild	Mild photosens.	Mild paresth.
3			Moderate	Mod photosens.	Mod paresth.
4	Intermit. w/ dry heaves	Beads	Mod severe	Mod severe visual halluc.	Mod severe hallucinations
5			Severe	Severe	Severe
6			Very severe	Very severe	Very severe
7	Constant	Drenching	Cont.	Continuous	Continuous
SCORE: <8 none to minimal withdrawal; 8–15 mild; 16–20 moderate; >20 severe					

OTHER

Ideal body weight (IBW) = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 feet

Body surface area (BSA, m^2) = $\sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

		Disease	
		Present	Absent
Test	⊕	a (true ⊕)	b (false ⊕)
	⊖	c (false ⊖)	d (true ⊖)

Sensitivity = $\frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a + c}$ **Specificity** = $\frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b + d}$

⊕ **Predictive value** = $\frac{\text{true positives}}{\text{all positives}} = \frac{a}{a + b}$

⊖ **Predictive value** = $\frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c + d}$

NOTES

ABBREVIATIONS

5′-NT	5′-nucleotidase
6-MP	6-mercaptopurine
AAA	abdominal aortic aneurysm
AAD	antiarrhythmic drug
Ab	antibody
ABE	acute bacterial endocarditis
ABG	arterial blood gas
abnl	abnormal
ABPA	allergic bronchopulmonary aspergillosis
abx	antibiotics
a/c	anticoagulation
AC	assist control
ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ACI	anemia of chronic inflammation
ACL	anticardiolipin antibody
ACLS	advanced cardiac life support
ACS	acute coronary syndrome
ACTH	adrenocorticotrophic hormone
ACV	acyclovir
ADA	adenosine deaminase
ADH	antidiuretic hormone
ADL	activities of daily living
AF	atrial fibrillation
AFB	acid-fast bacilli
AFL	atrial flutter
AFP	α-fetoprotein
AFTP	ascites fluid total protein
AG	aminoglycoside anion gap
Ag	antigen
AGN	acute glomerulonephritis
AI	adrenal insufficiency
	aortic insufficiency
	aromatase inhibitor
AIDS	acquired immunodefic. synd.

AIH	autoimmune hepatitis
AIHA	autoimmune hemolytic anemia
AIN	acute interstitial nephritis
AIP	acute interstitial pneumonia
AKI	acute kidney injury
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
AMI	anterior myocardial infarction
AML	acute myelogenous leukemia
amy	amylase
ANA	antinuclear antibody
ANCA	antineutrophilic cytoplasmic Ab
AoD	aortic dissection
AoV	aortic valve
APAP	acetyl-para-aminophenol
APC	activated protein C
APL	acute promyelocytic leukemia
APLA	antiphospholipid Ab
APS	antiphospholipid Ab synd.
ARB	angiotensin receptor blocker
ARDS	acute resp distress synd.
ARV	antiretroviral
ARVC	arrhythmogenic RV CMP
AS	aortic stenosis
ASA	aspirin
ASD	atrial septal defect
AST	aspartate aminotransferase
asx	asymptomatic
AT	atrial tachycardia
ATII	angiotensin II
ATIII	antithrombin III
ATN	acute tubular necrosis
ATRA	all-trans-retinoic acid
AV	atrioventricular
AVA	aortic valve area
AVB	atrioventricular block
AVNRT	AV nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	AV reciprocating tachycardia

a/w	associated with
AZA	azathioprine
Aϕ	alkaline phosphatase
BAL	bronchoalveolar lavage
βB	beta-blocker
BBB	bundle branch block
b/c	because
BCx	blood culture
BD	bile duct
BDZ	benzodiazepines
bili.	bilirubin
BiPAP	bilevel positive airway pressure
BiV	biventricular
BM	bone marrow bowel movement
BMD	bone mineral density
BMI	body mass index
BMS	bare metal stent
BNP	B-type natriuretic peptide
BP	blood pressure
BPH	benign prostatic hypertrophy
BRBPR	bright red blood per rectum
BS	breath sounds
BT	bleeding time
BUN	blood urea nitrogen
bx	biopsy
BYCE	buffered charcoal yeast extract
C′	complement
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CALLA	common ALL antigen
CAPD	chronic ambulatory peritoneal dialysis
CBC	complete blood count
CBD	common bile duct
CCB	calcium channel blocker
CCl4	carbon tetrachloride
CCP	cyclic citrullinated peptide
CCS	Canadian Cardiovascular Society
CCY	cholecystectomy
CD	Crohn’s disease

CEA	carcinoembryonic antigen
	carotid endarterectomy
ceph.	cephalosporin
c/f	concern for
CF	cystic fibrosis
Cftx	ceftriaxone
CFU	colony forming units
CHB	complete heart block
CHD	congenital heart disease
CHF	congestive heart failure
CI	cardiac index
CIAKI	contrast-induced AKI
CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt-Jakob disease
CK	creatine kinase
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CMC	carpometacarpal (joint)
CML	chronic myelogenous leukemia
CMML	chronic myelomonocytic leukemia
CMP	cardiomyopathy
CMV	cytomegalovirus
CN	cranial nerve
CNI	calcineurin inhibitor
CO	carbon monoxide cardiac output
COP	cryptogenic organizing PNA
COPD	chronic obstructive pulm dis.
COX	cyclo-oxygenase
CP	chest pain
CPAP	continuous positive airway pressure
CPP	cerebral perfusion pressure
CPPD	calcium pyrophosphate dihydrate
Cr	creatinine
CrAg	cryptococcal antigen
CRC	colorectal cancer
CrCl	creatinine clearance
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
c/s	consult
CsA	cyclosporine A
CSF	cerebrospinal fluid
	carotid sinus massage

CSM	
CT	computed tomogram
CTA	CT angiogram
CTD	connective tissue disease
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cerebrovascular disease
	collagen vascular disease
CVID	common variable immunodefic.
CVP	central venous pressure
CVVH	continuous veno-venous hemofiltration
c/w	compared with
	consistent with
CW	chest wall
cx	culture
CXR	chest radiograph
CYC	cyclophosphamide
d	day
D	death
ΔMS	change in mental status
DA	dopamine
DAD	diffuse alveolar damage
DAH	diffuse alveolar hemorrhage
DAT	direct antiglobulin test
DBP	diastolic blood pressure
d/c	discharge
	discontinue
DCCV	direct current cardioversion
DCIS	ductal carcinoma in situ
DCMP	dilated cardiomyopathy
DCT	distal collecting tubule
Ddx	differential diagnosis
DES	drug-eluting stent
DFA	direct fluorescent antigen detection
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
diff.	differential
DIP	desquamative interstitial pneumonitis
	distal interphalangeal (joint)
DKA	diabetic ketoacidosis
	diffusion capacity of the lung

DLCO	
DLE	drug-induced lupus
DM	dermatomyositis
	diabetes mellitus
DMARD	disease-modifying anti- rheumatic drug
DOE	dyspnea on exertion
DRE	digital rectal exam
DRESS	drug reaction w/ eosinophilia & systemic symptoms
DSE	dobutamine stress echo
DST	dexamethasone suppression test
DTRs	deep tendon reflexes
DU	duodenal ulcer
DVT	deep vein thrombosis
dx	diagnosis
EAD	extreme axis deviation
EAV	effective arterial volume
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EDP	end-diastolic pressure
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
EGPA	eosinophilic granulomatosis with polyangiitis
EI	entry inhibitor
EIA	enzyme-linked immunoassay
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMB	ethambutol
ENaC	epithelial Na channel
ENT	ears, nose, & throat
e/o	evidence of
EOM	extraocular movement/muscles
EP	electrophysiology
Epo	erythropoietin
EPS	electrophysiology study
ERCP	endoscopic retrograde cholangiopancreatography
ERV	expiratory reserve volume

ESA	erythropoiesis-stimulating agents
ESP	end-systolic pressure
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESV	end-systolic volume
ET	endotracheal tube
	essential thrombocythemia
EtOH	alcohol
ETT	endotracheal tube
	exercise tolerance test
EUS	endoscopic ultrasound
EVAR	endovascular aneurysm repair
FDP	fibrin degradation product
FEV1	forced expir. vol in 1 sec
FFP	fresh frozen plasma
FHx	family history
FI	fusion inhibitor
FMD	fibromuscular dysplasia
FMF	familial Mediterranean fever
FNA	fine-needle aspiration
FOB	fecal occult blood
FOBT	fecal occult blood testing
FQ	fluoroquinolone
FRC	functional residual capacity
FSGS	focal segmental glomerulosclerosis
FSH	follicle stimulating hormone
FTI	free thyroxine index
FUO	fever of unknown origin
f/up	follow-up
FVC	forced vital capacity
G6PD	glc-6-phosphate dehydrogenase
GB	gallbladder
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
GCS	Glasgow coma scale
G-CSF	granulocyte colony stimulating factor
GE	gastroesophageal
gen.	generation
GERD	gastroesophageal reflux disease
	glomerular filtration rate

GFR	
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GIB	gastrointestinal bleed
GIST	gastrointestinal stromal tumor
glc	glucose
GMCSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis
GNR	gram-negative rods
GnRH	gonadotropin-releasing hormone
GPA	granulomatosis w/ polyangiitis
GPC	gram-positive cocci
GPI	glycoprotein IIb/IIIa inhibitor
GRA	glucocorticoid-remediable aldosteronism
GU	gastric ulcer
GVHD	graft-versus-host disease
h	hour
H2RA	H2-receptor antagonist
HA	headache
HACA	human antichimeric antibody
HAV	hepatitis A virus
Hb	hemoglobin
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCMP	hypertrophic cardiomyopathy
Hct	hematocrit
HCV	hepatitis C virus
HCW	health care worker
HD	hemodialysis
HDL	high-density lipoprotein
HDV	hepatitis D virus
HELLP	hemolysis, abnl LFTs, low plts
HEV	hepatitis E virus
HF	heart failure
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HHS	hyperosmolar hyperglycemic state
HIT	heparin-induced thrombocytopenia
HK	hypokinesis
HL	Hodgkin lymphoma
h/o	history of

HOB	head of bed
HoTN	hypotension
hpf	high-power field
HPT	hyperparathyroidism
HR	heart rate
HRT	hormone replacement therapy
HS	hereditary spherocytosis
HSCT	hematopoietic stem cell transplantation
HSM	hepatosplenomegaly
HSP	Henoch-Schönlein purpura
HSV	herpes simplex virus
HTN	hypertension
HUS	hemolytic uremic syndrome
hx	history
I&D	incision & drainage
IABP	intra-aortic balloon pump
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity
ICa	ionized calcium
ICD	implantable cardiac defibrillator
ICH	intracranial hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IE	infective endocarditis
IGF	insulin-like growth factor
IGRA	interferon-γ release assay
II	integrase inhibitor
IIP	idiopathic interstitial PNA
ILD	interstitial lung disease
IMI	inferior myocardial infarction
infxn	infection
inh	inhaled
INH	isoniazid
INR	international normalized ratio
IPAA	ileal pouch-anal anastomosis
IPF	idiopathic pulmonary fibrosis
ITP	idiopathic thrombocytopenic purpura
IVB	intravenous bolus
IVC	inferior vena cava
IVDU	intravenous drug use(r)

IVF	intravenous fluids
IVIg	intravenous immunoglobulin
JVD	jugular venous distention
JVP	jugular venous pulse
KS	Kaposi's sarcoma
KUB	kidney-ureter-bladder (radiography)
LA	left atrium
	long-acting
	lupus anticoagulant
LABA	long-acting β2-agonist
LAD	left anterior descending coronary artery
	left axis deviation
LAE	left atrial enlargement
LAN	lymphadenopathy
LAP	left atrial pressure
	leukocyte alkaline phosphatase
LBBB	left bundle branch block
LCA	left coronary artery
LCIS	lobular carcinoma in situ
LCx	left circumflex cor. art.
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LE	lower extremity
LES	lower esophageal sphincter
LFTs	liver function tests
LGIB	lower gastrointestinal bleed
LH	luteinizing hormone
LLQ	left lower quadrant
LM	left main coronary artery
LMWH	low-molecular-weight heparin
LN	lymph node
LOC	loss of consciousness
LOS	length of stay
LP	lumbar puncture
lpf	low-power field
LQTS	long QT syndrome
LR	lactated Ringer's
LUSB	left upper sternal border
	left ventricle

LV	
LVAD	LV assist device
LVEDP	LV end-diastolic pressure
LVEDV	LV end-diastolic volume
LVESD	LV end-systolic diameter
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
LVSD	LV systolic dimension
mAb	monoclonal antibody
MAC	mitral annular calcification
	Mycobacterium avium complex
MAHA	microangiopathic hemolytic anemia
MALT	mucosa-assoc. lymphoid tissue
MAO	monoamine oxidase
MAP	mean arterial pressure
MAT	multifocal atrial tachycardia
MCD	minimal change disease
MCP	metacarpal phalangeal (joint)
MCS	mechanical circulatory support
MCTD	mixed connective tissue dis.
MCV	mean corpuscular volume
MDI	metered dose inhaler
MDMA	3,4-methylenedioxymetham- phetamine (Ecstasy)
MDR	multidrug resistant
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasia
MG	myasthenia gravis
MGUS	monoclonal gammopathy of uncertain significance
MI	myocardial infarction
min	minute
min.	minimal
MM	multiple myeloma
MMEFR	max. mid-expir. flow rate
MMF	mycophenolate mofetil
MN	membranous nephropathy
MNZ	metronidazole
mo	month
mod.	moderate
MODS	multiple organ dysfxn synd.
MPA	microscopic polyangiitis
MPGN	membranoproliferative glomerulonephritis

MPN	myeloproliferative neoplasm
MR	magnetic resonance
	mitral regurgitation
MRA	magnetic resonance angiography
MRCP	MR cholangiopancreatography
MRI	magnetic resonance imaging
MRSA	methicillin-resistant S. aureus
MS	mitral stenosis
MSA	multisystem atrophy
MTb	Mycobacterium tuberculosis
mTOR	mechanistic target of rapamycin
MTP	metatarsal phalangeal (joint)
MTX	methotrexate
MV	mitral valve
MVA	mitral valve area
MVP	mitral valve prolapse
MVR	mitral valve replacement
Mϕ	macrophage
NAC	N-acetylcysteine
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NG	nasogastric
NGT	nasogastric tube
NHL	non-Hodgkin lymphoma
niCMP	non-ischemic CMP
NIF	negative inspiratory force
NJ	nasojejunal
nl	normal
NM	neuromuscular
NMJ	neuromuscular junction
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNT	number needed to treat
NO	nitric oxide
NPJT	nonparoxysmal junctional tachycardia
NPO	nothing by mouth
NPPV	noninvasive positive pressure ventilation
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NS	normal saline
NSAID	nonsteroidal anti-inflam. drug
	non-small cell lung cancer

NSCLC	
NSF	nephrogenic systemic fibrosis
NTG	nitroglycerin
N/V	nausea and/or vomiting
NVE	native valve endocarditis
NYHA	New York Heart Association
O&P	ova & parasites
OA	osteoarthritis
OCP	oral contraceptive pill
O/D	overdose
OG	osmolal gap
OGT	orogastric tube
OGTT	oral glucose tolerance test
OI	opportunistic infection
OM	obtuse marginal cor. art.
OSA	obstructive sleep apnea
OTC	over-the-counter
o/w	otherwise
p/w	present(s) with
PA	pulmonary artery
PAC	pulmonary artery catheter
PAD	peripheral artery disease
PAN	polyarteritis nodosa
PASP	PA systolic pressure
PAV	percutaneous aortic valvuloplasty
pb	problem
PBC	primary biliary cholangitis
PCI	percutaneous coronary intervention
PCN	penicillin
PCP	Pneumocystis jiroveci pneumonia
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PCWP	pulmonary capillary wedge pressure
PD	Parkinson's disease
	peritoneal dialysis
PDA	patent ductus arteriosus
	posterior descending cor. art.
PE	pulmonary embolism
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure

PEF	peak expiratory flow
PET	positron emission tomography
PEx	physical examination
PFO	patent foramen ovale
PFT	pulmonary function test
PGA	polyglandular autoimmune syndrome
PHT	pulmonary hypertension
PI	protease inhibitor
PID	pelvic inflammatory disease
PIF	prolactin inhibitory factor
PIP	peak inspiratory pressure
	proximal interphalangeal (joint)
PKD	polycystic kidney disease
PM	polymyositis
PMF	primary myelofibrosis
PMHx	past medical history
PMI	point of maximal impulse
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear leukocyte
PMR	polymyalgia rheumatica
PMV	percutaneous mitral valvuloplasty
PMVT	polymorphic ventricular tachycardia
PNA	pneumonia
PND	paroxysmal nocturnal dyspnea
PNH	paroxysmal nocturnal hemoglobinuria
PNS	peripheral nervous system
PO	oral intake
POTS	postural orthostatic tachycardia syndrome
PPD	purified protein derivative
PPH	primary pulmonary HTN
PPI	proton pump inhibitors
Pplat	plateau pressure
PPM	permanent pacemaker
PPV	positive predictive value
Ppx	prophylaxis
PR	PR segment on ECG
	pulmonary regurgitation
PRBCs	packed red blood cells
PRL	prolactin
PRPP	phosphoribosyl-I-pyrophosphate
PRWP	poor R wave progression
	pressure support

PS	
	pulmonic stenosis
PSA	prostate specific antigen
PsA	Pseudomonas aeruginosa
PSC	primary sclerosing cholangitis
PSGN	post streptococcal glomerulonephritis
PSHx	past surgical history
PSV	pressure support ventilation
Pt	patient
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
PTH	parathyroid hormone
PTH-rP	PTH-related peptide
PTT	partial thromboplastin time
PTU	propylthiouracil
PTX	pneumothorax
PUD	peptic ulcer disease
PUVA	psoralen + ultraviolet A
PV	polycythemia vera
	portal vein
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
PZA	pyrazinamide
qac	before every meal
qhs	every bedtime
QoL	quality of life
Qw	Q wave
RA	refractory anemia
	rheumatoid arthritis
	right atrium
RAA	renin-angiotensin-aldosterone
RAD	right axis deviation
RAE	right atrial enlargement
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RAS	renal artery stenosis
RAST	radioallergosorbent test
RBBB	right bundle branch block
	red blood cell

RBC	
RBF	renal blood flow
RBV	ribavirin
RCA	right coronary artery
RCMP	restrictive cardiomyopathy
RCT	randomized controlled trial
RDW	red cell distribution width
RE	reticuloendothelial
RF	rheumatoid factor
	risk factor
RFA	radiofrequency ablation
RHD	rheumatic heart disease
r/i	rule in
RI	reticulocyte index
RIBA	recombinant immunoblot assay
RMSF	Rocky Mountain spotted fever
r/o	rule out
ROS	review of systems
RPGN	rapidly progressive glomerulonephritis
RR	respiratory rate
RRT	renal replacement therapy
RT	radiation therapy
RTA	renal tubular acidosis
RTX	rituximab
RUQ	right upper quadrant
RUSB	right upper sternal border
RV	residual volume
	right ventricle
RVAD	RV assist device
RVH	right ventricular hypertrophy
RVOT	RV outflow tract
RVSP	RV systolic pressure
Rx	therapy
RYGB	roux-en-Y gastric bypass
SA	sinoatrial
SAAG	serum-ascites albumin gradient
SAH	subarachnoid hemorrhage
SAS	sulfasalazine
SBE	subacute bacterial endocarditis
SBO	small bowel obstruction
	spontaneous bacterial peritonitis

SBP	systolic blood pressure
SBT	spontaneous breathing trial
SC	subcutaneous
SCD	sudden cardiac death
SCID	severe combined immunodefic.
SCLC	small-cell lung cancer
s/e	side effect
Se	sensitivity
sec	second
SERM	selective estrogen receptor modulator
sev.	severe
SHBG	steroid hormone binding globulin
SIADH	synd. of inappropriate ADH
SIBO	small intestine bacterial overgrowth
SIEP	serum immunoelectrophoresis
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SMX	sulfamethoxazole
SOS	sinusoidal obstructive synd.
s/p	status post
Sp	specificity
SPEP	serum protein electrophoresis
SR	sinus rhythm
s/s	signs and symptoms
SSCY	Salmonella, Shigella, Campylobacter, Yersinia
SSRI	selective serotonin reuptake inhibitor
SSS	sick sinus syndrome
ST	sinus tachycardia
STD	ST-segment depression
STE	ST-segment elevation
STI	sexually transmitted infection
SV	stroke volume
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
sx	symptom(s) or symptomatic

T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
T3RU	T3 resin uptake
TAA	thoracic aortic aneurysm
TB	tuberculosis
TBG	thyroid binding globulin
TCA	tricyclic antidepressant
TCD	transcranial Doppler
TCN	tetracycline
Tdap	tetanus, diphtheria, pertussis
TdP	torsades de pointes
TdT	terminal deoxynucleotidyl transferase
TEE	transesophageal echo
tfn	transfusion
TFTs	thyroid function tests
TG	triglycerides
TGA	transposition of the great arteries
TIA	transient ischemic attack
TIBC	total iron binding capacity
TINU	tubulointerstitial nephritis and uveitis
TIPS	transjugular intrahepatic portosystemic shunt
TKI	tyrosine kinase inhibitor
TLC	total lung capacity
TMP	trimethoprim
Tn	troponin
TP	total protein
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
Tpo	thrombopoietin
TPO	thyroid peroxidase
TR	tricuspid regurgitation
TRALI	transfusion-related acute lung injury
TRH	thyrotropin-releasing hormone
TRS	TIMI risk score
TRUS	transrectal ultrasound
TS	tricuspid stenosis
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome
	transsphenoidal surgery
TTE	transthoracic echo

TTKG	transtubular potassium gradient
TTP	thrombotic thrombocytopenic purpura
TV	tricuspid valve
Tw	T wave
TWF	T-wave flattening
TWI	T-wave inversion
Tx	transplant
TZD	thiazolidinediones
U/A	urinalysis
UA	unstable angina
UAG	urine anion gap
UC	ulcerative colitis
UCx	urine culture
UES	upper esophageal sphincter
UFH	unfractionated heparin
UGIB	upper gastrointestinal bleed
UIP	usual interstitial pneumonitis
ULN	upper limit of normal
UOP	urine output
UPEP	urine protein electrophoresis
UR	urgent revascularization
UrA	uric acid
URI	upper resp. tract infxn
U/S	ultrasound
UTI	urinary tract infection
V/Q	ventilation-perfusion
VAD	ventricular assist device
VAP	ventilator-associated PNA
VATS	video-assisted thoracoscopic surgery
VBI	vertebrobasilar insufficiency
VC	vital capacity
VD	vessel disease
VDRL	venereal disease research laboratory (test for syphilis)
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VLDL	very-low-density lipoproteins
VOD	veno-occlusive disease
VS	vital signs
VSD	ventricular septal defect
Vt	tidal volume

VT	ventricular tachycardia
VTE	venous thromboembolism
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZV	varicella zoster virus
w/	with
WBC	white blood cell (count)
WCT	wide-complex tachycardia
WHO	World Health Organization
wk	week
WM	Waldenström's macroglobulinemia
WMA	wall motion abnormality
w/o	without
WPW	Wolff-Parkinson-White syndrome
w/u	workup
XRT	radiation therapy

INDEX

A

A-a gradient, 2-18, 11-6
abdominal CT scan, P-7
abdominal pain, 10-1
acanthosis nigricans, 5-28
accessory pathway, 1-33
acetaminophen
  as cause of metabolic acidosis, 4-2
  hepatotoxicity, 3-19
achalasia, 3-1
acid-base disturbances, 4-1
acquired immunodeficiency syndrome (AIDS), 6-17
acromegaly, 7-2
activated protein C resistance, 5-11
acute abdomen, 10-1
acute aortic syndrome, 1-31
acute coronary syndromes, 1-6
acute interstitial nephritis, 4-12, 4-13
acute interstitial pneumonia, 2-10
acute kidney injury, 4-12
acute limb ischemia, 1-41
acute respiratory distress syndrome (ARDS), 2-22
acute tubular necrosis, 4-12
Addison's disease, 7-9
adnexal mass, non-pregnant woman, 10-3
adrenal disorders, 7-7
adrenal incidentalomas, 7-10
adrenal insufficiency, 7-9
adrenal mass, 7-10
advanced cardiac life support, ACLS-1
albuminuria, 4-14
alcohol withdrawal, 9-5
allergic bronchopulmonary aspergillosis, 2-10
alpha$_1$-antitrypsin deficiency
  as cause of cirrhosis, 3-24
  as cause of COPD, 2-5
alveolar gas equation, 11-6
amaurosis fugax, 9-6
amiodarone, thyroid disease and, 7-6
amyloidosis, 8-22
  cardiac manifestations, 1-19
anaphylaxis, 2-4
anaplasmosis, 6-21
anemia, 5-1
  aplastic, 5-3
  autoimmune hemolytic, 5-5, P-13
  of chronic inflammation, 5-2
  Cooley's, 5-2
  Fanconi's, 5-3
  folate deficiency, 5-3

hemolytic, 5-4
iron deficiency, 5-1, P-13
macrocytic, 5-3
megaloblastic, 5-3, P-13
microangiopathic hemolytic, 5-5
microcytic, 5-1
myelophthisic, 5-4
normocytic, 5-2
pernicious, 5-3
sickle cell, 5-4, P-14
sideroblastic, 5-2
angina, 1-3, 1-6
angioectasia, 3-3
angioedema, 2-4
angioplasty, 1-5
anion gap, 4-2, 11-7
ankylosing spondylitis, 8-7
anoxic brain injury, 9-2
antibiotics, 11-3
antibodies
anticardiolipin, 5-11, 8-16
anti-centromere, 8-11
anti-cyclic citrullinated peptide (CCP), 8-3
anti-ds-DNA, 8-15
anti-GBM, 4-17
anti-histone, 8-15
anti-Jo-1, 8-13
anti-La, 8-14, 8-16
anti-Mi-2, 8-13
antimitochondrial, 3-24
anti-MPO, 4-17, 8-18
antineutrophil cytoplasmic (ANCA), 4-17, 8-18
antinuclear (ANA), 8-2, 8-15
antiphospholipid, 5-11
anti-PR3, 4-17, 8-18
anti-Ro, 8-14, 8-15
anti-Scl-70, 8-11
anti-Sm, 8-15
anti-smooth muscle, 3-19
anti-SRP, 8-13
anti-TPO, 7-4, 7-5
anti-U1-RNP, 8-14, 8-15
autoantibodies, 8-2
in connective tissue diseases, 8-11
anticoagulants, 5-6, 5-10
anti-GBM disease, as cause of glomerulonephritis, 4-17
antiphospholipid syndrome, 5-11
aortic aneurysm, 1-30
aortic dissection, 1-31
aortic regurgitation, 1-21
aortic stenosis, 1-20
aortoenteric fistula, 3-4
arrhythmias, 1-32
arthralgias, 8-1
arthritis, 8-1
IBD-associated (enteropathic), 8-7
infectious, 8-9
osteoarthritis, 8-1
psoriatic, 8-7

reactive, 8-7
rheumatoid, 8-3
asbestosis, 2-10
ascites, 3-26
treatment of, in cirrhotics, 3-21
aspergillosis, 6-4
asplenia, 6-4
asthma, 2-2
atrial fibrillation, 1-32, 1-35
atrial flutter, 1-32, 1-36
Auer rod, 5-17
autoimmune polyglandular syndromes (APS), 7-2
auto-PEEP, 2-20
AV block, 1-32
AV dissociation, 1-32

B

babesiosis, 6-21
bacillary angiomatosis, 6-18
back pain, 9-11
bacteremia, 6-12
Barrett's esophagus, 3-2
Bartter's syndrome, 4-5, 4-10, 7-8
basophilia, 5-12
basophilic stippling, 5-2, 11-8
Beck's triad, 1-26
Behçet's syndrome, 8-20
Bell's palsy, 6-11
Bernard-Soulier disease, 5-9
berylliosis, 2-10
bilevel positive airway pressure (BiPAP), 2-19
biliary tract disease, 3-27
bite cells, 5-4, 11-7
biventricular pacing, 1-16, 1-39
blastomycosis, 6-4
body surface area, 11-9
Boerhaave syndrome, 1-3
bone infections, 6-8
bone marrow transplantation, 5-26
bradycardia, 1-32
breast cancer, 5-30
Brockenbrough sign, 1-18
bronchiectasis, 2-8
bronchitis, chronic, 2-5
Brudzinski's sign, 6-9
Brugada syndrome, 1-34
B-type natriuretic peptide, 1-14, 2-1
Budd-Chiari syndrome, 3-25
bundle branch blocks, 1-1
burr cells, 11-7
bursitis, 8-1, 8-10

C

calciphylaxis, 4-14
calcium disorders, 7-11
calcium pyrophosphate dehydrate deposition disease, 8-6
Cameron's lesions, 3-4

cancer of unknown primary site, 5-37
Candida species, 6-3
carbon monoxide poisoning, 2-18
carcinoid, 3-6
cardiac output, 1-12, 11-5
cardiac resynchronization therapy, 1-16, 1-39
cardiac shunt, 11-5
cardiomyopathy, 1-17
  arrhythmogenic RV, 1-17, 1-34
  dilated, 1-17
  hypertrophic, 1-18
  peripartum, 1-17
  restrictive, 1-19
  vs. constrictive pericarditis, 1-19
  Takotsubo, 1-17
cardiorenal syndrome, 4-13
carotid revascularization, 9-7
cat scratch disease, 6-6
cauda equina syndrome, 9-11
celiac disease, 3-7
cellulitis, 6-6
central venous catheter-related
  blood streams infections, 6-12
cerebrovascular disease, 9-6
Chagas, 1-17
Charcot's triad, 3-28
Chediak-Higashi syndrome, 5-9
chemotherapy side effects, 5-37
chest pain, 1-3
chest tubes, 10-2
Child-Turcotte-Pugh scoring system, 11-7
chimeric antigen receptor (CAR)-T cells, 5-37
cholangitis, 3-28
cholecystitis, 3-27
choledocholithiasis, 3-28
cholelithiasis, 3-27
cholera, 3-5
cholestasis, 3-16
cholesterol emboli syndrome, 1-5
chronic kidney disease, 4-13
chronic obstructive pulmonary disease (COPD), 2-5, P-1
Churg-Strauss syndrome, 8-19
  as cause of asthma, 2-2
  as cause of glomerulonephritis, 4-17
  as cause of interstitial lung disease, 2-10
Chvostek's sign, 7-12
cirrhosis, 3-21
claudication, neurogenic *vs.* vascular, 9-12
clinical institute withdrawal assessment for alcohol (CIWA-Ar), 11-9
clostridial myonecrosis, 6-7
Clostridium difficile infection, 3-6
coagulation cascade, 5-6
coagulopathies, 5-10
coarctation of aorta, 1-28
coccidioidomycosis, 6-3
cold caloric, 9-1
colonic polyps, 3-9
colonic pseudo-obstruction, 3-8
colonoscopy, screening, 5-33

colorectal cancer (CRC), 5-33
coma, 9-1
compartment syndrome, 10-2
confusion, 9-1
connective tissue diseases, 8-11
Conn's syndrome, 7-8
constipation, 3-8
constrictive pericarditis, 1-27
continuous positive airway pressure (CPAP), 2-19, 2-20
continuous veno-venous hemofiltration, 4-16
contrast-induced acute kidney injury, 4-13
conus medullaris syndrome, 9-11
cord compression, 5-36, 9-11
coronary angiography, 1-5, P-13
  computed tomographic, 1-4
coronary arteries, P-13
coronary artery bypass grafting (CABG), 1-5
coronary artery calcium score, 1-4
coronary revascularization, 1-5
Courvoisier's sign, 5-34
creatinine clearance, 11-7
CREST syndrome, 8-12
Crohn's disease, 3-10
cryoglobulinemia, 8-21
Cryptococcus, 6-3
cryptogenic organizing pneumonia, 2-10
crystal deposition arthritides, 8-5
Cullen's sign, 3-13
Cushing's reflex, 3-20
Cushing's syndrome, 7-7
cutaneous leukocytoclastic angiitis, 8-20
CXR/chest CT scan, P-1, P-5
cyanide poisoning, 2-18
cyanosis, 2-18
cystic fibrosis, 2-8
cystitis, 6-5
cytomegalovirus, 6-19

D

dactylitis, 8-7
decubitus ulcer, 10-2
deep venous thrombosis, 2-13
delirium, 9-1
delirium tremens, 9-5
delta-delta, 4-2, 11-7
dementia, 9-1
dengue, 6-23
dermatomyositis, 8-12
desquamative interstitial pneumonia, 2-10
diabetes insipidus, 4-8, 4-9
diabetes mellitus, 7-13
diabetic foot, 6-7
diabetic ketoacidosis (DKA), 7-14
dialysis, 4-15
diarrhea, 3-5
Dieulafoy's lesion, 3-4
diffuse alveolar damage, 2-22
diffuse alveolar hemorrhage, 2-10, 5-27

diplopia, 10-4
direct oral anticoagulants (DOACs), 5-10
disc herniation, 9-12
discriminant function, 3-19
disseminated gonococcal arthritis, 8-10
disseminated intravascular coagulation (DIC), 5-10
diuresis, 4-15
diverticular disease, 3-9
dizziness, 9-5
Döhle bodies, 5-12, 11-8
doll's eyes, 9-1
Dressler's syndrome, 1-11, 1-25
Duke treadmill score, 1-4
duodenal ulcer, 3-2
dyslipidemias, 7-16
dysphagia, 3-1
dyspnea, 2-1
dysuria, 6-5

E

Eaton-Lambert syndrome, 5-28, 9-9
echocardiography, P-9
Ehlers-Danlos syndrome, 1-30, 1-31
ehrlichiosis, 6-21
electrocardiography, 1-1
emphysema, 2-5
encephalitis, viral, 6-11
endocarditis, 6-12
endomyocardial fibrosis, 1-19
enthesitis, 8-7
eosinophilia, 5-12
eosinophilic granulomatosis with polyangiitis, 8-19
  as cause of asthma, 2-2
  as cause of glomerulonephritis, 4-17
  as cause of interstitial lung disease, 2-10
eosinophilic pneumonias, 2-10
epidural abscess, 6-8
epidural hematoma, 9-7
epilepsy, 9-3
erosive gastropathy, 3-3
erysipelas, 6-6
erythema migrans, 6-20
erythema multiforme, 6-22
erythema nodosum, 2-9, 6-23, 8-8, 8-20
erythrocyte sedimentation rate, 8-2
erythromelalgia, 5-15
esophageal reflux, 3-1
esophageal ring, 3-1
esophageal spasm, 1-3
esophageal web, 3-1
esophagitis, 3-1, 3-3
essential thrombocythemia, 5-15
ethylene glycol intoxication, 4-2
exercise tolerance test, 1-4
F
factor V Leiden, 5-11
familial adenomatous polyposis, 5-33
familial hypocalciuric hypercalcemia, 7-11

familial Mediterranean fever, 6-22
Fanconi's syndrome, 4-3
Felty's syndrome, 8-3
fever
  neutropenia and, 5-35
  Pel-Ebstein, 5-23
  syndromes, 6-22
fibromyalgia, 8-13
Fitz-Hugh-Curtis syndrome, 8-10
focal segmental glomerulosclerosis, 4-18
folate deficiency, 5-3
folliculitis, 6-6
food poisoning, 3-5
Fournier's gangrene, 6-7
fractional excretion of Na, 4-12, 11-7
fractional flow reserve (FFR), 1-5
free H_2O deficit, 4-8, 11-7
fungal infections, 6-3
G
Gaisböck's syndrome, 5-15
Gallavardin effect, 1-20
gallstone, 3-13
gallstone ileus, 3-27
gas gangrene, 6-7
gastric antral vascular ectasia, 3-4
gastric ulcer, 3-2
gastroesophageal reflux disease (GERD), 3-1
gastrointestinal bleeding, 3-3
gastroparesis, 3-8
gastrostomy tubes, 10-2
giant cell arteritis, 8-17
Gitelman's syndrome, 4-5, 4-10, 7-8
Glanzmann's thromboasthenia, 5-9
Glasgow Coma Scale, 9-1
glaucoma, 10-4
glomerulonephritis, 4-17
glucose-6-phosphate dehydrogenase (G6PD) deficiency, 5-4
glycemic control, in critical care, 2-23
goiter, 7-3, 7-5
Goodpasture's syndrome
  as cause of alveolar hemorrhage, 2-10
  as cause of glomerulonephritis, 4-17
Gottron's papules, 8-13
gout, 8-5
graft-versus-host disease (GVHD), 5-26, 5-27
granulomatosis with polyangiitis, 8-18
  as cause of glomerulonephritis, 4-17
  as cause of interstitial lung disease, 2-10
Graves' disease, 7-5
Grey Turner's sign, 3-13
Guillain-Barré syndrome, 9-8

H

Hamman-Rich syndrome, 2-10
Hashimoto's thyroiditis, 7-3
headache, 9-10
heart failure, 1-14
  with preserved EF, 1-16

Heinz bodies, 5-4, 11-8
Helicobacter pylori infection, 3-2
heliotrope rash, 8-13
hematemesis, 3-3
hematochezia, 3-3
hematopoietic stem cell transplantation, 5-26
hematuria, 4-20
hemochromatosis
  as cause of cirrhosis, 3-23
  as cause of DCM, 1-17
  as cause of RCM, 1-19
hemodialysis, 4-15
hemolytic-uremic syndrome, 5-9
hemophilia, 5-10
hemoptysis, 2-7
hemostasis disorders, 5-6
Henoch-Schönlein purpura, 8-19
  as cause of glomerulonephritis, 4-17
heparin-induced thrombocytopenia, 5-8
heparin nomograms, 11-8
hepatic encephalopathy, 3-22
hepatic hydrothorax, 2-12, 3-22
hepatitis, 3-17
  alcoholic, 3-19
  autoimmune, 3-19
  ischemic, 3-19
  viral, 3-17
hepatocellular carcinoma, 3-23, 5-35
hepatopulmonary syndrome, 3-23
hepatorenal syndrome, 3-22
hereditary nonpolyposis colorectal cancer, 5-33
hereditary spherocytosis, 5-5
Hermansky-Pudlak syndrome, 5-9
herpes zoster, 6-11
Heyde syndrome, 3-4, 5-9
histoplasmosis, 6-3
Howell-Jolly bodies, 5-5, 11-8
human immunodeficiency virus (HIV), 6-17
hyperaldosteronism, 7-8
  as cause of hypokalemia, 4-10
  as cause of metabolic alkalosis, 4-4
hyperbilirubinemia, 3-15
hypercalcemia, 7-11
hypercapnia, 2-18
hypercholesterolemia, 7-16
hypercoagulable states, 5-11
hypercortisolism, 7-7
hyperhomocysteinemia, 5-11
hyperkalemia, 4-11
hypernatremia, 4-8
hyperosmolar hyperglycemic state, 7-15
hyperparathyroidism, 7-11
  secondary, 4-14
hyperpituitary syndrome, 7-2
hyperprolactinemia, 7-2
hypersensitivity pneumonitis, 2-10
hypersensitivity vasculitis, 8-20
hypersplenism, 5-5
hypertension, 1-28

hypertensive crisis, 1-29
hyperthyroidism, 7-4
hypertriglyceridemia, 7-16
hypertrophic pulmonary
  osteoarthropathy, 5-28
hypoaldosteronism, 7-9
  as cause of hyperkalemia, 4-11
  as cause of metabolic acidosis, 4-3
hypocalcemia, 7-12
hypoglycemia, 7-15
hypokalemia, 4-10
hypomagnesemia, 4-11
hyponatremia, 4-6
hypoparathyroidism, 7-12
hypopituitary syndromes, 7-1
hypothermia, induced, 9-2
hypothyroidism, 7-3
hypoxemia, 2-18

I

ICU medications, 11-1
ideal body weight, 11-9
idiopathic interstitial pneumonia, 2-10
idiopathic pulmonary fibrosis, 2-10
IgA nephropathy, 4-18
IgG4-related disease, 8-20
ileus, 3-6, 3-8
immune checkpoint inhibitors, 5-37
immune thrombocytopenic purpura, 5-7
immunotherapy side effects, 5-37
impetigo, 6-6
implantable cardiac defibrillator, 1-16, 1-39
infections in susceptible hosts, 6-4
inflammatory bowel disease, 3-10
inflammatory markers, 8-2
influenza, 6-2
instantaneous wave-free ratio (iFR), 1-5
interstitial lung disease, 2-9
intestinal ischemia, 3-12
intracranial hemorrhage (ICH), 9-7
intraductal papillary mucinous neoplasm, 5-34
intramural hematoma (aortic), 1-31
iron deficiency, 5-1
irritable bowel syndrome (IBS), 3-7, 3-8
ischemic colitis, 3-12
isopropyl alcohol intoxication, 4-3

J

Janeway lesions, 6-13
jaundice, 3-15
Jod-Basedow effect, 7-6
joint fluid, analysis, 8-1

K

Kaposi’s sarcoma, 6-19
Kernig’s sign, 6-9

ketoacidosis, 4-2
kidney transplantation, 4-16
koilonychia, 5-1
Kussmaul's sign, 1-27

L

lactic acidosis, 4-2
lactose intolerance, 3-6
Lady Windermere syndrome, 2-8
Langerhans cell granulomatosis, 2-10
left ventricular hypertrophy, 1-1
left ventricular noncompaction, 1-17
left ventricular thrombus, 1-11
leukemia, 5-17, P-14
  acute lymphoblastic, 5-18
  acute myelogenous, 5-17
  acute promyelocytic, 5-18
  chronic lymphocytic, 5-23
  chronic myelogenous, 5-19
  hairy cell, 5-21
leukostasis, 5-17
Libman-Sacks endocarditis, 8-15
Liddle's syndrome, 4-5, 4-10, 7-8
Light's criteria, 2-11
limb ischemia, acute, 1-41, 10-1
lipodystrophy, 6-18
liver failure, 3-20
liver tests, abnormal, 3-15
liver transplantation, 3-23
Loeys-Dietz syndrome, 1-30, 1-31
Löffler's endocarditis, 1-19
Löffler's syndrome, 2-10
Löfgren's syndrome, 2-9
long QT syndrome, 1-1, 1-34
lung cancer, 5-28
lung transplantation, 2-24
lupus anticoagulant, 5-11
lupus pernio, 2-9
Lyme disease, 6-20
lymphadenopathy, 5-12
lymphangioleiomyomatosis, 2-10
lymphocytic interstitial pneumonia, 2-10
lymphocytosis, 5-12
lymphoma, 5-20
  CNS, 6-19
  Hodgkin, 5-20
  non-Hodgkin, 5-21
  small lymphocytic, 5-23

M

macro-ovalocytes, 5-3
malabsorption, 3-7
malaria, 6-23
Mallory-Weiss tear, 1-3, 3-4
mammography, 5-30
Marfan syndrome, 1-30, 1-31
mechanical circulatory support, 1-15
mechanical ventilation, 2-19
mechanic's hands, 8-13

Meckel's diverticulum, 3-4
Meigs' syndrome, 2-11, 3-26
MELD score, 3-21
melena, 3-3
membranoproliferative glomerulonephritis, 4-18
membranous nephropathy, 4-18
Meniere's disease, 9-5
meningitis
  acute bacterial, 6-9
  aseptic, 6-10
mental status, change in, 9-1
mesenteric ischemia, acute, 3-12
metabolic acidosis, 4-2
metabolic alkalosis, 4-4
metabolic syndrome, 7-16
methanol intoxication, 4-2
methemoglobinemia, 2-18
microscopic colitis, 3-7
microscopic polyangiitis, 8-19
  as cause of glomerulonephritis, 4-17
  as cause of interstitial lung disease, 2-10
migraine headache, 9-10
milk-alkali syndrome, 7-11
minimal change disease, 4-18
Mirizzi syndrome, 3-27
mitral regurgitation, 1-22
mitral stenosis, 1-23
mitral valve prolapse, 1-23
mixed connective tissue disease (MCTD), 8-14
molluscum contagiosum, 6-18
monoclonal gammopathy of uncertain significance, 5-25
monocytosis, 5-12
mucinous cystic neoplasm of pancreas, 5-34
Mucor infection, 6-4
multiple endocrine neoplasia (MEN) syndromes, 7-2
multiple myeloma, 5-24
murmurs, eponymous
  Austin Flint, 1-21
  Graham Steel, 2-14, 2-16
Murphy's sign, 3-27
myalgias, 8-13
myasthenia gravis, 9-9
Mycobacterium avium complex, disseminated, 6-19
mycosis fungoides, 5-21
myelodysplastic syndromes, 5-14
myelofibrosis, primary, 5-16
myeloid neoplasms, 5-14
myeloproliferative neoplasms, 5-15
myocardial infarction (MI)
  non-ST elevation, 1-7
  ST elevation, 1-9
myocardial viability, 1-4
myocarditis, 1-3, 1-17
myopathies, 8-12, 9-9
myositis, 8-12
myxedema, 7-4

N

necrotizing fasciitis, 6-7
nephrogenic systemic fibrosis, 4-13
nephrolithiasis, 4-20
nephrotic syndrome, 4-18
nerve root compression, 9-11
neuropathies, 9-8
neutropenia, 5-12, 5-36, 6-4
neutropenic enterocolitis, 5-35
neutrophilia, 5-12
New York Heart Association
  classification, 1-14
nonalcoholic fatty liver disease (NAFLD), 3-19
noninvasive ventilation, 2-19
non-TB mycobacterium, 2-8
nonspecific interstitial pneumonia, 2-10
nutrition, in hospitalized Pt, 3-8

O

ocular motor palsies, 10-4
oculocephalic maneuver, 9-1
Ogilvie's syndrome, 3-8
optic neuritis, 10-4
optic neuropathy, ischemic, 10-4
oral hairy leukoplakia, 6-18
orbital cellulitis, 10-4
orthostatic hypotension, 1-37
Osler's nodes, 6-13
osmolal gap, 4-3, 11-7
osteoarthritis, 8-1
osteomyelitis, 6-8

P

pacemakers, 1-39
Paget's disease
  of bone, 7-11
  of breast, 5-30
Pancoast's syndrome, 5-28
pancreatic cancer, 5-34
pancreatic insufficiency, 3-7
pancreatitis, 3-13
pancytopenia, 5-3
panhypopituitarism, 7-1
papillary muscle rupture, 1-10
Pappenheimer bodies, 5-2
paroxysmal nocturnal hemoglobinuria, 5-4
patent foramen ovale, 9-7
PEEP, 2-20, 2-22
peptic ulcer disease (PUD), 1-3, 3-2, 3-3
percutaneous coronary intervention (PCI), 1-5
pericardial effusion, 1-25
pericardial tamponade, 1-26
pericarditis, 1-25
periodic paralysis
  hyperkalemic, 4-11
  hypokalemic, 4-10
peripheral arterial disease, 1-41
peripheral smear, findings in, 11-7

peritoneal dialysis, 4-16
peritonitis, 3-26
petechiae, 5-6
pheochromocytoma, 7-10
phlegmasia cerulea dolens, 2-13
pica, 5-1
pituitary disorders, 7-1
pituitary tumors, 7-1
plasma cell dyscrasias, 5-24
platelet disorders, 5-7
pleural effusion, 2-11, P-4
pleuritis, 1-3
Plummer-Vinson syndrome, 5-1
pneumoconioses, 2-10
Pneumocystis jiroveci pneumonia, 6-19
pneumonia, 6-1, P-2
pneumothorax, P-4
POEMS syndrome, 5-24
polyarteritis nodosa, 8-18
polycystic kidney disease, 4-13
polycythemia vera, 5-15
polydipsia, 4-9
polymyalgia rheumatica, 8-13, 8-18
polymyositis, 8-12
polyuria, 4-9
porphyria cutanea tarda, 3-18
portal hypertension, 3-21, 3-26
portal vein thrombosis (PVT), 3-25
portopulmonary hypertension, 2-16, 3-23
Pott's disease, 6-8, 6-15
preexcitation, 1-33
pregnancy, ectopic, 10-3
preoperative risk assessment, 1-40
prerenal azotemia, 4-12
primary biliary cholangitis, 3-24
primary sclerosing cholangitis, 3-24
Prinzmetal's angina, 1-6
progressive multifocal leukoencephalopathy, 6-19
prolactinoma, 7-1, 7-2
propofol infusion syndrome, 2-21
propylene glycol intoxication, 4-2
prostate cancer, 5-32
prostate-specific antigen (PSA) testing, 5-32
prostatitis, 6-5
prosthetic heart valves, 1-24
proteinuria, 4-19
prothrombin mutation, 5-11
pseudogout, 8-6
pseudo-hypoparathyroidism, 7-12
pseudo-Pelger-Huët cells, 5-14, 11-8
pseudotumor cerebri, 9-10
pulmonary alveolar proteinosis, 2-10
pulmonary artery catheter, 1-12, 11-5
pulmonary edema
  CXR pattern in, P-2
  treatment of, 1-15, 11-2
pulmonary embolism, 2-14, P-6
pulmonary fibrosis, idiopathic, 2-10, P-6
pulmonary function tests, 2-1

pulmonary hypertension, 2-16
pulmonary infiltrates with eosinophilia, 2-10
pulsus paradoxus, 1-26
pure red cell aplasia, 5-2
purified protein derivative (PPD) test, 6-15
purpura, 5-6
pyelonephritis, 6-5
pyoderma gangrenosum, 3-10, 8-8

Q

QT interval, 1-1

R

radiculopathies, 9-11
radioactive iodine uptake scan, 7-3
Raynaud's phenomenon, 8-14
red eye, 10-4
Reed-Sternberg cells, 5-20
refeeding syndrome, 3-8
Reiter's syndrome, 8-7
relapsing polychondritis, 8-4
renal abscess, 6-5
renal artery stenosis, 1-28
renal failure, 4-12
renal osteodystrophy, 7-12
renal replacement therapy, 4-15
renal tubular acidosis, 4-3
respiratory acidosis, 4-5
respiratory alkalosis, 4-5
respiratory bronchiolitis-associated interstitial lung disease, 2-10
respiratory failure, 2-18
reticulocyte index, 5-1
Reynolds' pentad, 3-28
rhabdomyolysis, 4-13
rheumatoid factor, 8-3
Rhizopus infection, 6-4
Richter's syndrome, 5-23
Rocky Mountain spotted tick fever (RMSF), 6-21
Roth spots, 6-13

S

salicylate intoxication, 4-2
Samter's syndrome, 2-2
sarcoidosis, 2-9, P-6
    cardiac manifestations of, 1-19
schistocytes, 5-5, 11-7, P-14
sciatica, 9-11
scleroderma, 8-11
seizures, 9-3
sepsis, 2-23
Sequential Organ Failure Assessment (SOFA), 2-23
seronegative spondyloarthritis, 8-7
serum-ascites albumin gradient, 3-26
Sézary syndrome, 5-21
Sheehan's syndrome, 7-1
shock, 1-13, 11-2

cardiogenic, 1-13
septic, 2-23
sicca syndrome, 8-13
sick euthyroid syndrome, 7-5
sick sinus syndrome, 1-32
silicosis, 2-10
sinusoidal obstruction syndrome, 3-25, 5-26
Sjögren's syndrome, 8-13
small intestinal bacterial overgrowth, 3-7
smudge cells, 5-23
soft tissue infections, 6-6
solitary pulmonary nodule, 2-7
spinal cord compression, 5-36, 9-11
spinal stenosis, 9-12
splenic vein thrombosis, 3-25
splenomegaly, 5-5
spontaneous bacterial peritonitis, 3-26
treatment of in cirrhosis, 3-22
spur cells, 11-7, P-14
statistics, 11-9
status epilepticus, 9-4
ST depression, 1-2
ST elevation, 1-2
stent thrombosis, 1-5
steroids, in critical care, 2-23
Still's disease, adult onset, 6-22, 8-4
stool osmotic gap, 3-7
stress test, 1-4
stroke, 9-6
struma ovarii, 7-4
subarachnoid hemorrhage, 9-7
subdural hematoma, 9-7
superior vena cava syndrome, 5-28
syncope, 1-37
syndrome of inappropriate antidiuretic hormone (SIADH), 4-7
systemic lupus erythematosus (SLE), 8-15
systemic sclerosis, 8-11

T

tachycardias, 1-32
atrial, 1-32
atrioventricular reciprocating, 1-32, 1-34
AV nodal reentrant tach, 1-32
multifocal atrial, 1-32
nonparoxysmal junctional, 1-32
sinus, 1-32
supraventricular, 1-32
ventricular, 1-34
wide-complex, 1-34
Takayasu's arteritis, 8-17
target cells, 11-7
targeted temperature management, 9-2
teardrop cells, 5-16, P-14
temporal arteritis, 8-17
thalassemias, 5-2
thrombocytopenia, 5-7
thrombotic microangiopathies, 5-9
thrombotic thrombocytopenic purpura, 5-9

thrush, 6-18
thyroid disorders, 7-3
thyroid function tests, 7-3
thyroiditis, 7-4, 7-5
thyroid cancer, 7-6
thyroid nodules, 7-6
thyroid storm, 7-5
TIMI risk score for UA/NSTEMI, 1-8
Todd's paralysis, 9-3
torsades de pointes, 1-34
total body water, 11-7
toxic megacolon, 3-6, 3-10
toxic shock syndrome, 6-6
toxicology, 2-24
toxoplasmosis, 6-19
tracheostomy, 10-2
transfusion-related acute lung injury, 2-22, 5-13
transfusion therapy, 5-13
transient ischemic attack (TIA), 9-6
trans-tubular potassium gradient, 4-10, 11-7
tricuspid regurgitation, 1-24
triglycerides, 7-16
troponin, 1-3, 1-6
Trousseau's
  sign of hypocalcemia, 7-12
  syndrome of malignancy, 5-34
tuberculosis, 6-15
tularemia, 6-21
tumor lysis syndrome, 5-36
T wave inversion, 1-2
typhlitis, 5-35
typhoid fever, 6-23

U

ulcerative colitis, 3-10
ulcers, 3-2
unstable angina, 1-7
uremia, 4-14
uremic bleeding, 5-9
urethritis, 6-5
urinalysis, 4-19
urinary tract infection (UTI), 6-5
urine anion gap, 4-3
urine osmolality, 4-6
urine sediment, 4-19, P-15
usual interstitial pneumonia, 2-10
uveitis, 8-7

V

vaginal bleeding, 10-3
vaginal discharge, 10-3
varices, 3-4, 3-22
vasculitis, 8-17
veno-occlusive disease
  hepatic, 3-25, 5-26
  pulmonary, 2-16
venous thromboembolism, 2-13

ventricular aneurysm, 1-11
ventricular pseudoaneurysm, 1-11
ventricular septal defect, 1-10
Verner-Morrison syndrome, 3-6
vertigo, 9-5
vestibular caloric stimulation, 9-1
Virchow's node, 5-34
visual changes, 10-4
visual field defect, 10-4
vitamin B_{12} deficiency, 5-3
vitamin D deficiency, 7-12
vitamin K deficiency, 5-10
von Willebrand's disease, 5-9
V/Q mismatch, 2-18

W

Waldenström's macroglobulinemia, 5-25
warfarin loading nomogram, 11-8
warfarin overdose, 5-10
Wegener's granulomatosis, 8-18
  as cause of glomerulonephritis, 4-17
  as cause of interstitial lung disease, 2-10
Wernicke's encephalopathy, 9-5
Whipple's disease, 3-7
Wilson disease, 3-24
Wolff-Chaikoff effect, 7-6
Wolff-Parkinson-White syndrome, 1-33

X

xanthelasma, 7-16
xanthomas, 7-16

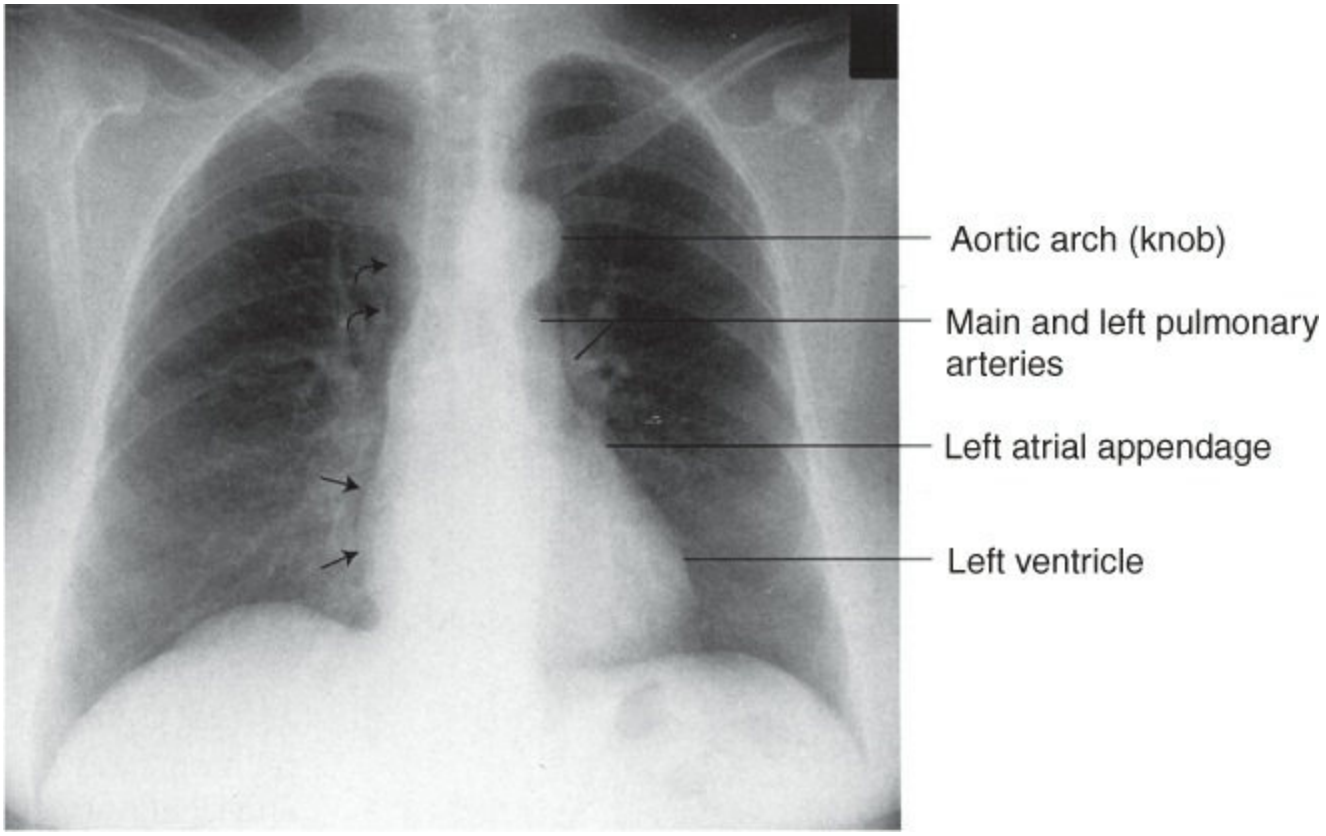
Y

yellow-nail syndrome, 2-11

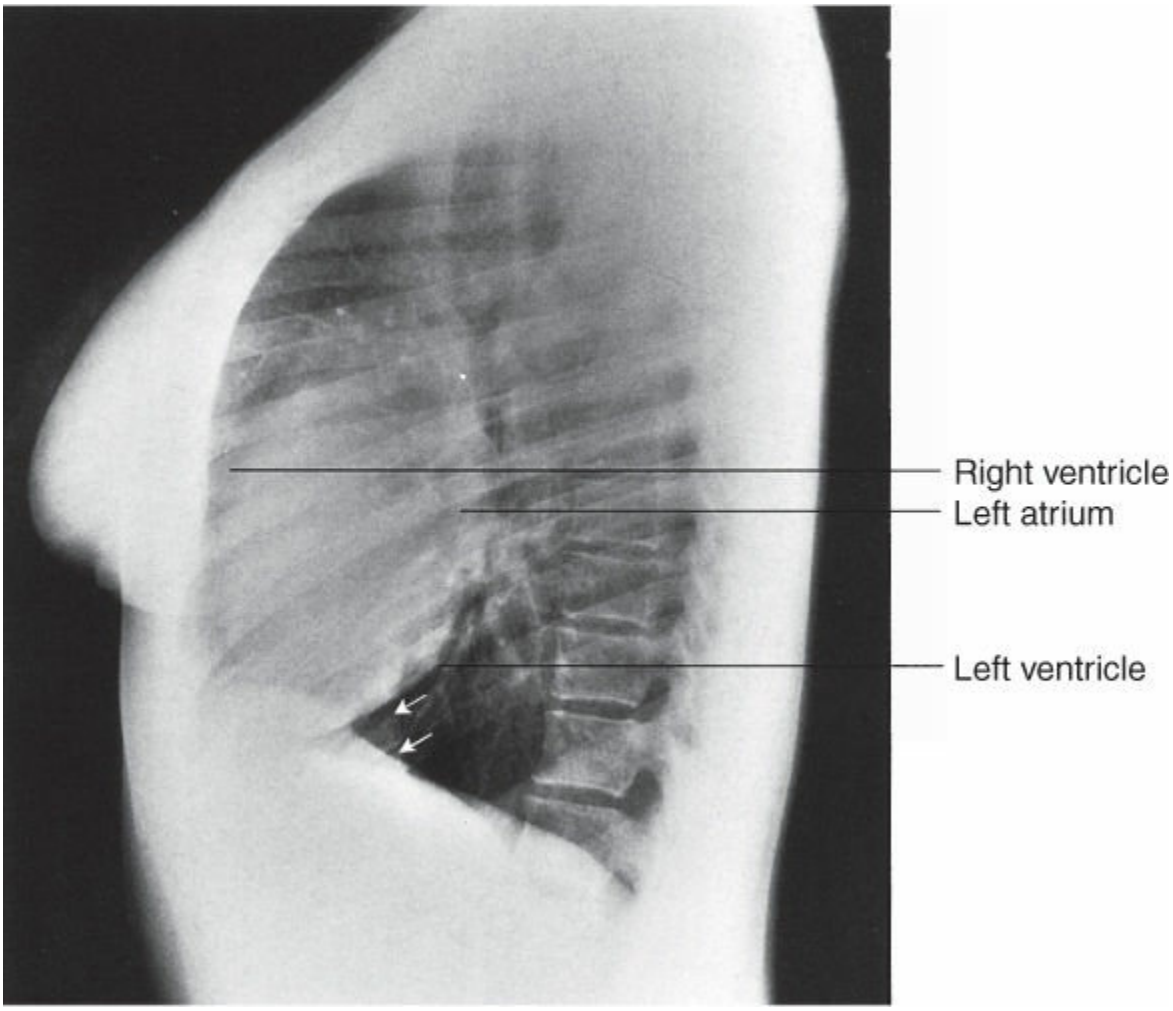
Z

Zenker's diverticulum, 3-1
Zollinger-Ellison syndrome, 3-2, 3-6
zoster, 6-11
zygomycetes, 6-4

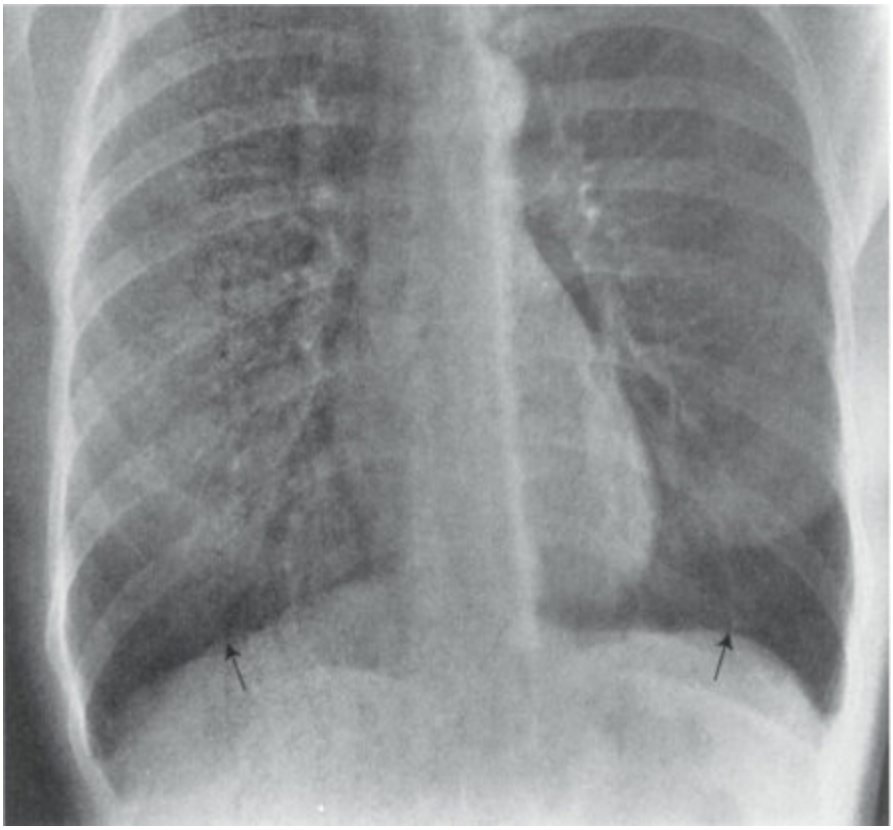
Radiology



1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology* 101, 3rd ed, 2009.)



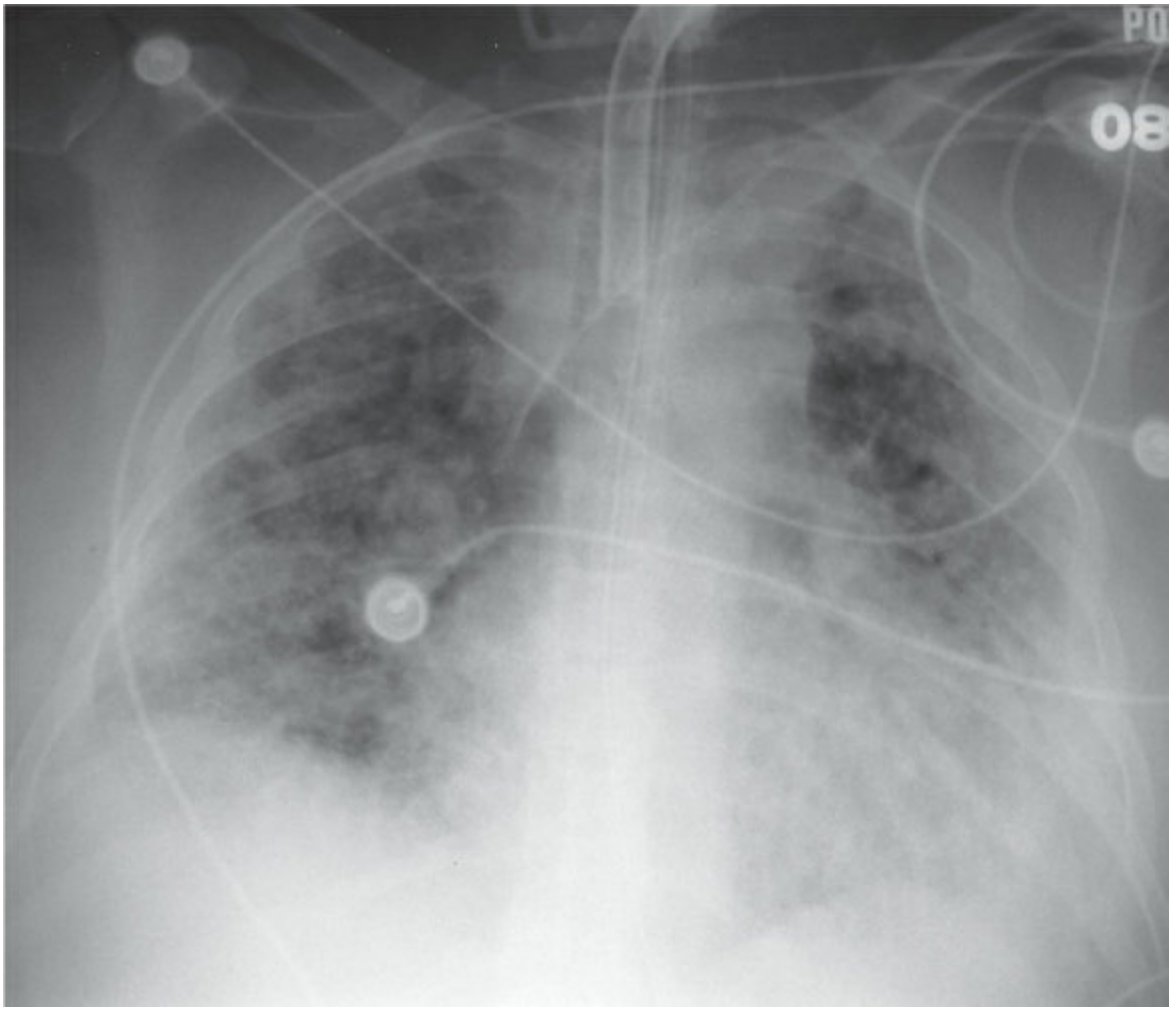
2 Normal lateral CXR. (*Radiology* 101, 3rd ed, 2009.)



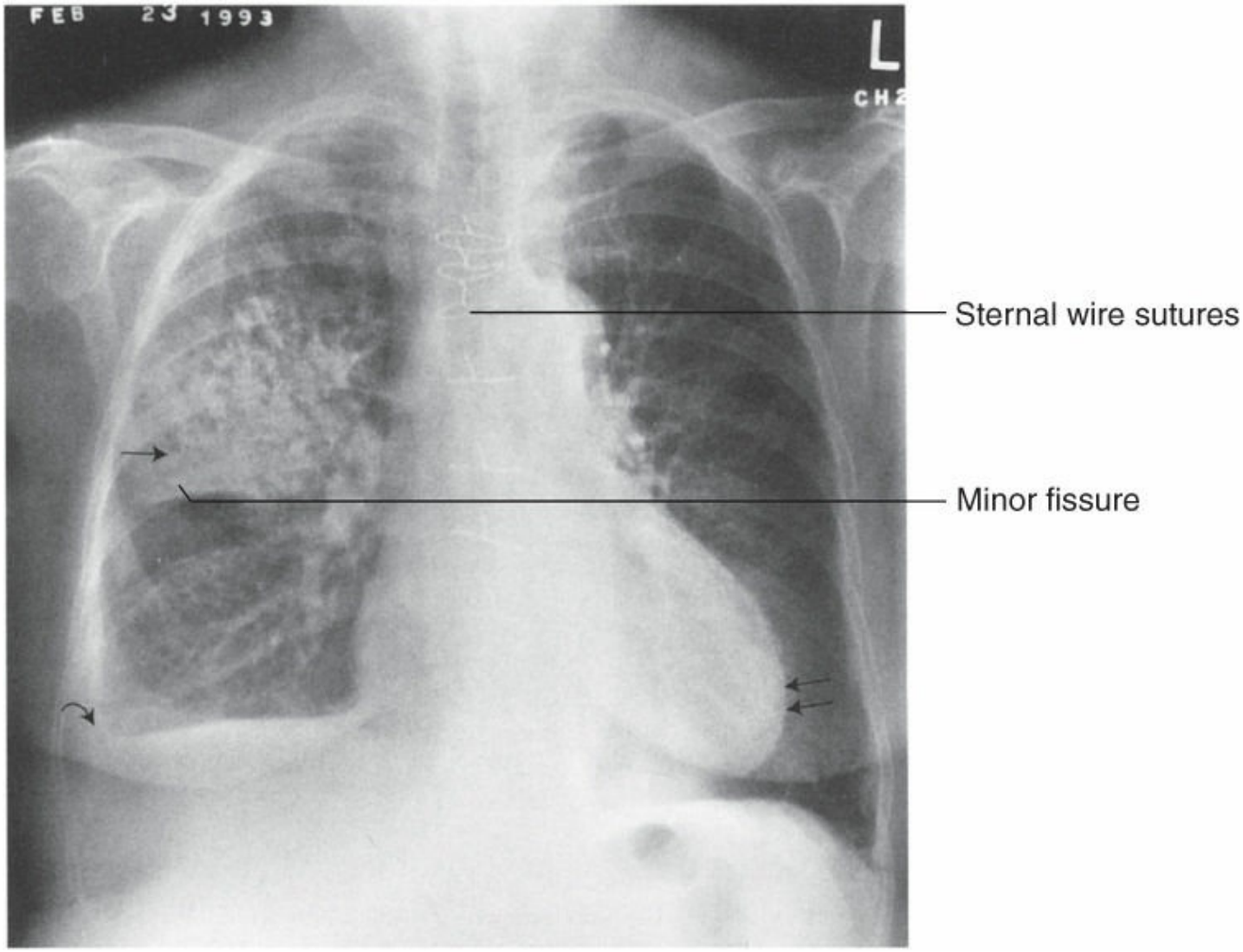
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology* 101, 3rd ed, 2009.)



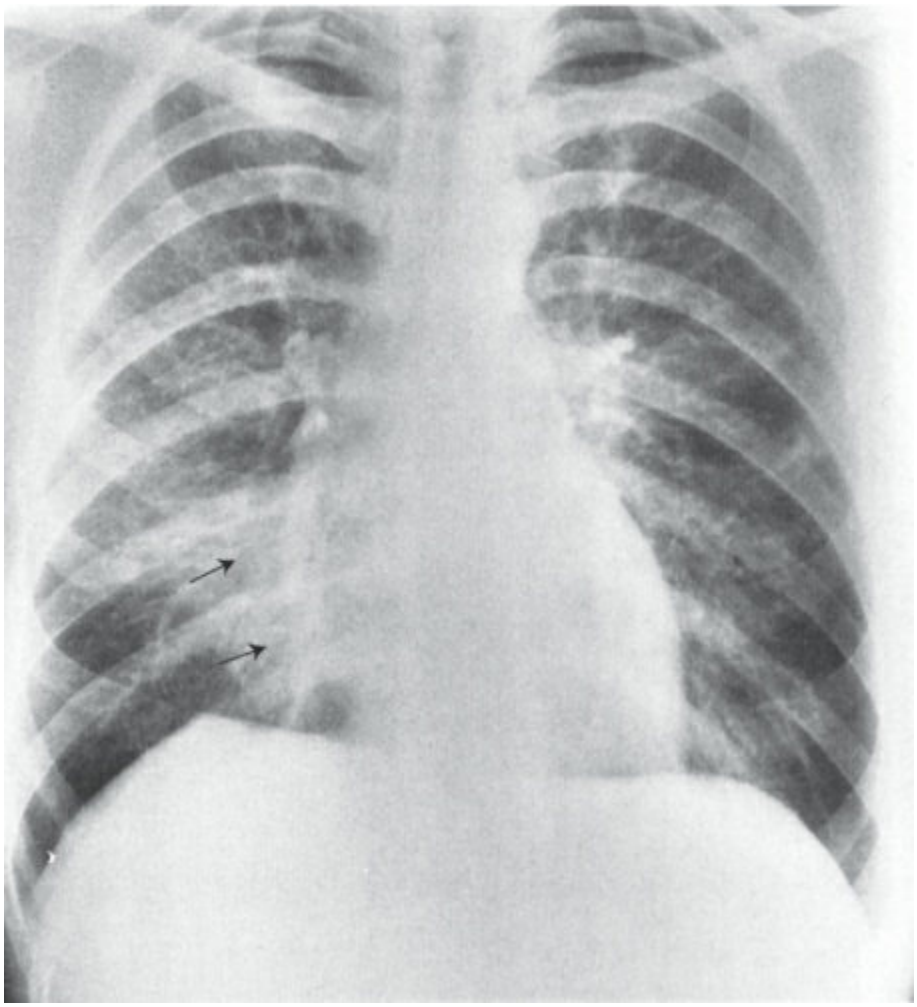
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



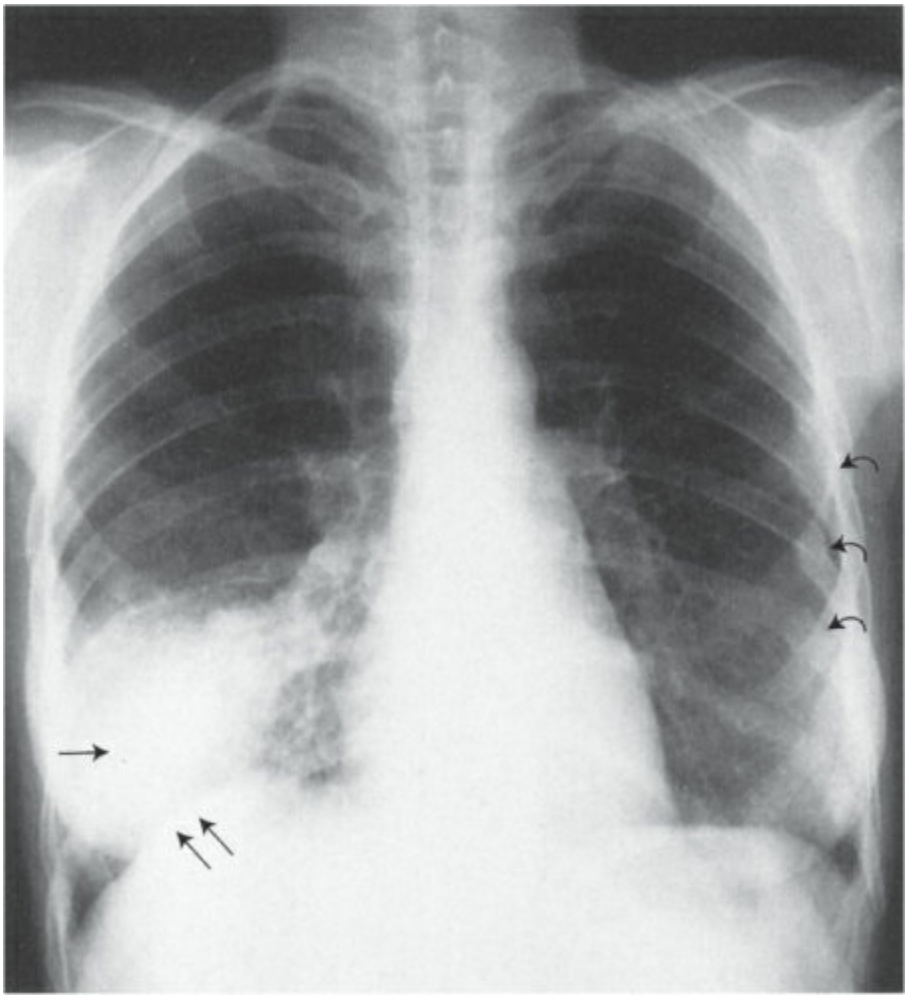
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology* 3rd ed, 2006.)



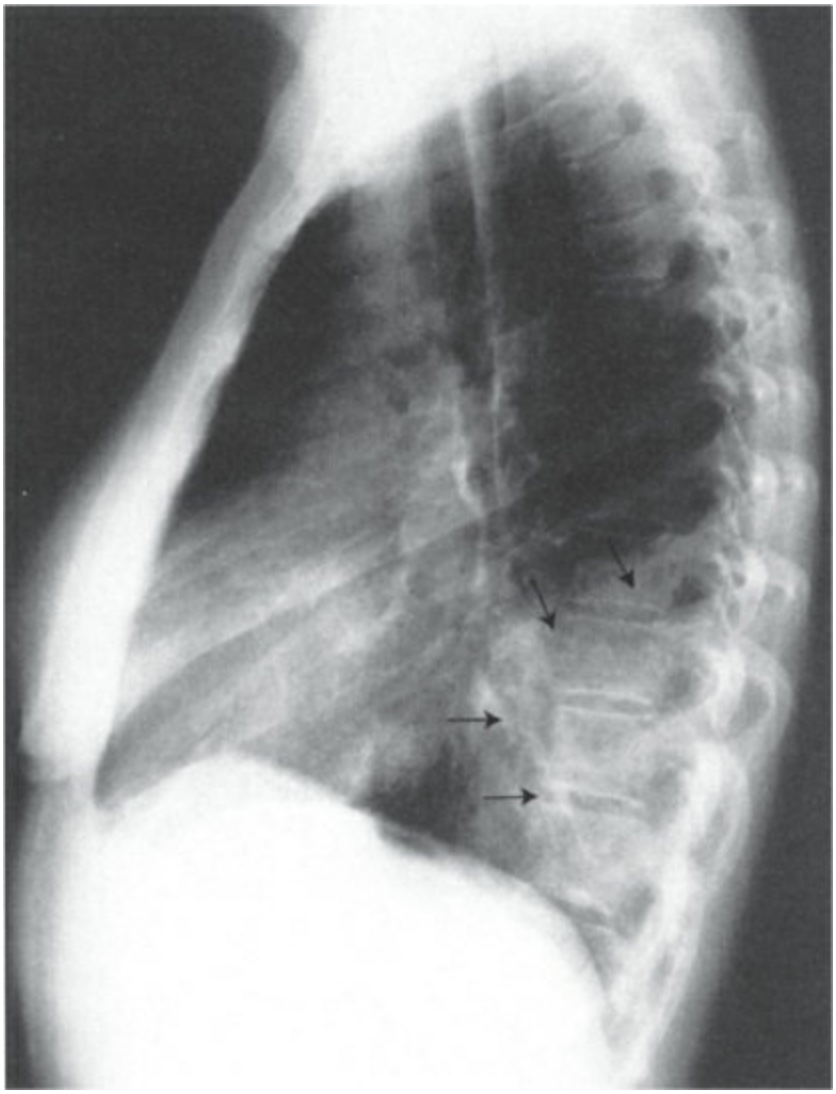
6 Right upper lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



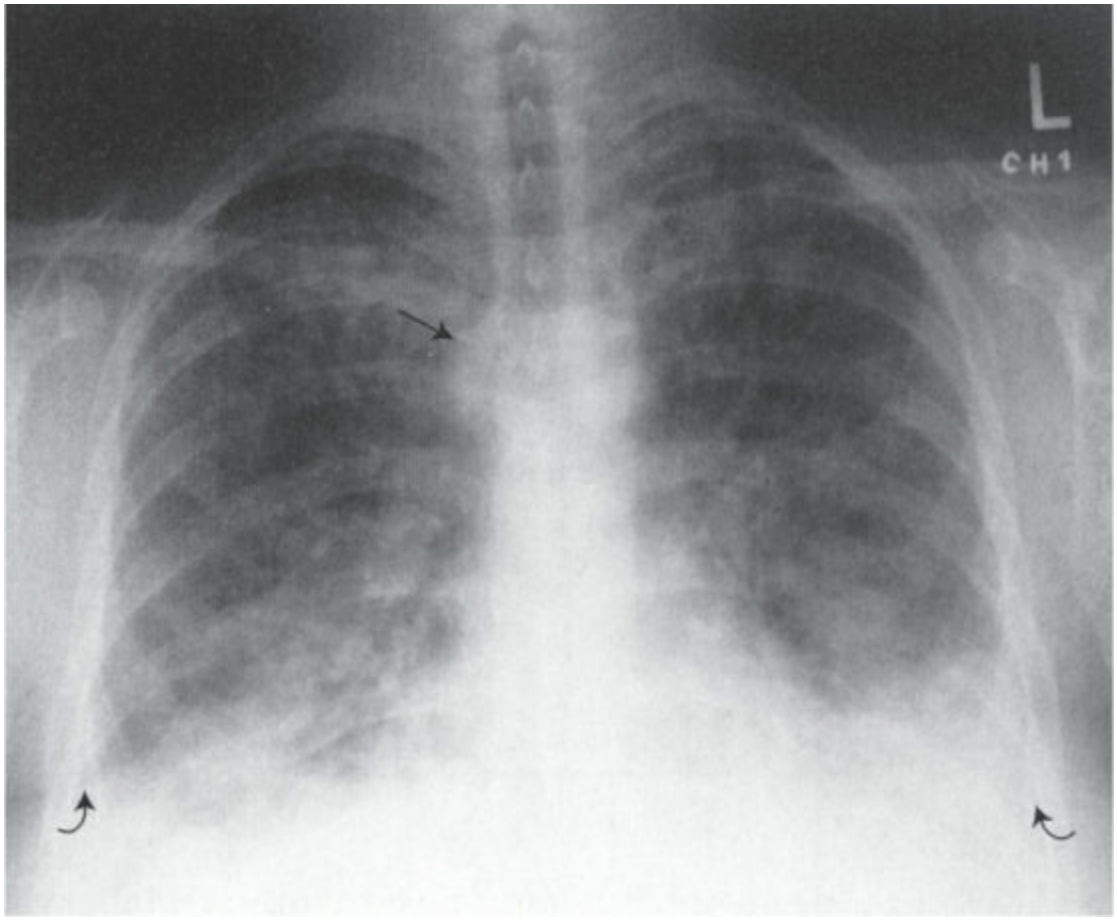
7 Right middle lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



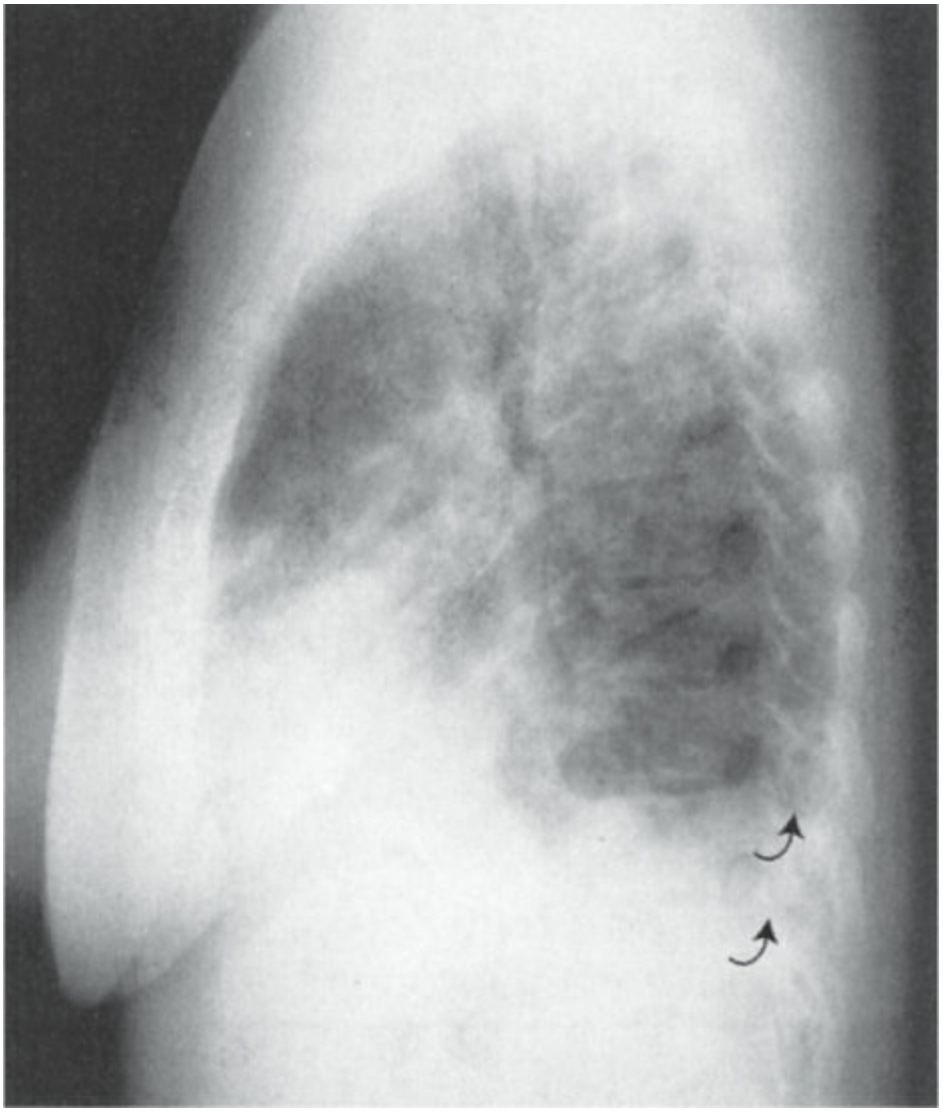
8 Right lower lobe pneumonia (PA). (*Radiology* 101, 3rd ed, 2009.)



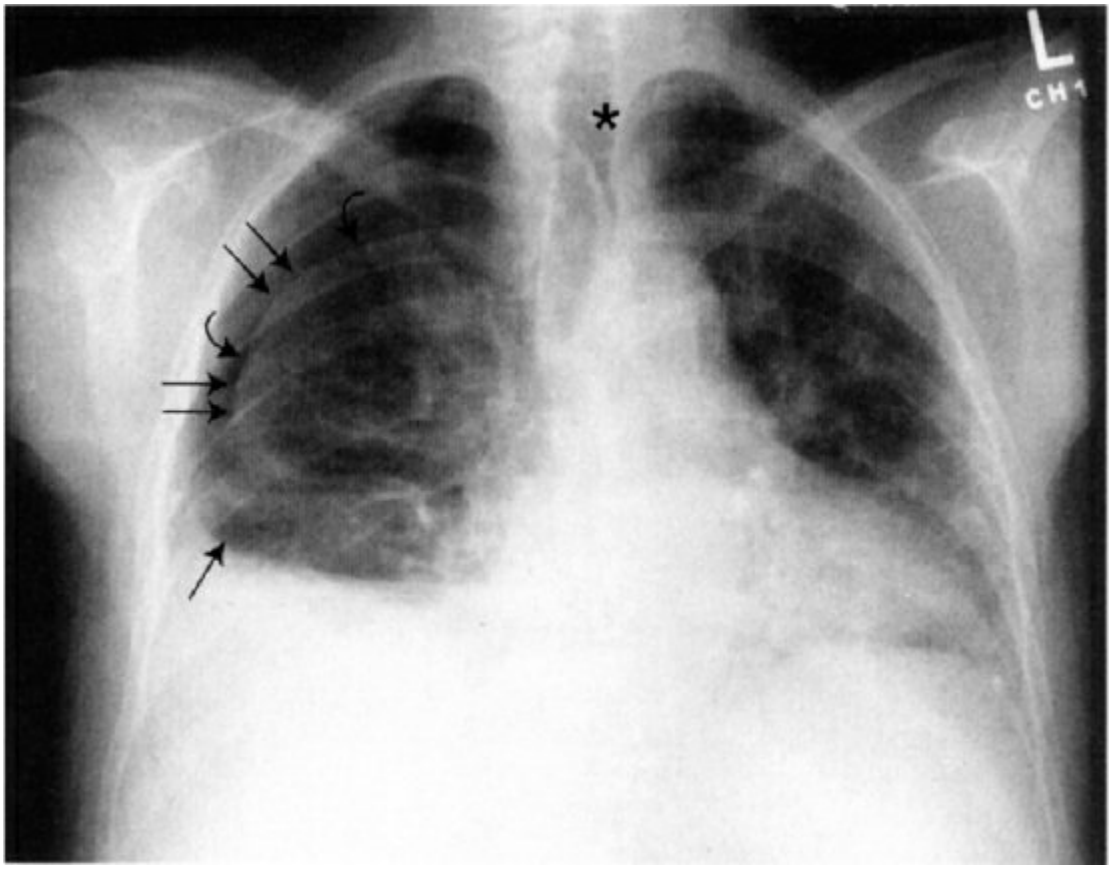
9 Right lower lobe pneumonia (lateral). (*Radiology* 101, 3rd ed, 2009.)



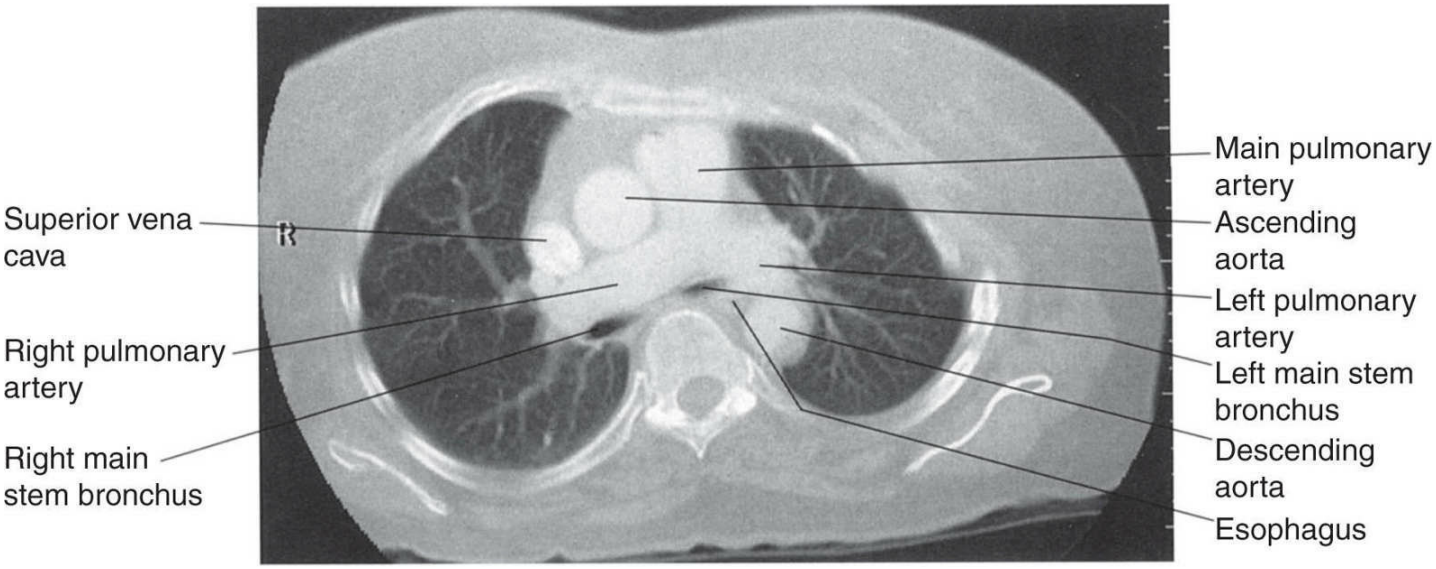
10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (*Radiology* 101, 3rd ed, 2009.)



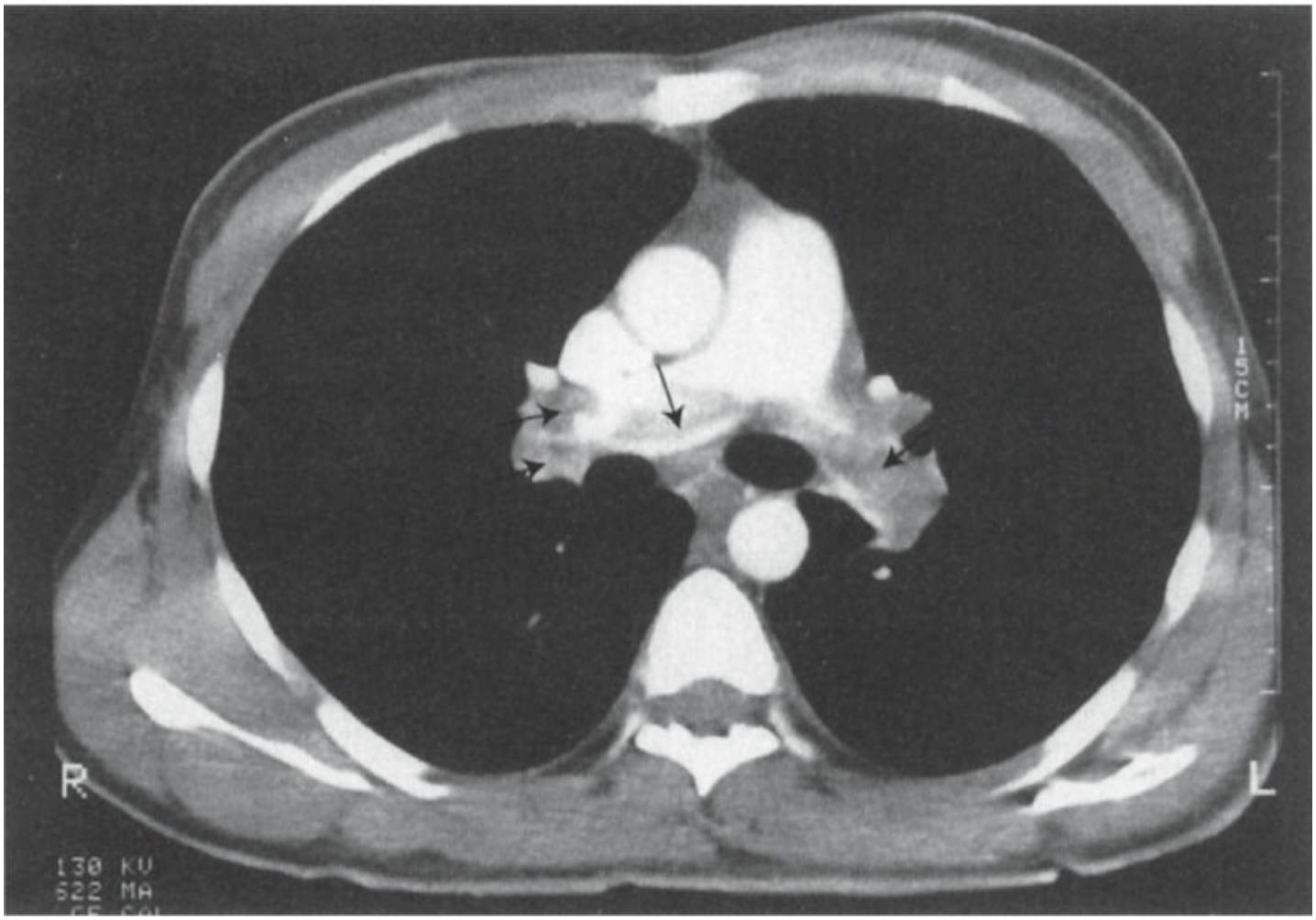
11 Bilateral pleural effusions (curved arrows) (lateral). (*Radiology* 101, 3rd ed, 2009.)



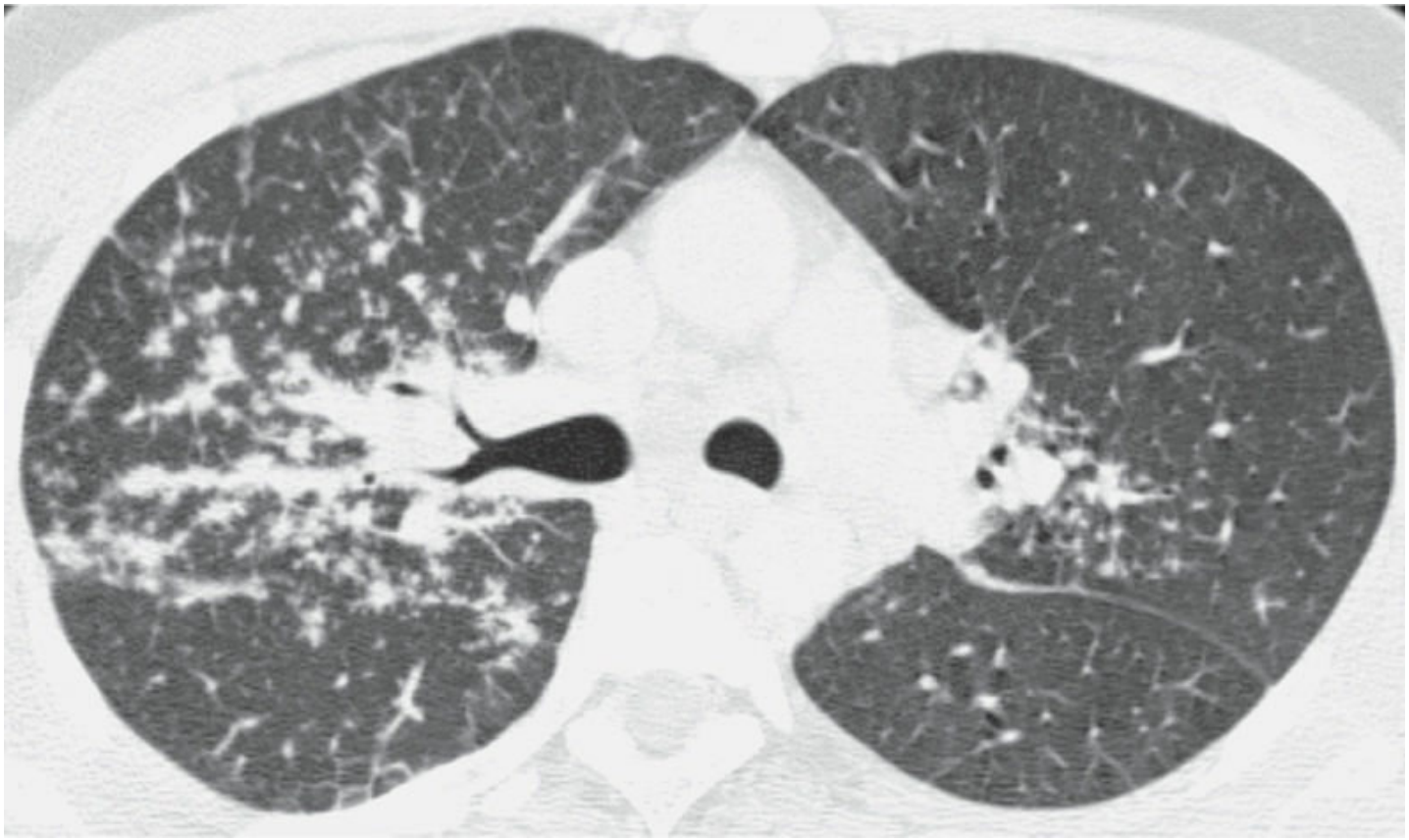
12 Pneumothorax. (*Radiology* 101, 3rd ed, 2009.)



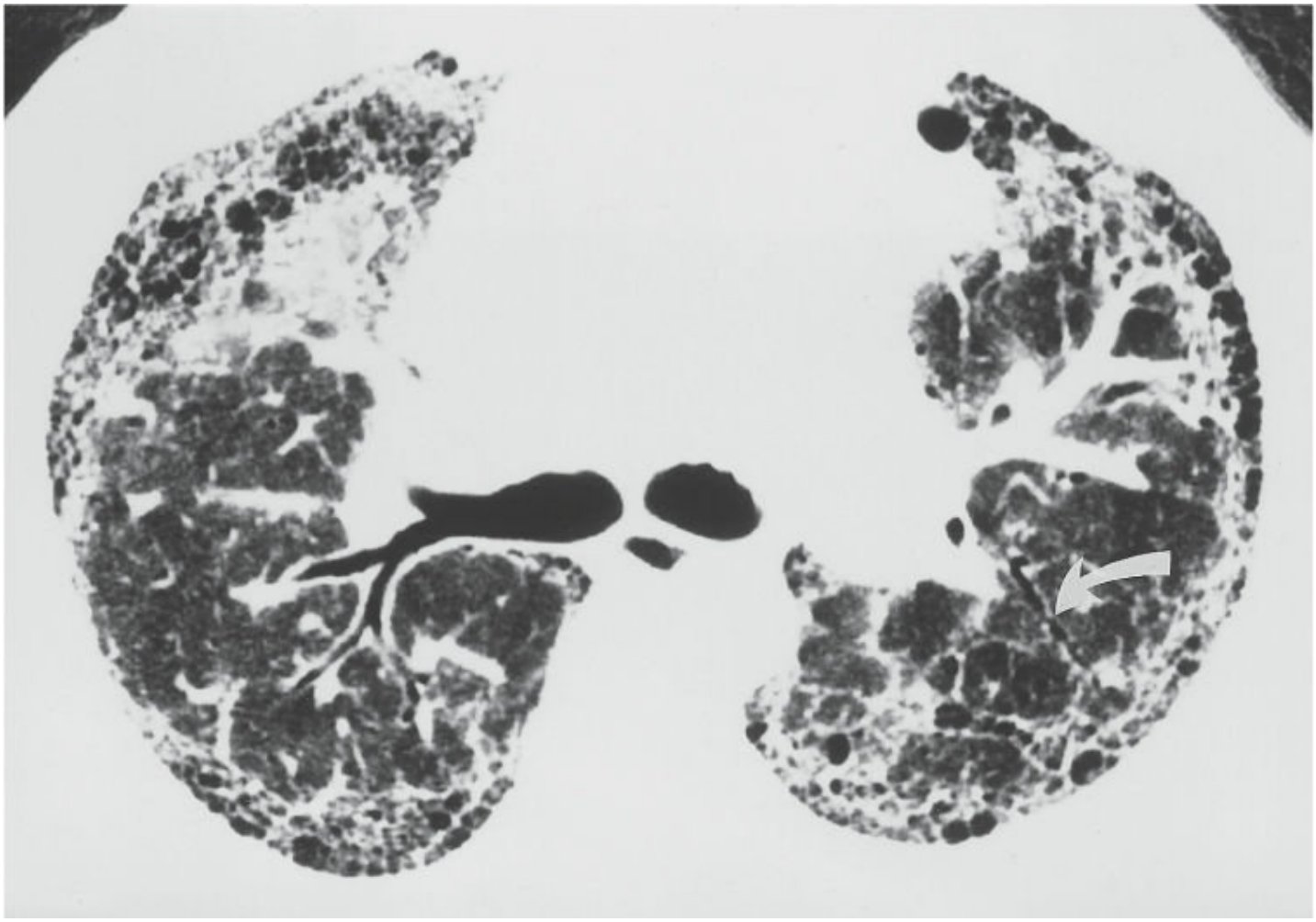
13 Normal chest CT at level of pulmonary arteries (parenchymal windows). (*Radiology* 101, 3rd ed, 2009.)



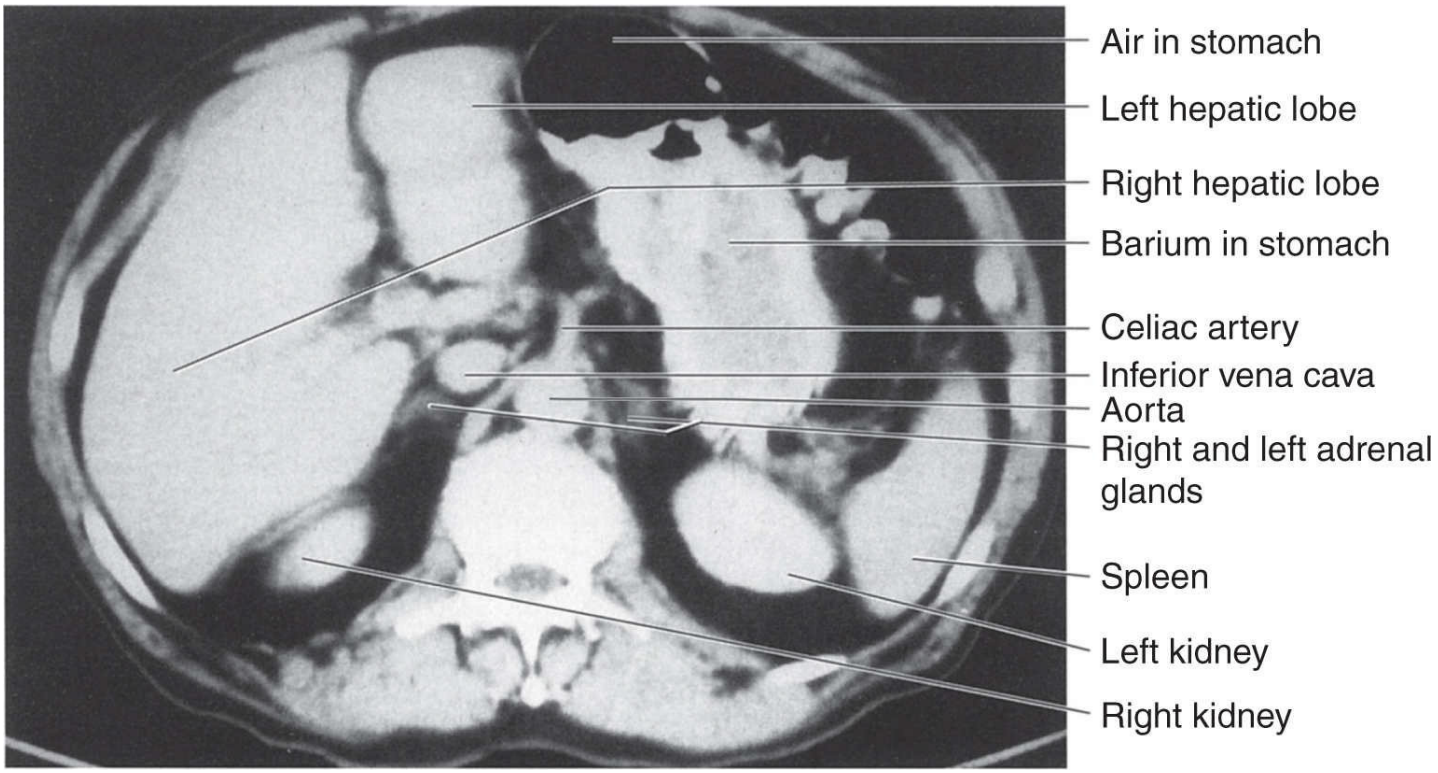
14 Bilateral PE (mediastinal windows). (*Radiology* 101, 3rd ed, 2009.)



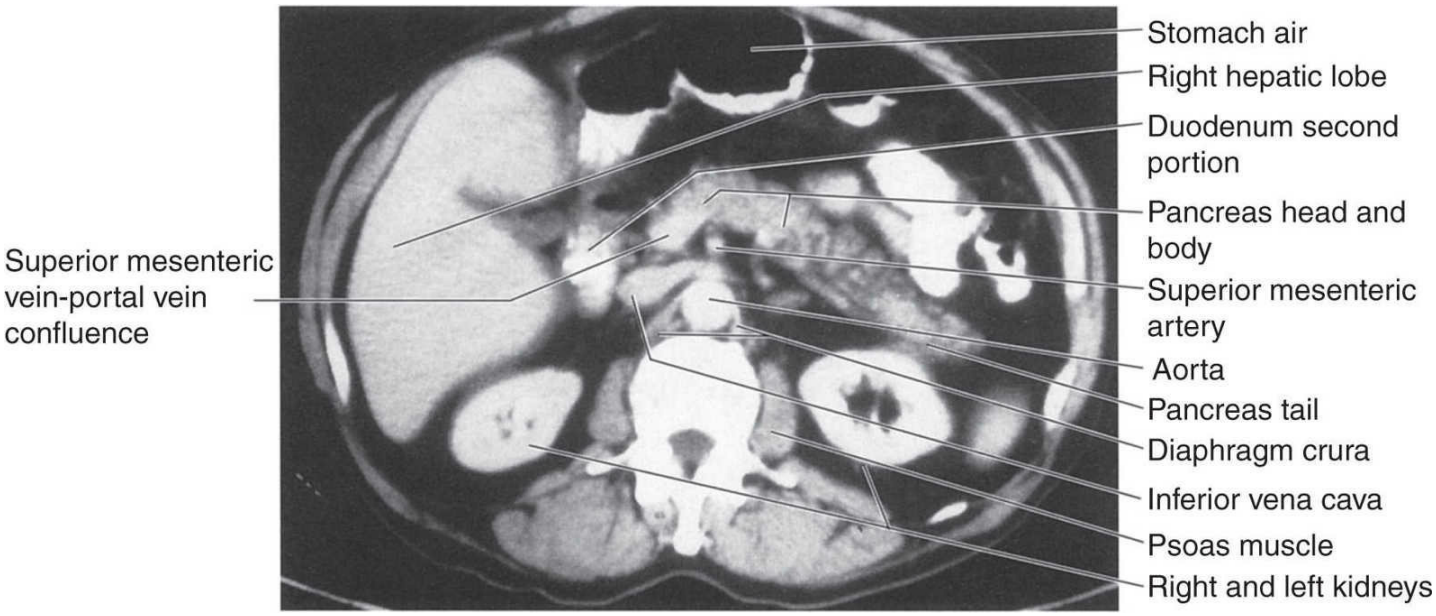
15 Sarcoidosis with perilymphatic nodules. (*Fund. Diag. Radiology* 3rd ed, 2006.)



16 Idiopathic pulmonary fibrosis. (*Fund. Diag. Radiology* 3rd ed, 2006.)

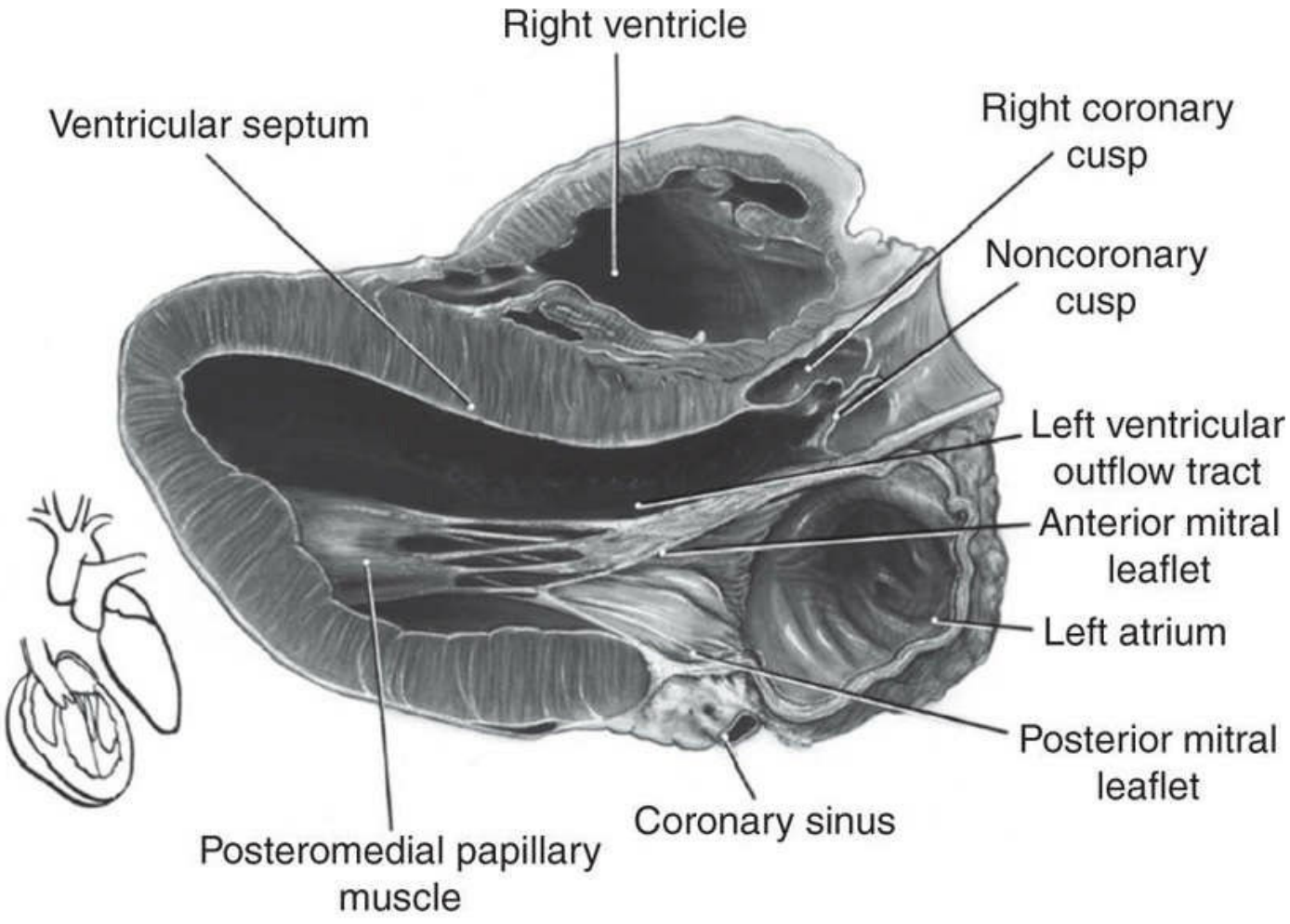


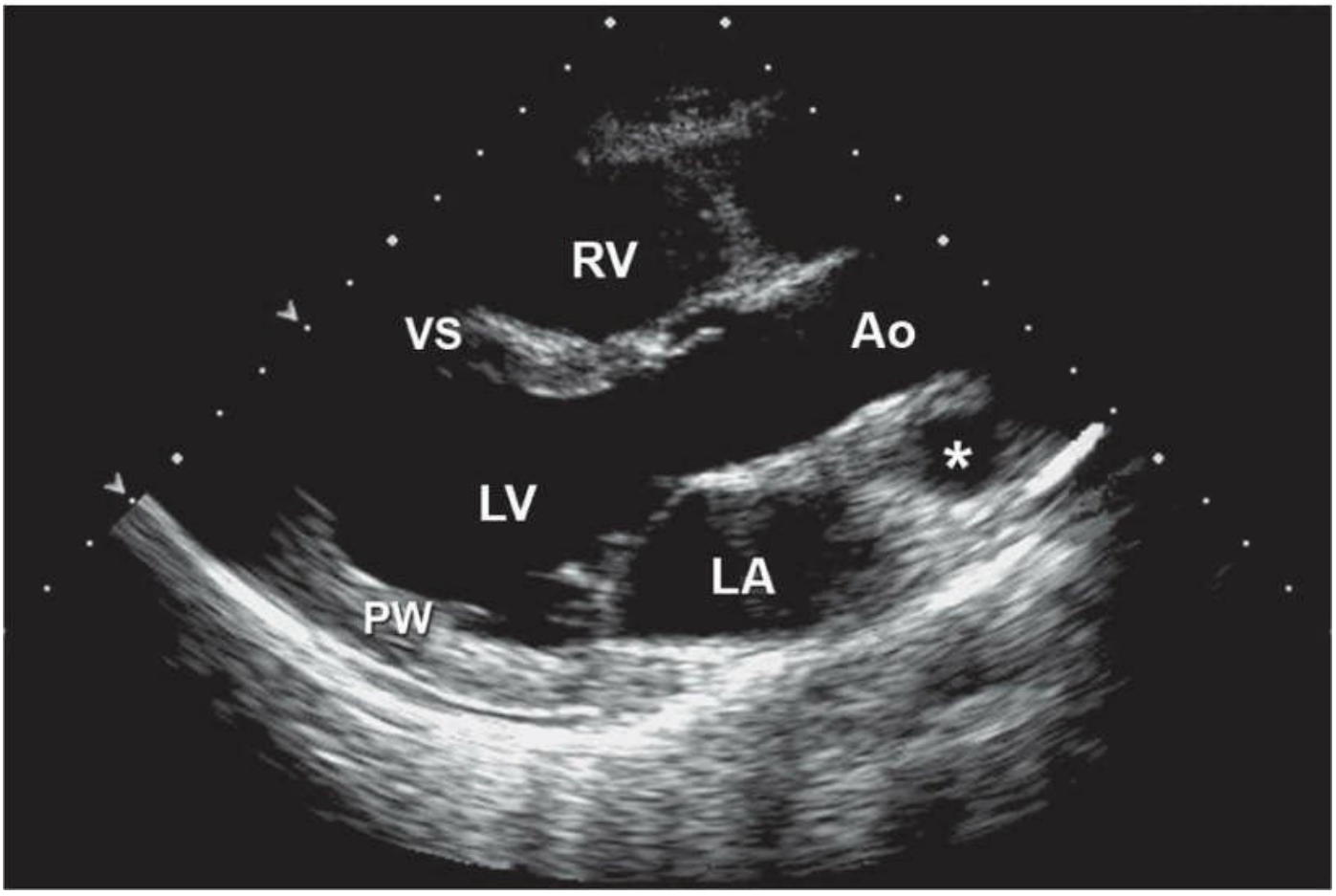
17 Normal abdomen CT at level of liver & spleen. (*Radiology* 101, 3rd ed, 2009.)



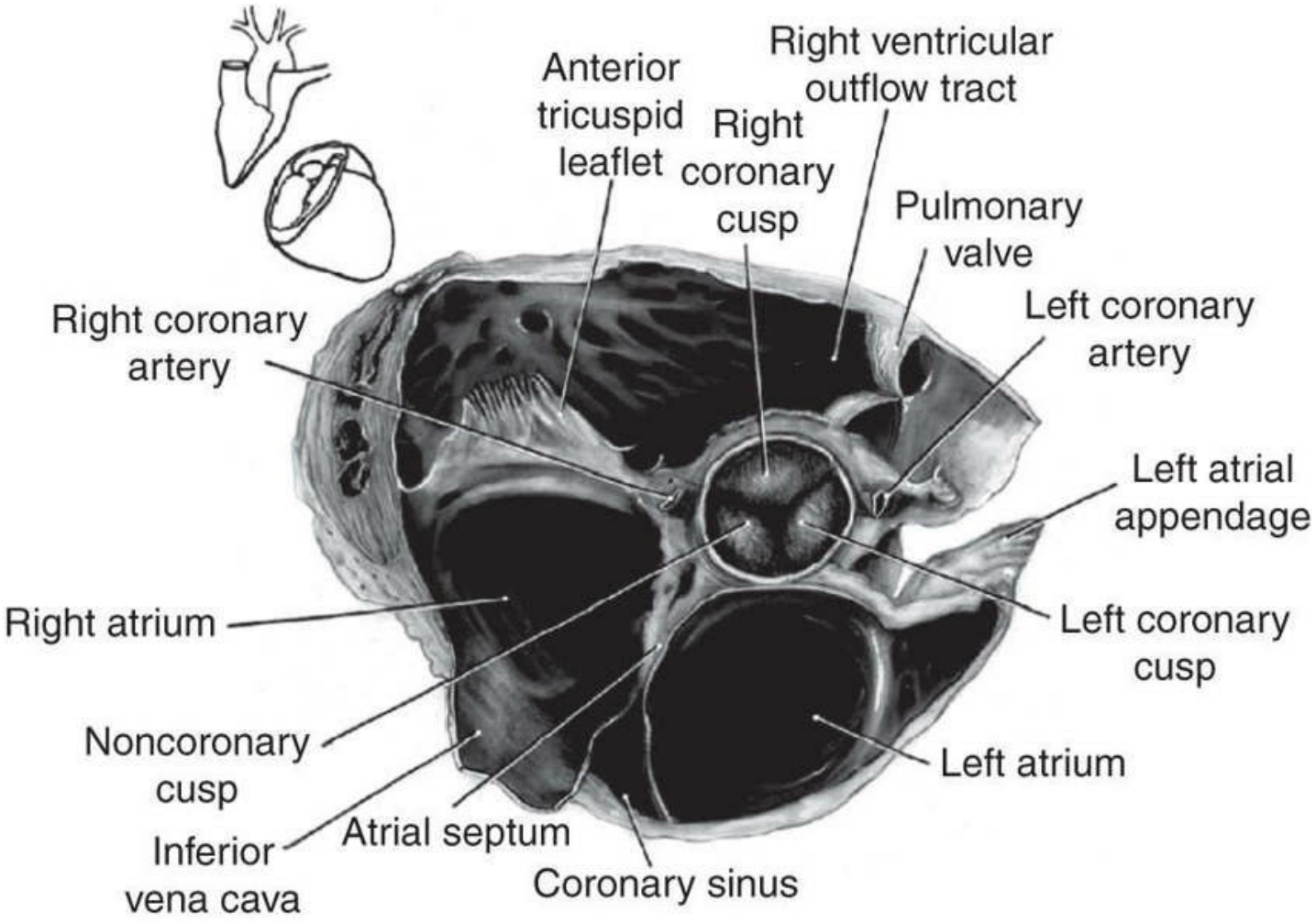
18 Normal abdomen CT at level of pancreas. (*Radiology* 101, 3rd ed, 2009.)

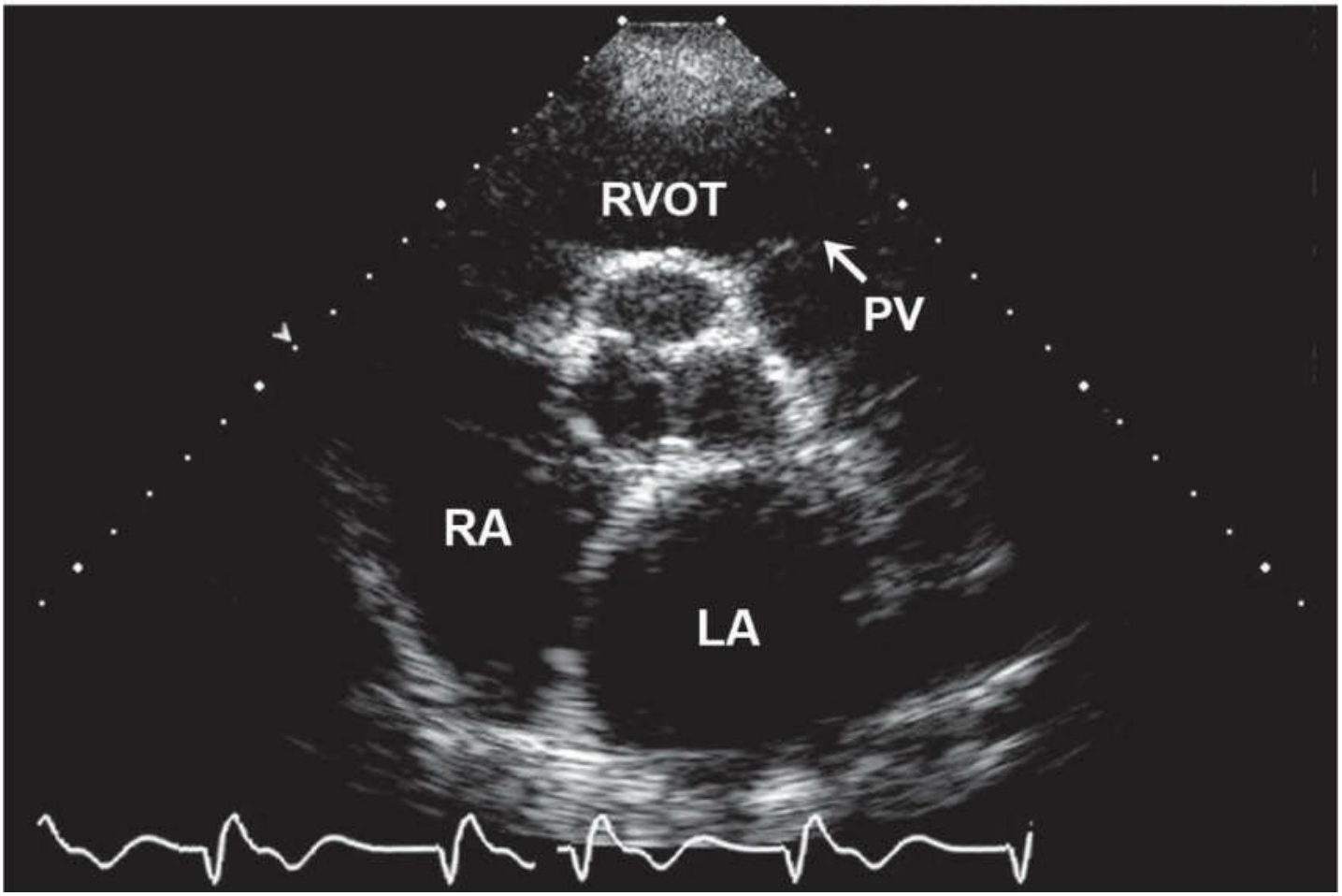
Echocardiography


Right ventricle
Ventricular septum
Right coronary cusp
Noncoronary cusp
Left ventricular outflow tract
Anterior mitral leaflet
Left atrium
Posterior mitral leaflet
Coronary sinus
Posteromedial papillary muscle

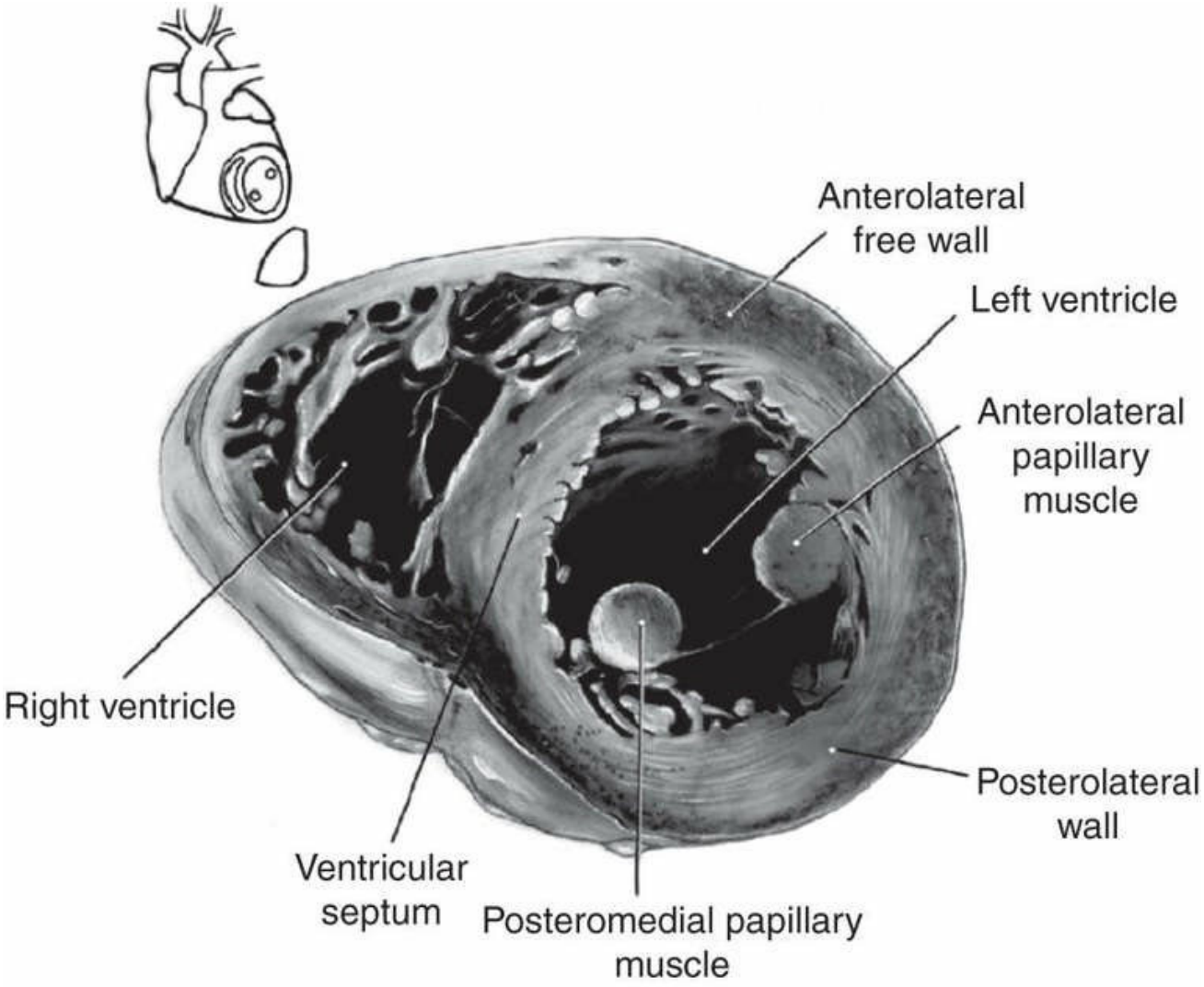

RV
VS
Ao
*
LV
LA
PW

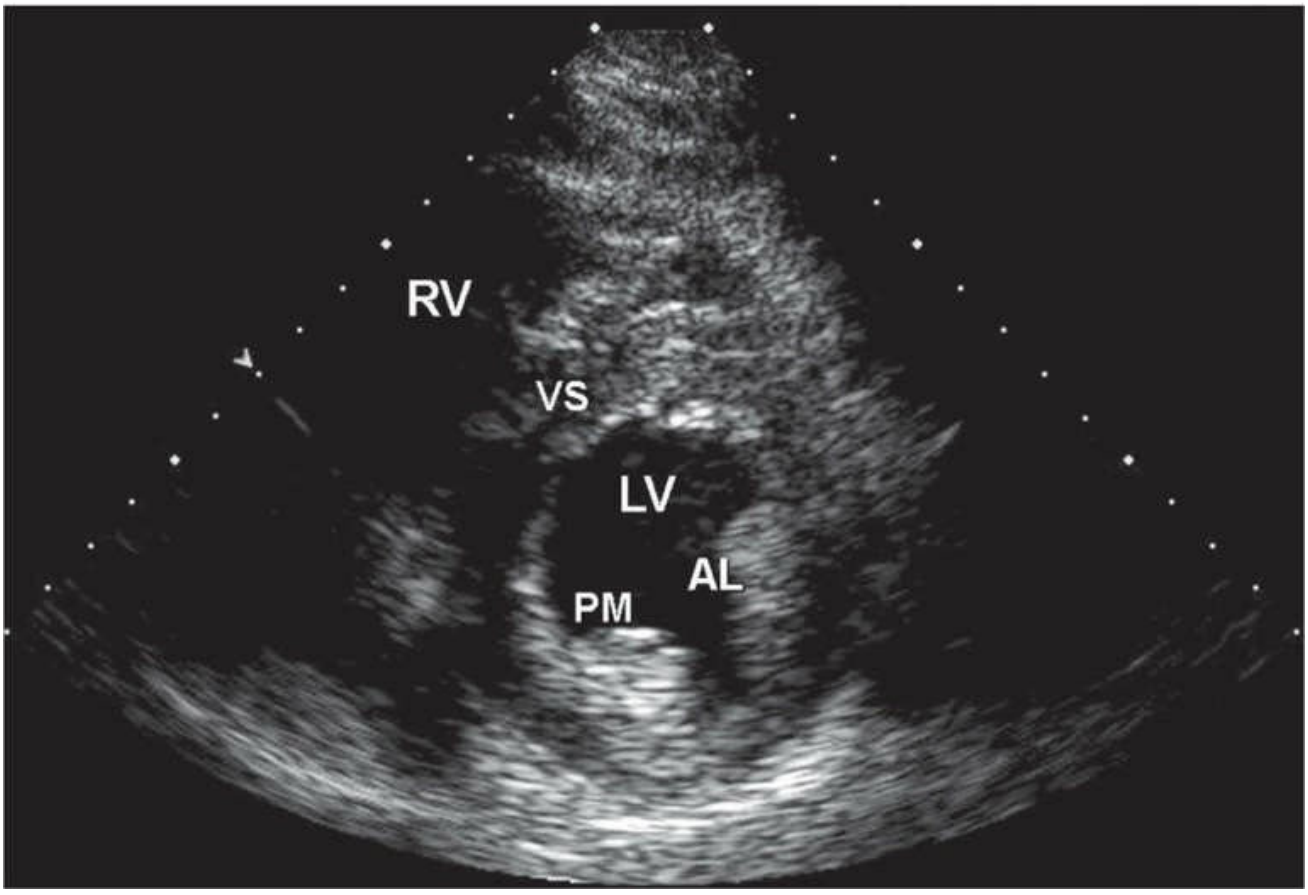
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ven- tricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, *3rd ed*. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Anterior tricuspid leaflet
Right ventricular outflow tract
Right coronary cusp
Pulmonary valve
Right coronary artery
Left coronary artery
Left atrial appendage
Right atrium
Left coronary cusp
Noncoronary cusp
Left atrium
Inferior vena cava
Atrial septum
Coronary sinus

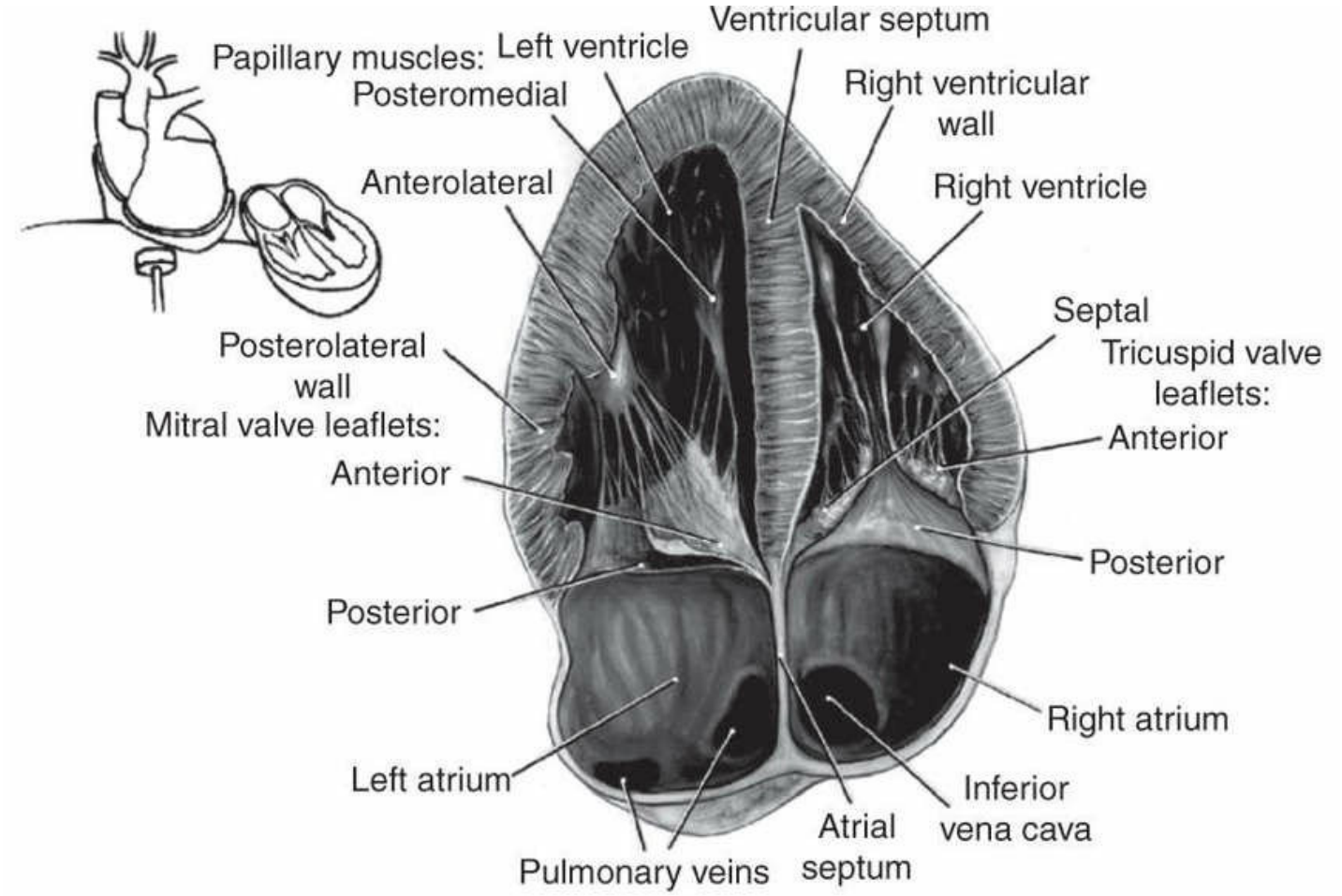

RVOT
PV
RA
LA

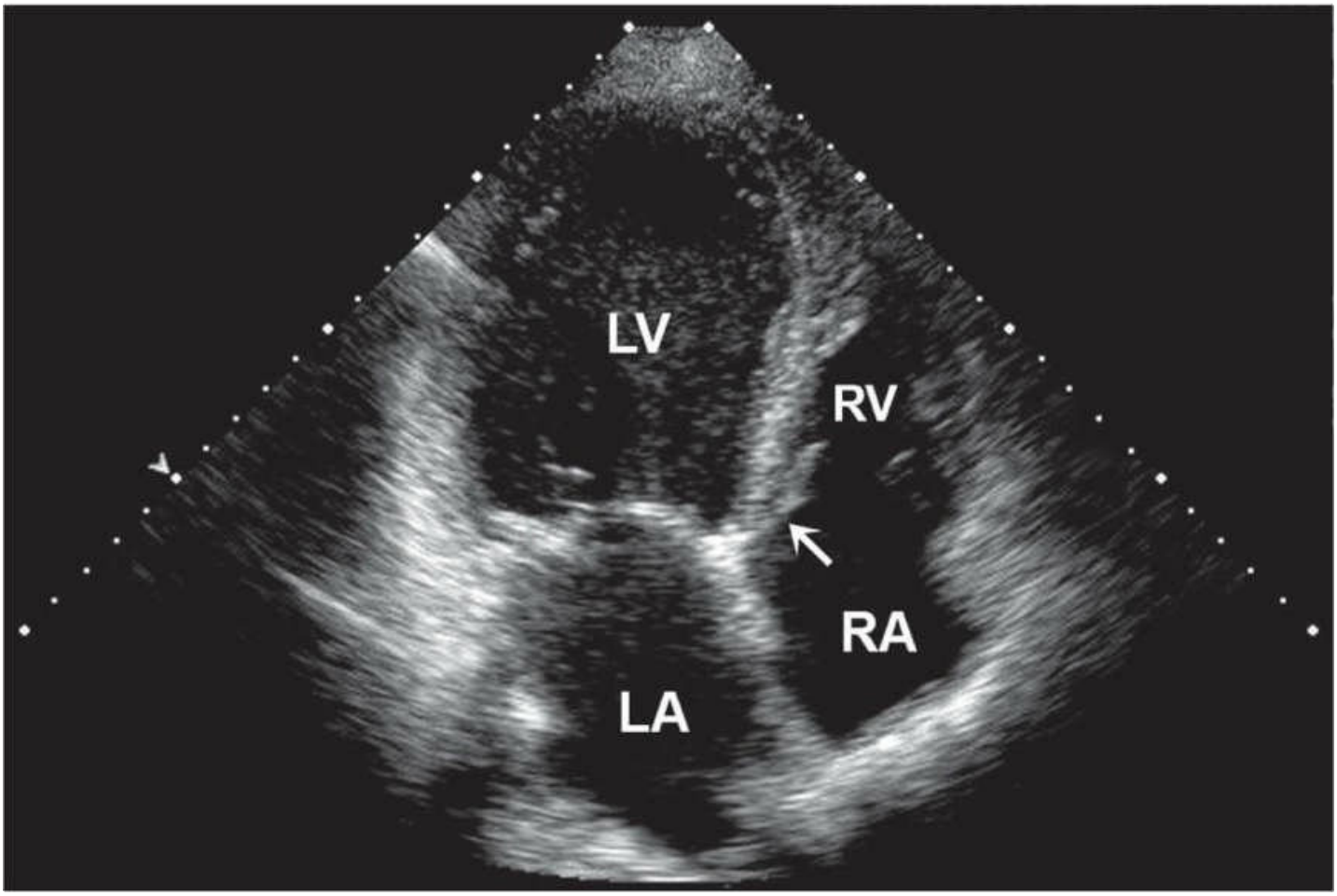
2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From Mayo Clinic Proceedings [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)


Anterolateral
free wall
Left ventricle
Anterolateral
papillary
muscle
Right ventricle
Posterolateral
wall
Ventricular
septum
Posteromedial papillary
muscle


RV
VS
LV
AL
PM

3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left ventricle. (Top: From *Mayo Clinic Proceedings* [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

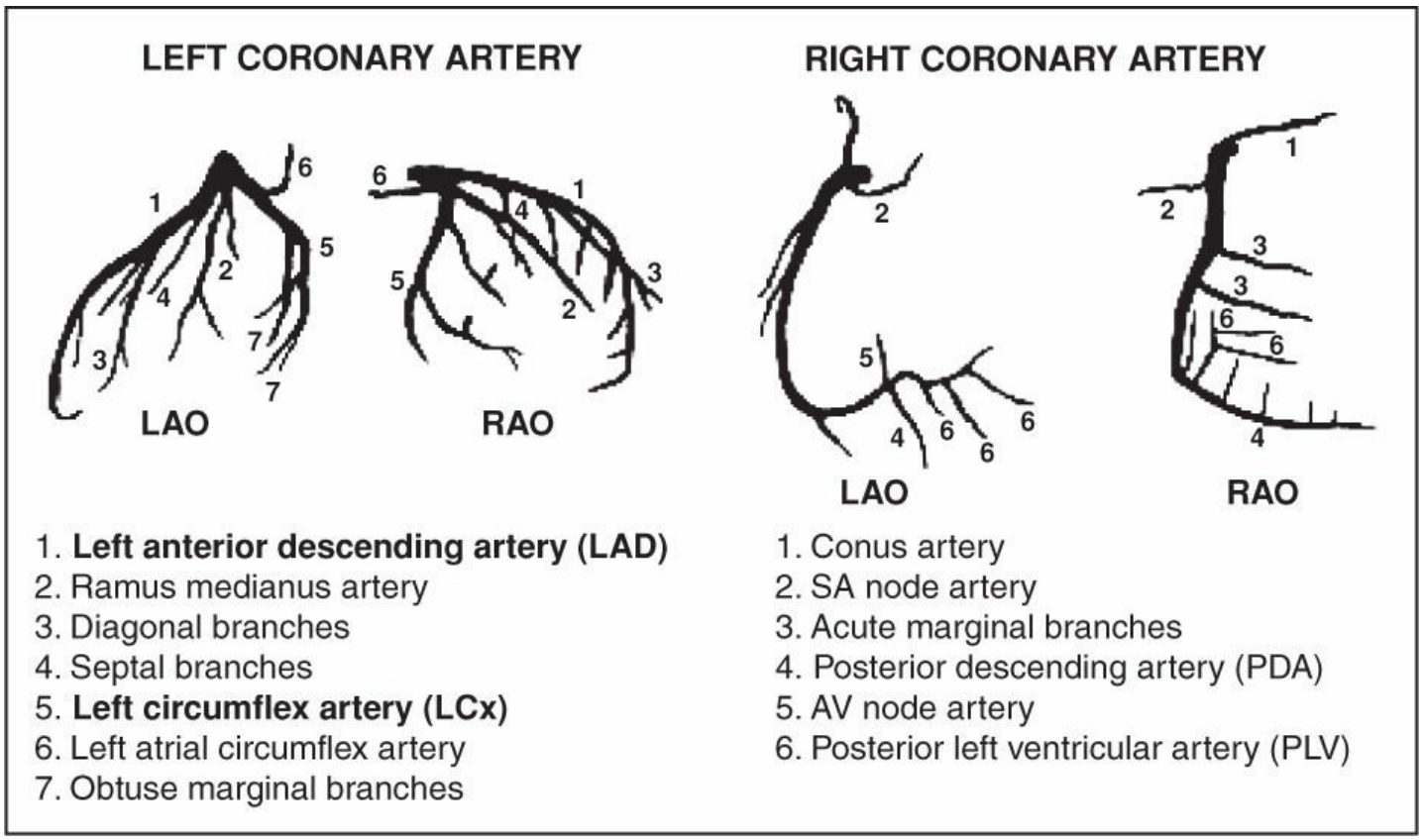




4 Apical four-chamber view: Note that at some institutions the image is reversed so that the left side of the heart appears on

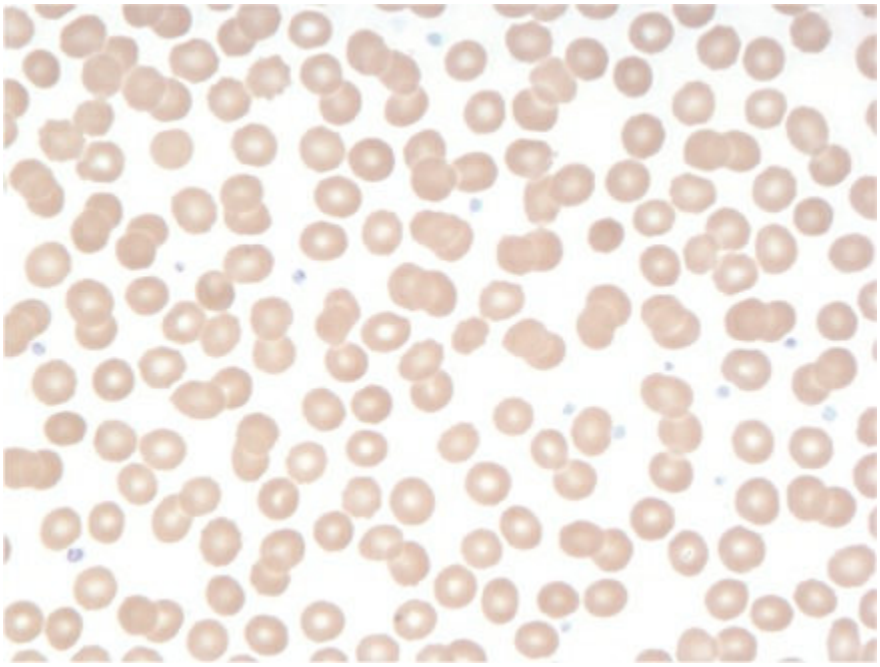
the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From *Mayo Clinic Proceedings* [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. *Mayo Clinic Proceedings*, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Coronary Angiography

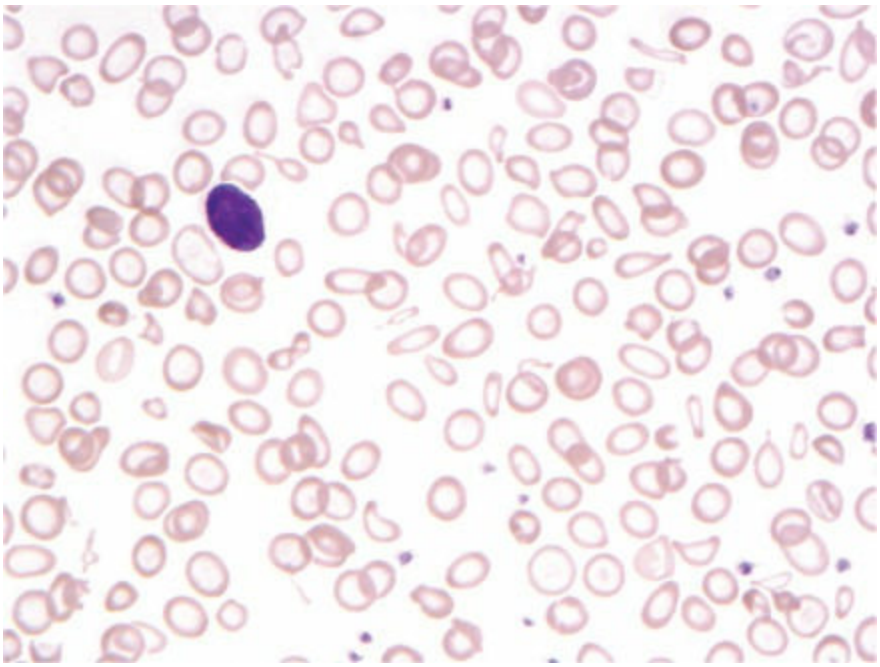


Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

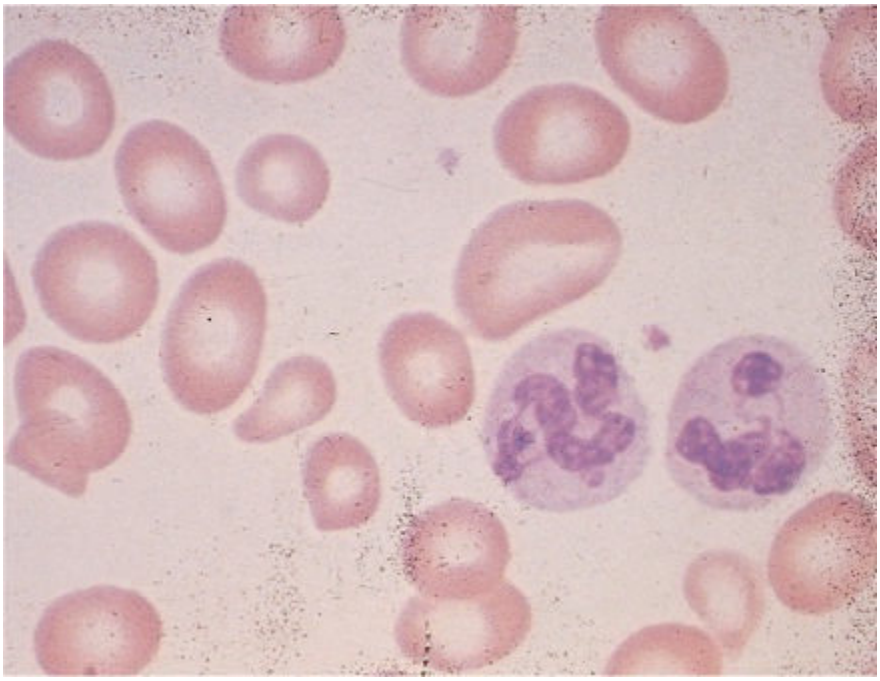
Peripheral Blood Smears



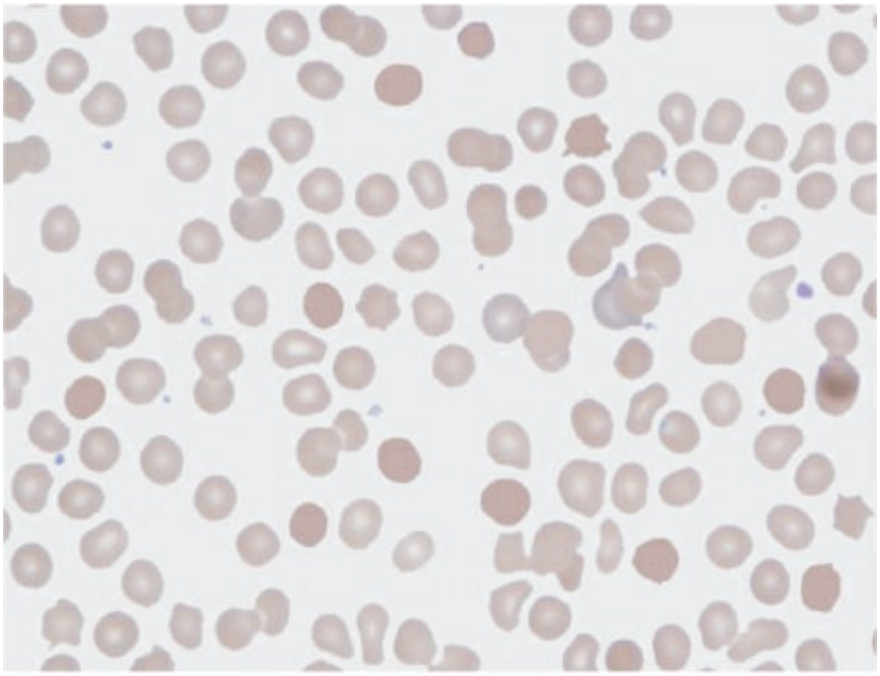
1 Normal smear.



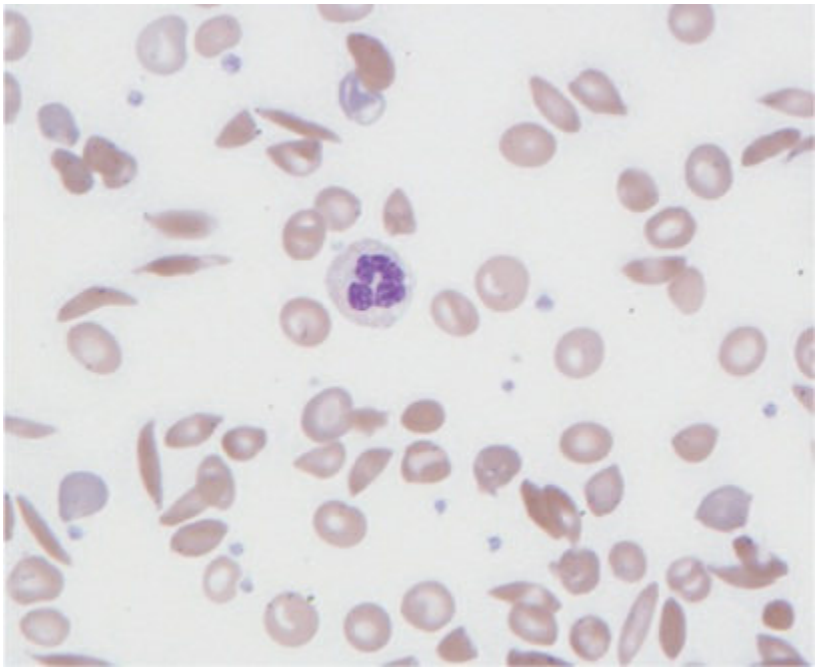
2 Hypochromic, microcytic anemia due to iron-deficiency.



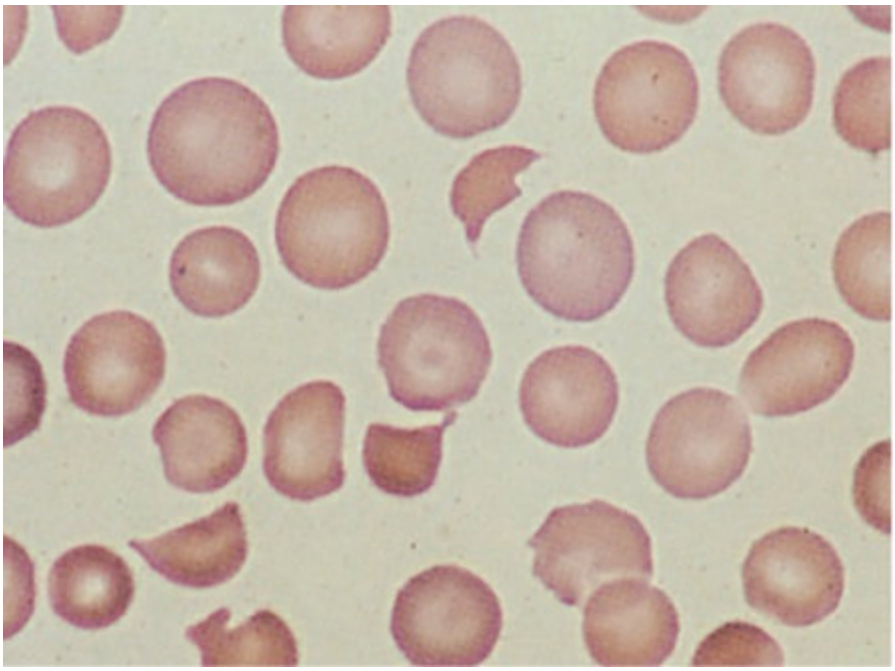
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



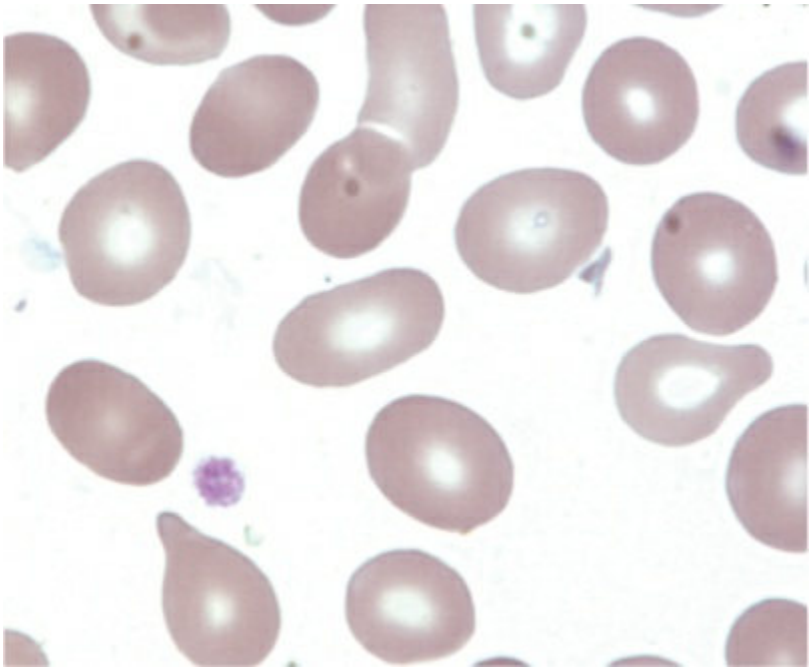
4 Spherocytes due to autoimmune hemolytic anemia.



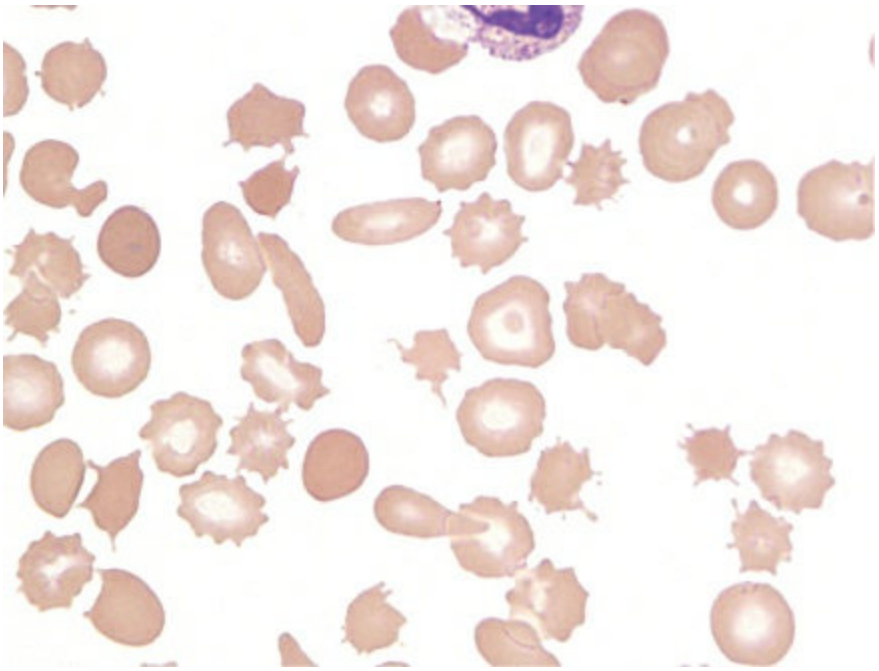
5 Sickle cell anemia.



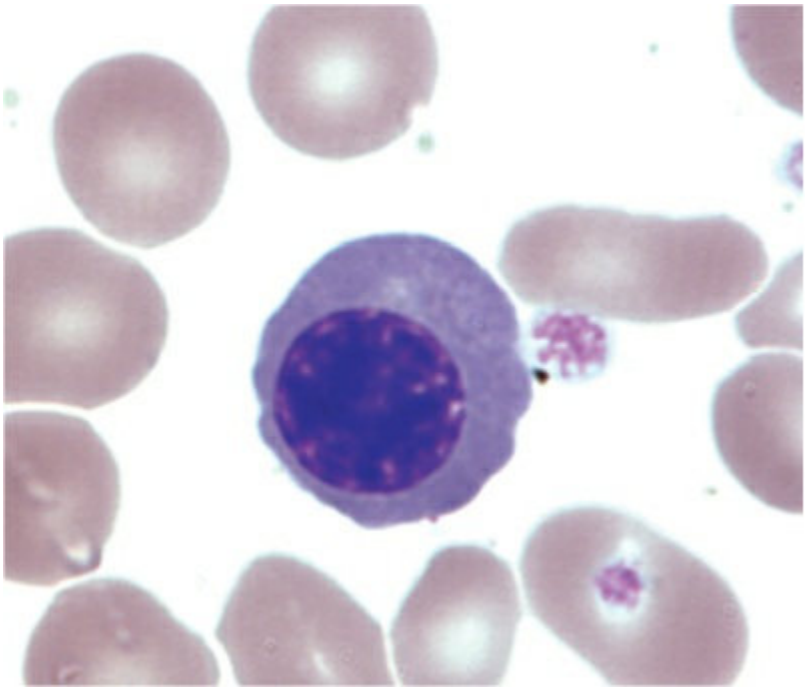
6 Schistocytes.



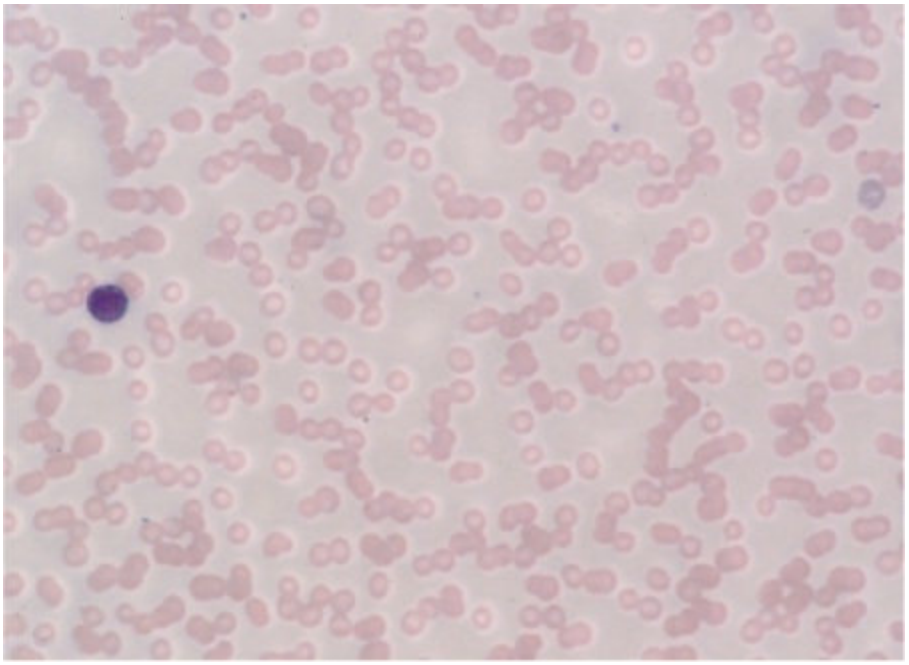
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

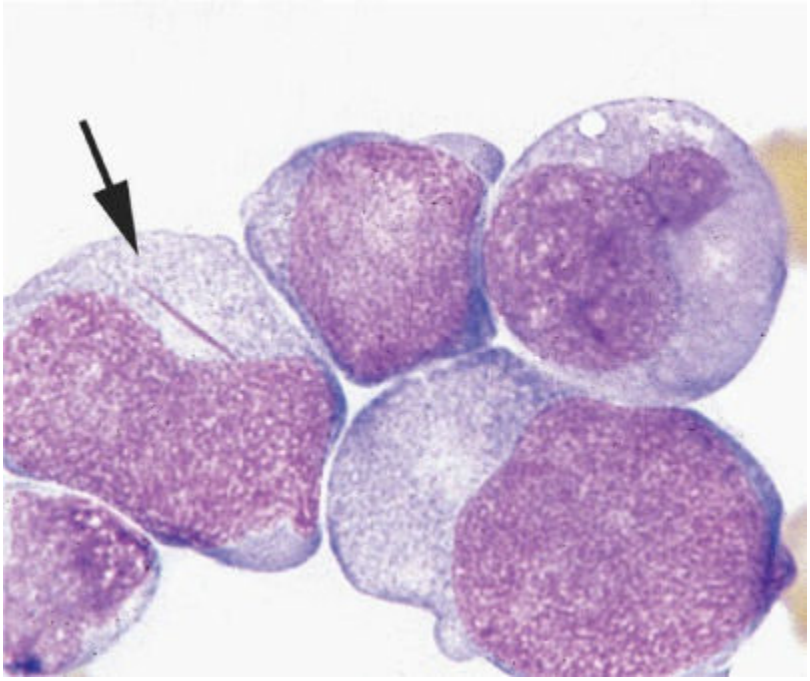


9 Nucleated RBC.

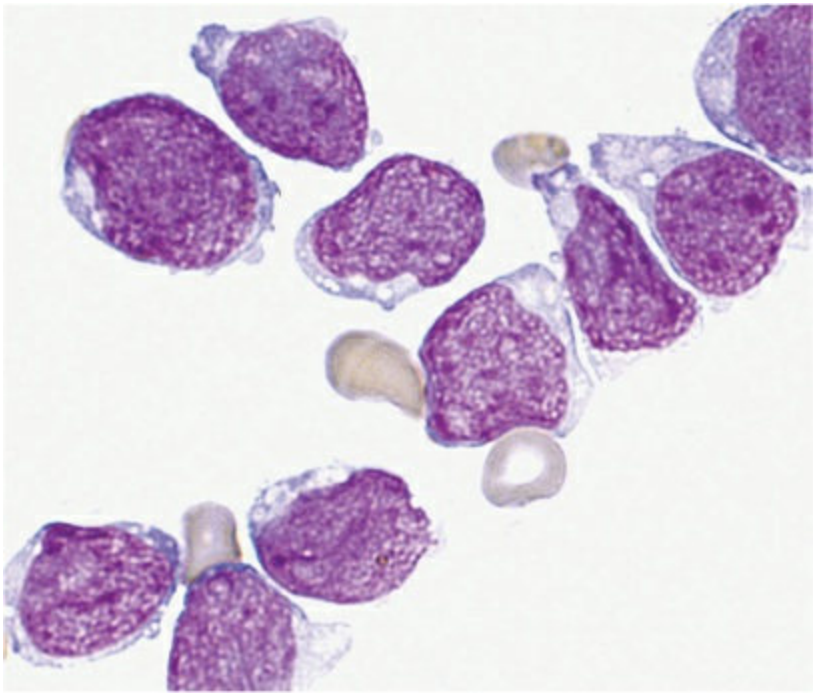


10 Rouleaux.

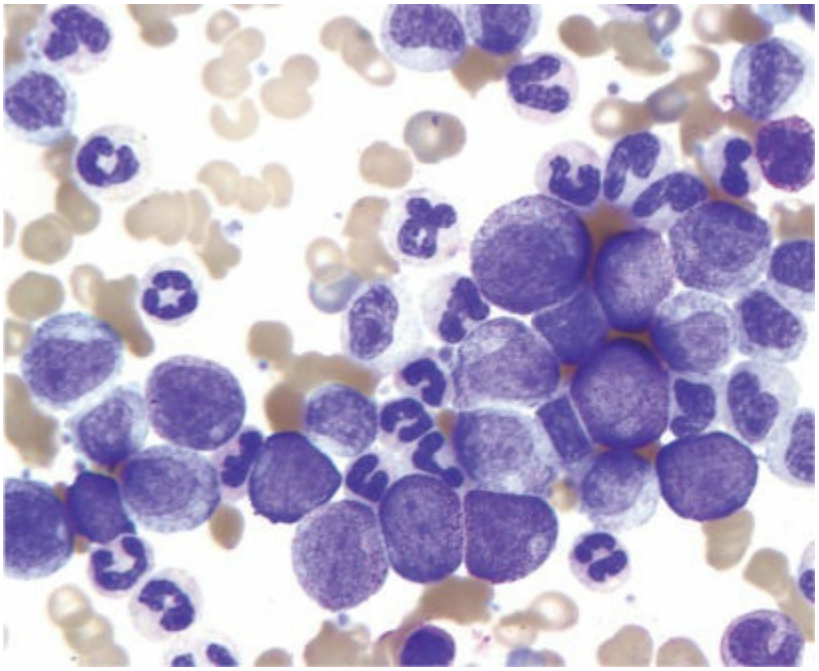
Leukemias



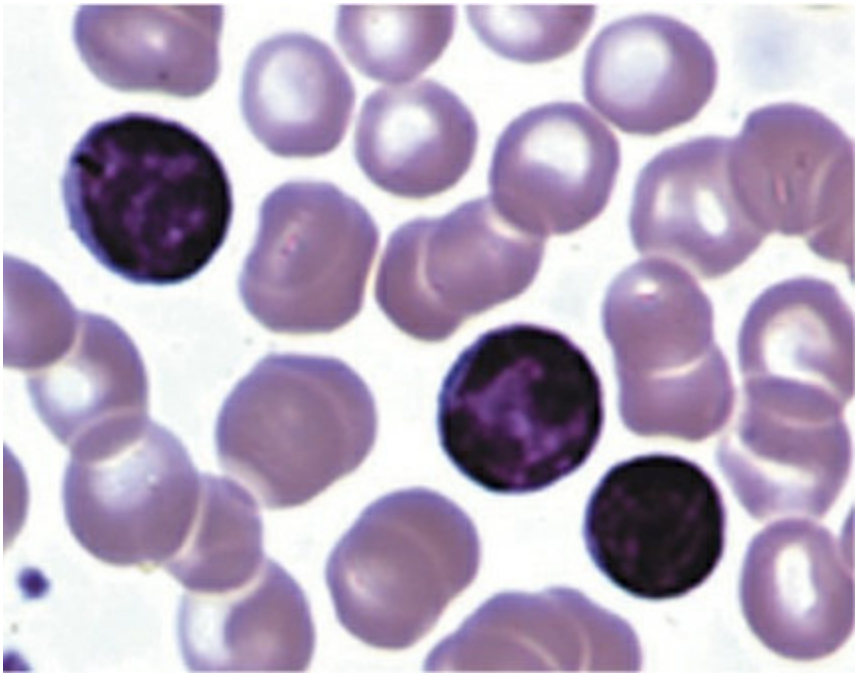
1 AML with Auer rod.



2 ALL.



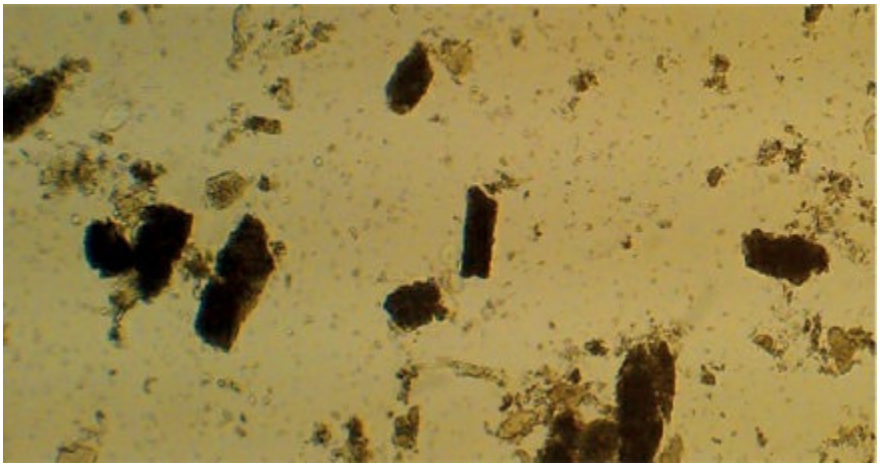
3 CML.



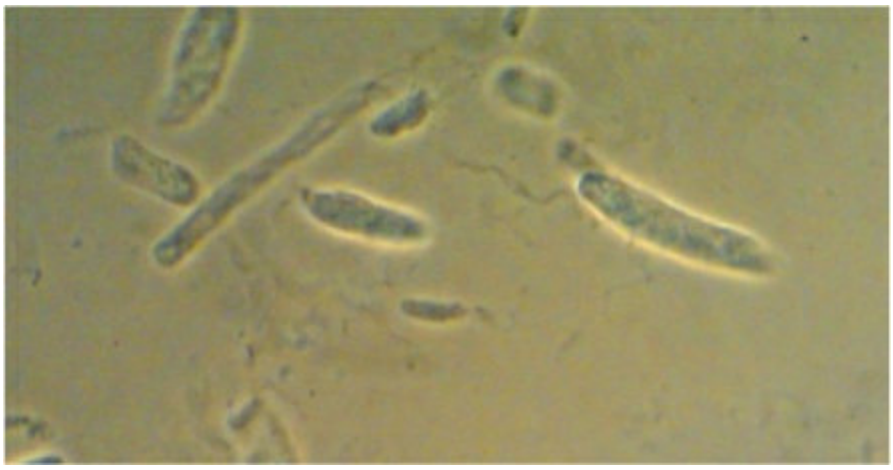
4 CLL.

All photos excluding Leukemias Fig. 4: From Wintrobe's *Clin. Hematol*. 12th ed, 2009: Leukemias. Fig. 4: From Devita, Hellman, and Rosenberg's *Cancer: Princip. & Prac. of Oncol*. 8th ed, 2008.

Urinalysis



1 “Muddy brown” or granular cast (courtesy Nicholas Zwang, MD)



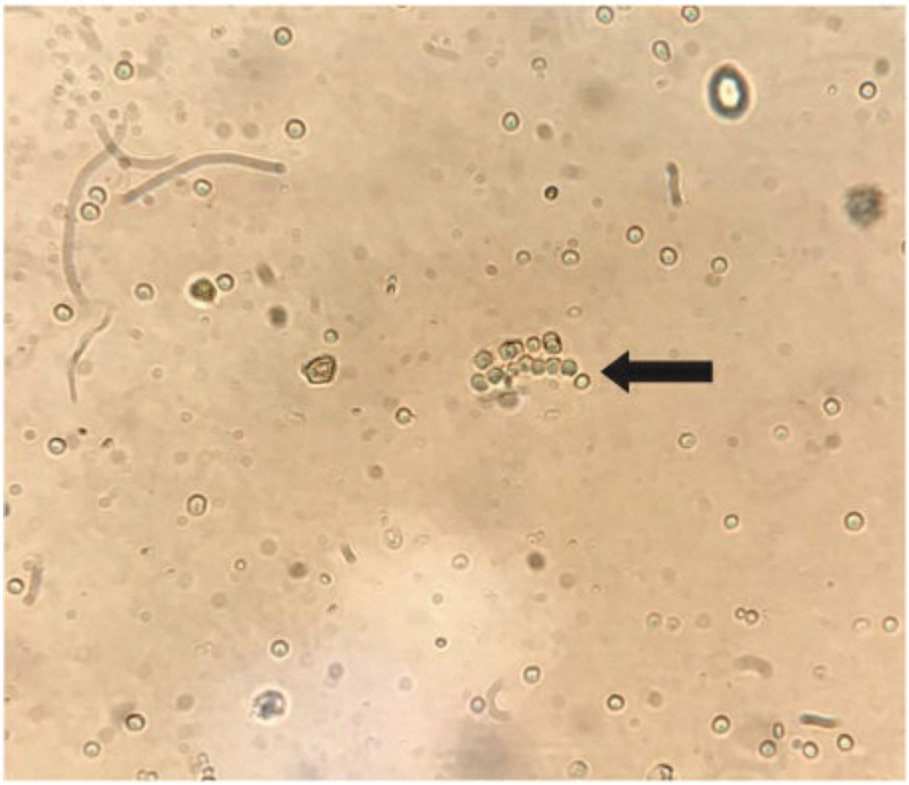
2 Hyaline cast (courtesy Nicholas Zwang, MD)



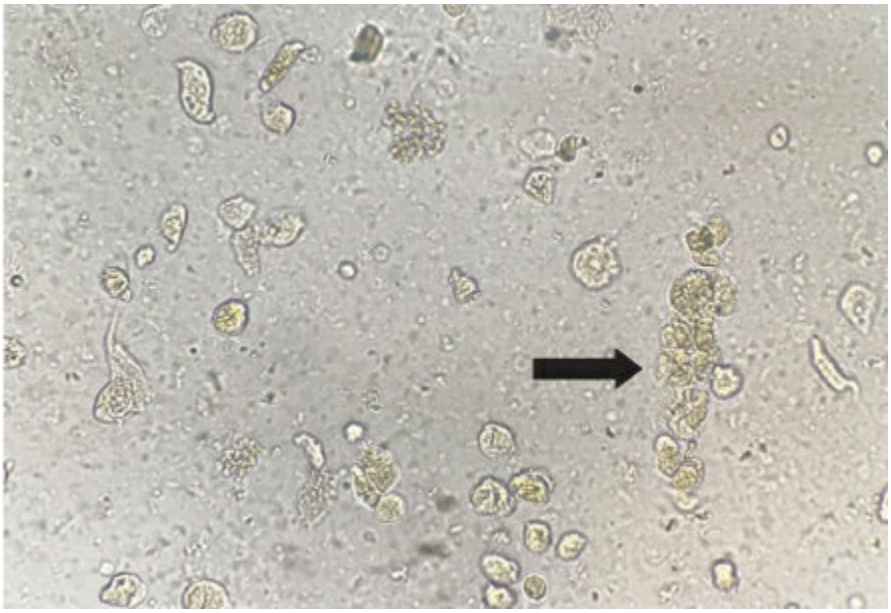
3 “Waxy broad” cast (courtesy Nicholas Zwang, MD)



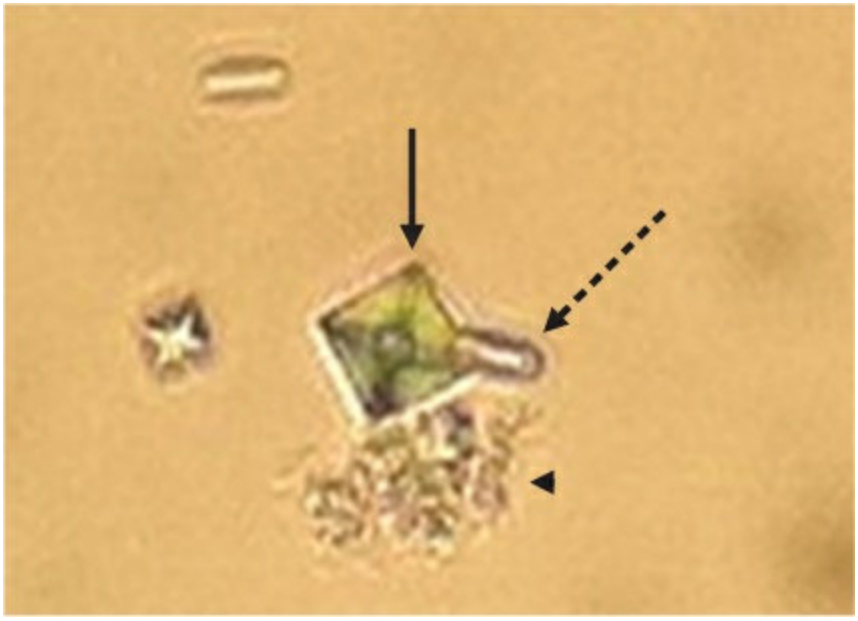
4 Renal tubular epithelial cell (courtesy Nicholas Zwang, MD)



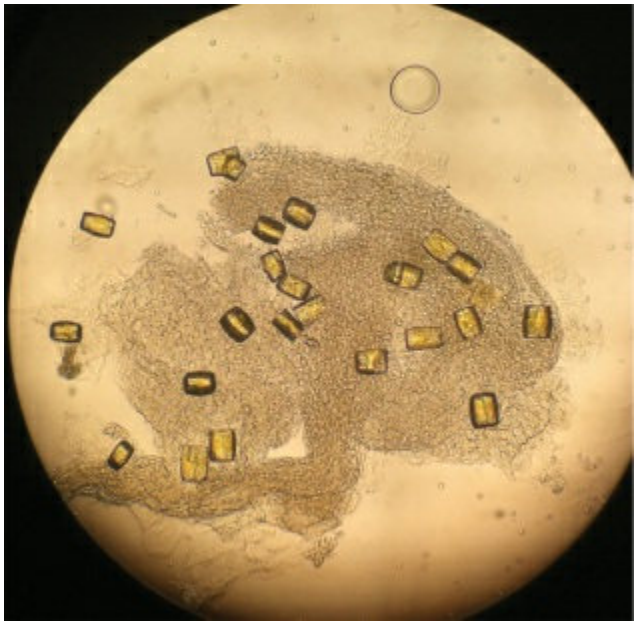
5 RBC cast (courtesy Harish Seethapathy, MBBS)



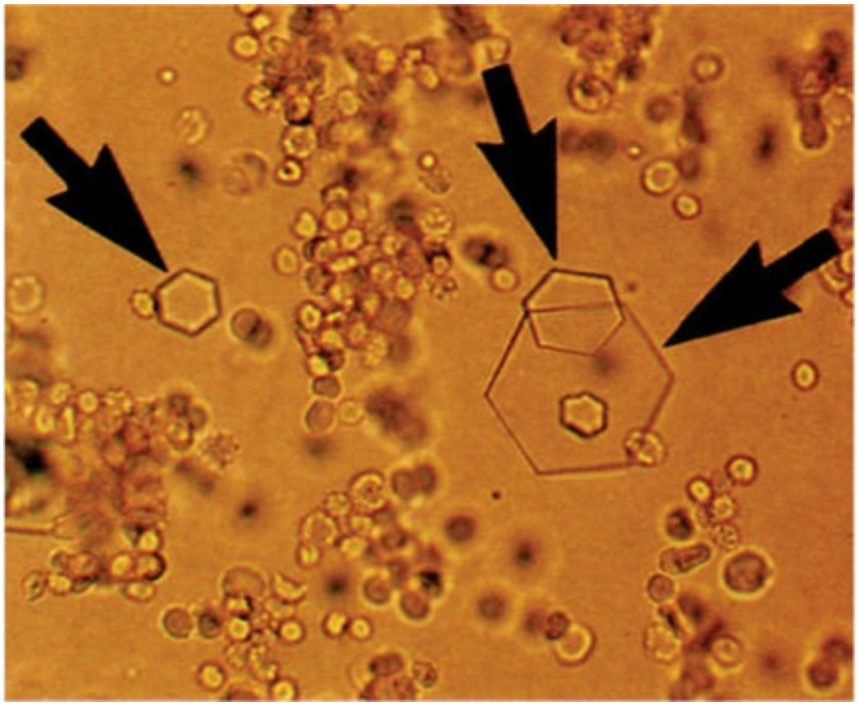
6 WBC cast (courtesy Harish Seethapathy, MBBS)



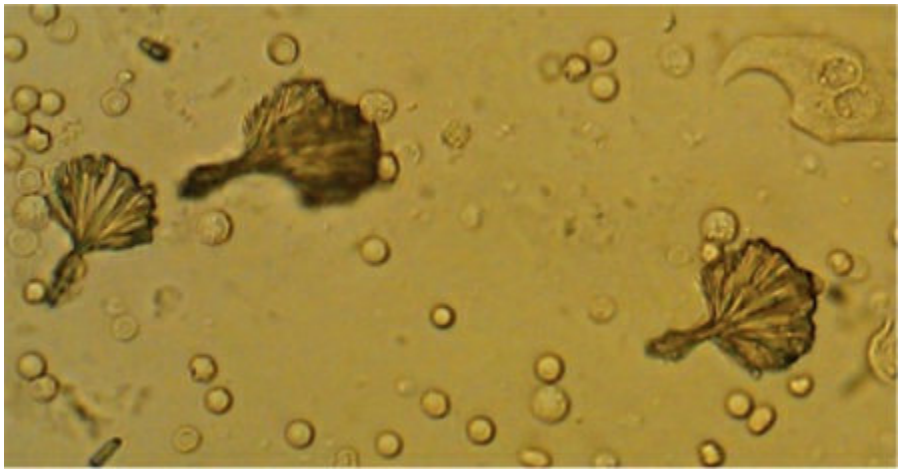
7 Calcium oxalate crystals (courtesy Mallika Mendu, MD). Calcium dihydrate (arrow), calcium monohydrate (dashed arrow), and amorphous calcium crystals (arrow-head)



8 “Struvite” magnesium ammonia phosphate crystals (courtesy Brett Carroll, MD)



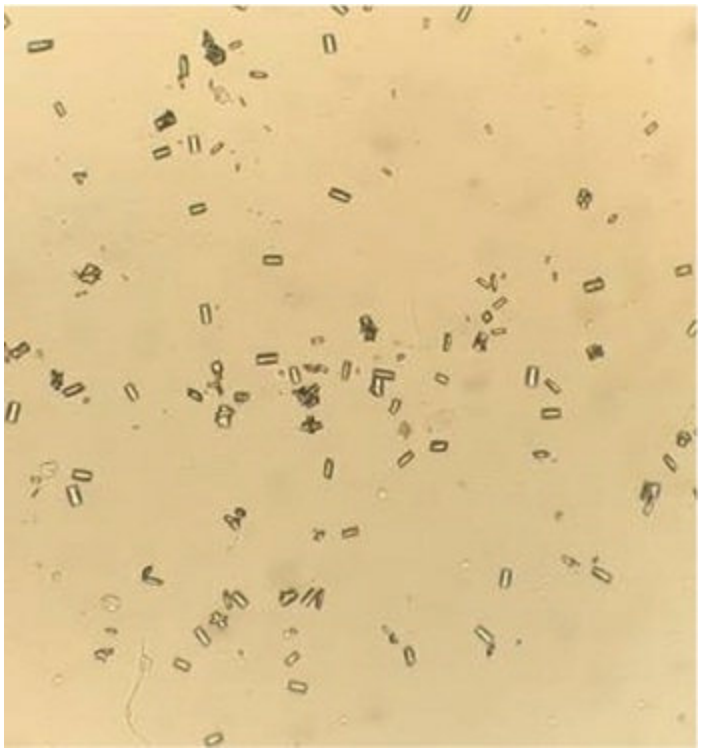
9 Cystine crystals (*Clin. Lab. Medicine*, 1994.)



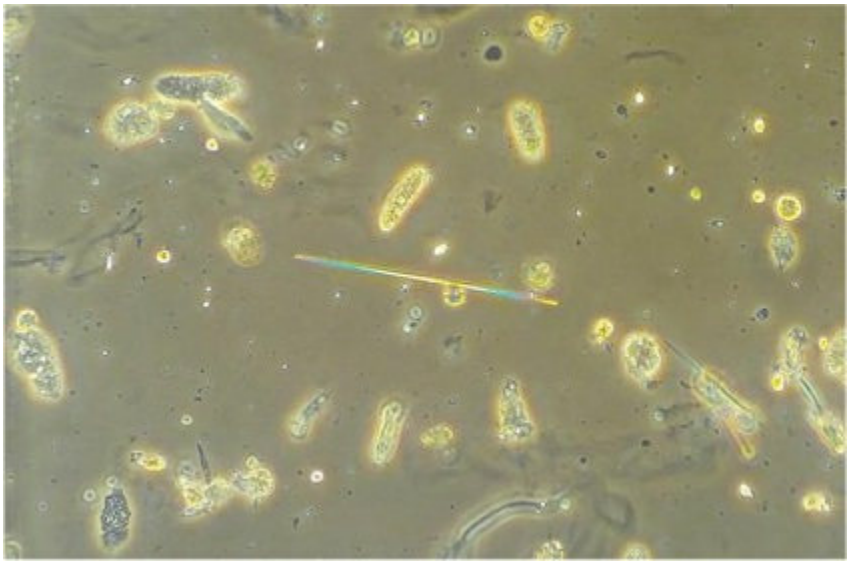
10 Sulfadiazine “shock of wheat” crystals (courtesy Nicholas Zwang, MD)



11a Uric acid crystals under polarized light (courtesy Harish Seethapathy, MBBS)

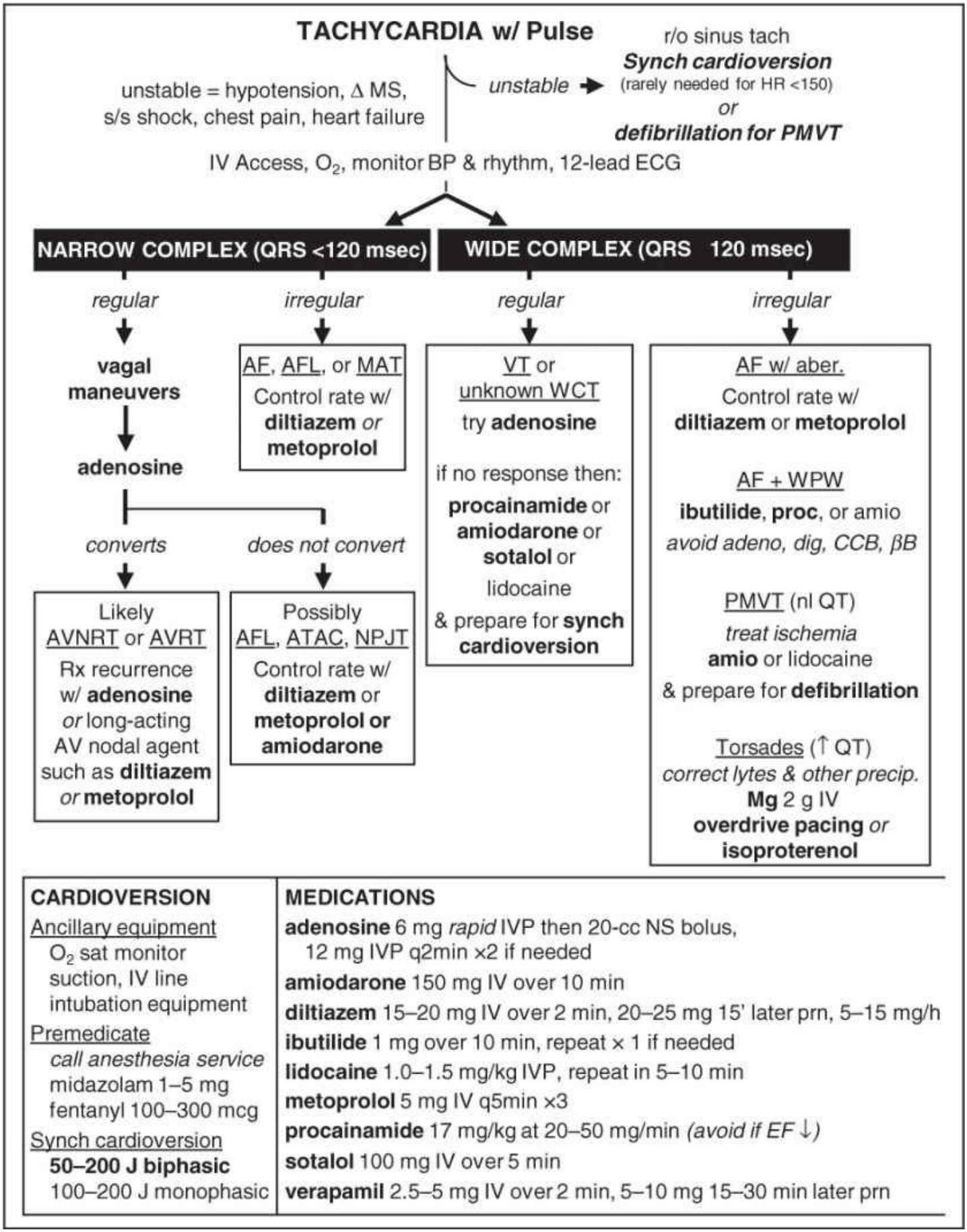


11b Uric acid crystals under normal light (courtesy Harish Seethapathy, MBBS)



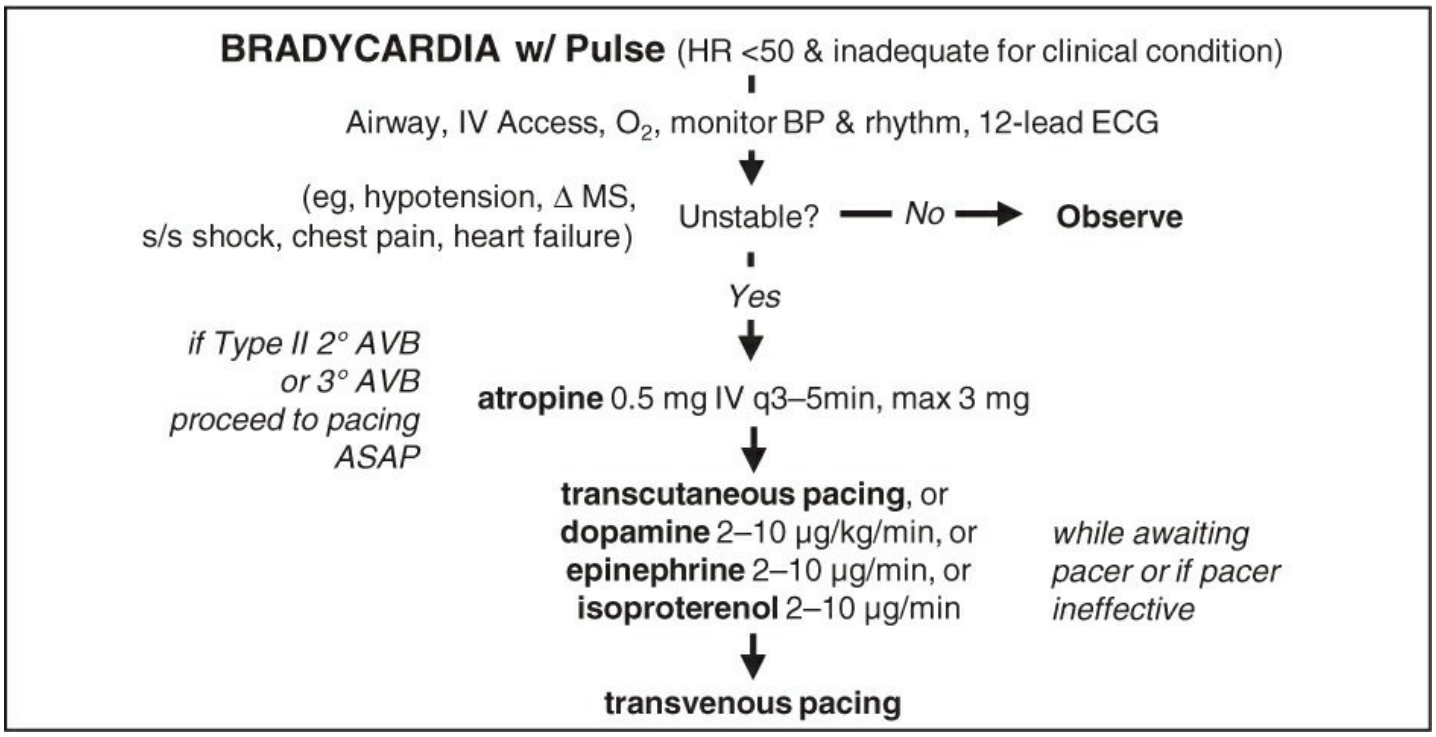
12 Acyclovir needle crystals (courtesy Yuvaram Reddy, MBBS)

Figure ACLS-1 ACLS Tachycardia Algorithm



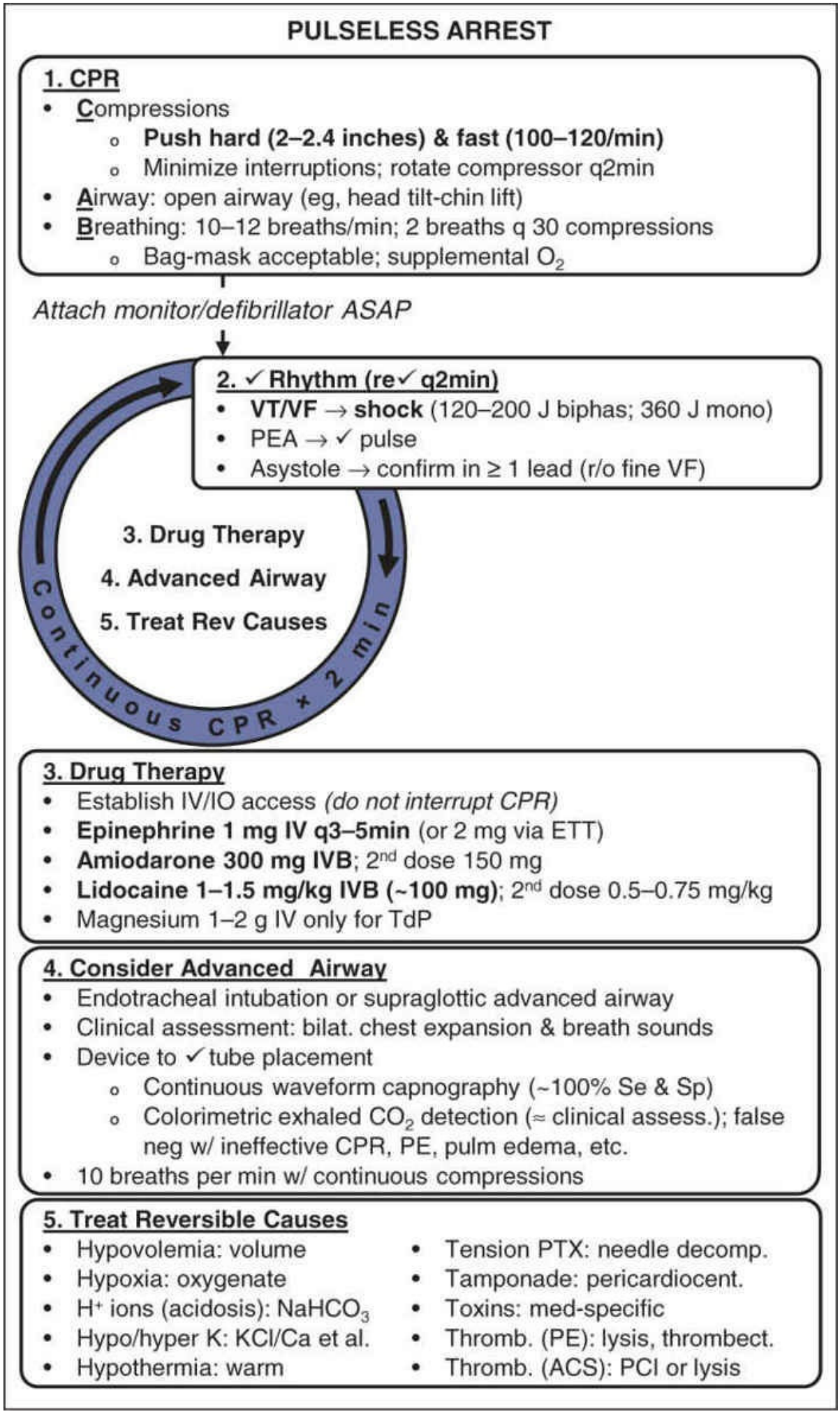
(Adapted from ACLS 2015 *Guidelines & Circ* 2016;133:e506)

Figure ACLS-2 ACLS Bradycardia Algorithm



(Adapted from ACLS 2015 Guidelines)

Figure ACLS-3 VF/Pulseless VT, Asystole & PEA Algorithms



(Adapted from ACLS 2018 *Guidelines & Circ* 2018;138:e740)